A Resource Guide

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OARS
Occupational Alliance for Risk Science

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1. Web Resources

Name of the Resources	Organization	Short Description of the Resource	Link to the Resource
Hazard And Toxicology Databases	Environmental Protection Agency (EPA)	EPA's Integrated Risk Information System (IRIS) is a human health assessment program that evaluates information on health effects that may result from exposure to environmental contaminants	www.epa.gov/iris
	US-National Library of Medicine	TOXNET-HSDB is a Comprehensive, peer-reviewed toxicology data for about 5,000 chemicals.	http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB
	US-National Library of Medicine	ITER- Risk information for over 600 chemicals from authoritative groups worldwide.	http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?iter
	European Commission Institute for Health and Consumer Protection	ESIS- European chemical substances information system provides information on chemicals	http://esis.jrc.ec.europa.eu/
	World Health Organization (WHO)	Concise International Chemical Assessment Documents (CICAD) provides internationally accepted reviews on the effects on human health and the environment of chemicals and the combination of chemicals	http://www.who.int/ipcs/publications/cicad/en/
	World Health Organization (WHO)	Environmental Health Criteria (EHC) documents provide international, critical reviews on the effects of chemicals or combinations of chemicals and physical and biological agents on human health and the environment	http://www.who.int/ipcs/publications/ehc/en/
	IFA (Institute for Occupational Safety and Health of the German Social Accident Insurance)	Information system on hazardous substances of the German Social Accident Insurance (GESTIS) contains information for the safe handling of hazardous substances and other chemical substances at work	http://limitvalue.ifa.dguv.de/Webform_gw.aspx http://www.dguv.de/ifa/en/gestis/stoffdb/index.jsp
	Wiley online library	The MAK collection of occupational health and safety. Nearly 3,000 publications by the Commission for the Investigation of Health	http://onlinelibrary.wiley.com/book/10.1002/352760041818

		Hazards of Chemical Compounds in the Work Area (MAK-Commission) provide essential information on hazardous compounds at the workplace	
	Centers for Disease Control and Prevention (CDC)	Current Intelligence Bulletin 61: A Strategy for assigning new NIOSH skin notations	http://www.cdc.gov/niosh/review/peer/HISA/skinnot-pr.html
	Centers for Disease Control and Prevention (CDC)	Workplace safety and Health topics (Hazards and Exposures)	http://www.cdc.gov/niosh/topics/hazards.html
Exposure limit resources	United States Environmental Protection Agency (US EPA)	Development of Acute Exposure Guideline Levels (AEGLs) is a collaborative effort of the public and private sectors worldwide. AEGLs are intended to describe the risk to humans resulting from once-in-a-lifetime, or rare, exposure to airborne chemicals	http://www.epa.gov/opptintr/aegl/
	American Industrial Hygiene Association (AIHA)	Workplace environmental exposure levels (WEEL™)committee develops guides on exposure levels for chemical and physical agents and stresses when no legal or authoritative limits exist	http://www.aiha.org/insideaiha/GuidelineDevelopment/weel/Pages/default.aspx
	Toxicological Excellence for Risk Assessment (TERA)	The occupational alliance for risk science (OARS) is an initiative to facilitate sharing of information with workers and occupational health and safety professional	http://www.tera.org/OARS/index.html
	American Conference of Governmental Industrial Hygienists (ACGIH)	Product store for Threshold Limit Values (TLVs®) and Biological Exposure Indices (BEIs®)	https://www.acgih.org/store/
	US Dept. of Energy	The Department of Energy's (DOE's) Chemical Safety web pages provide a forum for the exchange of best practices, lessons learned, and guidance in the area of chemical management	www.eh.doe.gov/chem_safety/teel.html; www.orau.gov/emi/scapa/teels.htm
	Centers for Disease Control and Prevention (CDC)	This publication documents the criteria and information sources that have been used by the National Institute for Occupational Safety and Health (NIOSH) to determine immediately dangerous to life or health (IDLH) values	http://www.cdc.gov/niosh/idlh/
	Centers for	The NIOSH Pocket Guide to Chemical	http://www.cdc.gov/niosh/

	Disease Control and Prevention (CDC)	Hazards (NPG) is intended as a source of general industrial hygiene information on several hundred chemicals/classes for workers, employers, and occupational health professionals	npg/default.html
	Centers for Disease Control and Prevention (CDC)	Occupational Health Guidelines for Chemical Hazards summarizes information on permissible exposure limits, chemical and physical properties, and health hazards	http://www.cdc.gov/niosh/docs/81-123/
	European Commission Employment , Social Affairs & Inclusion	The Scientific Committee on Occupational Exposure Limits (SCOEL) advise the European Commission on occupational exposure limits for chemicals in the workplace	http://ec.europa.eu/social/main.jsp?catId=148&langId=en&intPageId=684
	European Agency for Safety and Health at Work Place	Occupational safety and health directives	https://osha.europa.eu/en/legislation/directives/exposure-to-chemical-agents-and-chemical-safety/osh-directives
	Office of Environmental Health Hazard Assessment (OEHHA)	OEHHA's Acute, 8-hour and Chronic Reference Exposure Levels (chRELs)	http://www.oehha.ca.gov/air/allrels.html
	International Labor Organization	Chemical Exposure Limits- The most widely used limits, called threshold limit values (TLVs), are those issued in USA by ACGIH	http://www.ilo.org/safework/info/WCMS_151534/lang--en/index.htm
	Safe work Australia	Australia Exposure Standards for Atmospheric Contaminants	http://www.safeworkaustralia.gov.au/sites/swa/about/publications/pages/ns1995adoptedexposurestandards
	UK- Govt. Health and Safety Executive (HSE)	Contains the list of workplace exposure limits for use with the Control of Substances Hazardous to Health Regulations 2002 (as amended)	http://www.hse.gov.uk/pubns/books/eh40.htm
	The Nordic Expert Group	A Nordic collaboration for production of criteria documents on chemicals for occupational exposure limits.	http://www.av.se/arkiv/neg/the_neg/
Integrated Emergency	US Dept. of Health and	Radiation Emergency Medical Management (REMM). Guidance on diagnosis &	http://www.remm.nlm.gov/

Response Information	Human Services	treatment for health care providers	
	United States Environmental Protection Agency (US EPA)	Development of Acute Exposure Guideline Levels (AEGLs) is a collaborative effort of the public and private sectors worldwide. AEGLs are intended to describe the risk to humans resulting from once-in-a-lifetime, or rare, exposure to airborne chemicals	http://www.epa.gov/opptintr/aegl/
	US National Library of Medicine	Wireless Information System for Emergency Responders (WISER) is a system designed to assist first responders in hazardous material incidents	http://wiser.nlm.nih.gov/
	US Dept. of Health and Human Services	Chemical hazards emergency medical management (CHEMM) is a complete resource containing information on planning, preparing for, and responding to, chemical emergencies	http://chemm.nlm.nih.gov/
	American Industrial Hygiene Association (AIHA)	Emergency response planning (ERP) Committee develops guidelines for responding to potential releases of airborne substances for use in community emergency planning	http://www.aiha.org/insideaiha/GuidelineDevelopment/ERPG/Pages/default.aspx
	Chemical Safety Program	This site allows users to access the U.S. Department of Energy's (DOE's) current data set of Protective Action Criteria (PAC) values in a variety of ways: as a searchable database, as an Excel file, and as a series of tables in PDF format. It also provides archived versions of the PACs for reference.	http://www.atlintl.com/doe/teels/teel.html
Emergency response safety and health databases	Centers for Disease Control and Prevention (CDC)	Developed by NIOSH in response to the needs of emergency response community. Contains concise information on high priority chemical, biological &radiological agents	http://www.cdc.gov/niosh/ershdb/about.html

United States department of Labor

The Occupational Safety and Health (OSH) Act

http://www.dol.gov/compliance/laws/comp-osha.htm

Extremely low frequency radiation
http://www.osha.gov/SLTC/elfradiation/index.html

International labor organization

Safety and health at work

http://www.ilo.org/global/topics/safety-and-health-at-work/lang--en/index.htm

International occupational safety and health information center

http://www.ilo.org/safework/cis/lang--en/index.htm

International labor office- Geneva

Guidelines on occupational safety and health management systems ILO-OSH 2001

http://www.ilo.org/wcmsp5/groups/public/@dgreports/@dcomm/@publ/documents/publication/wcms_publ_9221116344_en.pdf

Canadian center for occupational health and safety

Healthy work places

http://www.ccohs.ca/keytopics/healthy_wplaces.html

Chemicals and product safety

http://www.ccohs.ca/keytopics/chem_safety.html

European agency for safety and health at workplace

Organizations and strategies

https://osha.europa.eu/en/organisations

A step wise approach to risk assessment

http://osha.europa.eu/en/topics/riskassessment/index_html

Emergency Services: A Literature Review on Occupational Safety and Health Risks

http://osha.europa.eu/en/publications/literature_reviews/emergency_services_occupational_safety_and_health_risks

European Commission (At work)

http://ec.europa.eu/health-eu/my_environment/at_work/index_en.htm

Centers for disease control and prevention (CDC)

Workplace safety and health

http://www.cdc.gov/Workplace/

Hazards and exposures

http://www.cdc.gov/niosh/topics/hazards.html

NIOSH pesticide poisoning monitoring program protects farm workers

http://www.cdc.gov/niosh/docs/2012-108/

Diseases and Injuries

http://www.cdc.gov/niosh/topics/diseases.html

Skin exposures and effects

http://www.cdc.gov/niosh/topics/skin/

Skin exposures and effects

http://www.cdc.gov/niosh/topics/skin/recommendations.html

Skin exposures and effects

http://www.cdc.gov/niosh/topics/skin/finiteSkinPermCalc.html

Nanotechnology

http://www.cdc.gov/niosh/topics/nanotech/news.html

Welding and manganese: potential neurologic effects

http://www.cdc.gov/niosh/topics/welding/

National Institute of Occupational Safety and Health (NIOSH)

Current Intelligence Bulletin 61: A strategy for assigning new NIOSH skin notations

http://www.cdc.gov/niosh/review/peer/HISA/skinnot-pr.html

Emergency responder health monitoring and surveillance (ERHMS)

http://www.cdc.gov/niosh/topics/erhms/

Toxicological Excellence for Risk Assessment (TERA)

Occupational toxicology

http://www.tera.org/art/occupational.html

Risk assessments

http://www.tera.org/art/Assessments.html

Occupational health hazard risk assessment project for California

http://www.cdph.ca.gov/programs/hesis/Documents/riskreport.pdf

http://www.cdph.ca.gov/programs/hesis/Documents/risksummary.pdf

Ministry of man power, Singapore

Work place safety and health

http://www.mom.gov.sg/workplace-safety-health/Pages/default.aspx

Health and safety executive, UK

Health and Safety at Work etc Act 1974

http://www.hse.gov.uk/legislation/hswa.htm

British Health and Research Foundation (identification of prognostic factors for people diagnosed with occupational contact dermatitis)

http://www.bohrf.org.uk/downloads/OCD-PrognosticFactors.pdf

Environmental protection agency

Guidelines for neurotoxicity risk assessment

http://www.epa.gov/raf/publications/pdfs/NEUROTOX.PDF

Occupational Health and Safety Management System Standard Certification (OHSAS 18001safety manual) [first tier of documentation]

http://www.ohsas18001certification.us/ohsas-18001-safety-manual.htm

LITERATURE—Links

Book on---Quantitative risk assessment for environmental and occupational health

http://books.google.com/books?hl=en&lr=&id=Ur5qG6-sOAEC&oi=fnd&pg=PA1&dq=occupational+risk+assessment&ots=_h8ajaOyZA&sig=oJ7lvNRDhT3htI3SXdmkG2kr0tA

Risk Assessment: Evaluating Risks to Human Health and Safety

http://www.ncbi.nlm.nih.gov/books/NBK43454/

Wikipedia: Occupational Safety and Health

http://en.wikipedia.org/wiki/Occupational_safety_and_health

A Practical Guide to Dose-Response Analyses and Risk Assessment in Occupational Epidemiology

http://journals.lww.com/epidem/Abstract/2004/01000/A_Practical_Guide_to_Dose_Response_Analyses_and.11.aspx

Occupational Disease Britannica Encyclopedia

http://www.britannica.com/EBchecked/topic/424257/occupational-disease

OSHA enforcement and workplace injuries: A behavioral approach to risk assessment (Journal of Risk and Uncertainty)
http://www.springerlink.com/content/n03147211t764m50/
Risk assessment of chemicals: An introduction
http://books.google.com/books?hl=en&lr=&id=-ltZ0K1TcqAC&oi=fnd&pg=PR9&dq=workplace+risk+assessment&ots=vvHiH8FCFJ&sig=--IrXKOC4b6rF3KDF3_MU30gEbk#v=onepage&q=workplace%20risk%20assessment&f=false
A practical guide to risk assessment
http://www.pwc.com/us/en/issues/enterprise-risk-management/publications/guide-to-risk-assessment-risk-management-from-pwc.jhtml
Risk assessment Wikipedia
http://en.wikipedia.org/wiki/Risk_assessment
Risk Assessment for Occupational Exposure to Chemicals. A review of current methodology (IUPAC technical report)
http://pac.iupac.org/publications/pac/pdf/2001/pdf/7306x0993.pdf
Good practice guidance on Occupational Health Risk Assessment (International Council of Mining and Metals)
http://www.icmm.com/page/14660/good-practice-guidance-on-occupational-health-risk-assessment (click on PDF)
Methods for quantitative risk assessment (The American Statistician)
http://www.jstor.org/discover/10.2307/2683028?uid=3739840&uid=2129&uid=2&uid=70&uid=4&uid=3739256&sid=21101422968401
Biomonitoring for occupational health risk assessment (BOHRA) (Journal of toxicol lett)
http://www.ncbi.nlm.nih.gov/pubmed/19446015

2. OEL Methodology References

"Environmental Management Guidelines: Occupational Health Assessment."

(1969). "Permissible levels of occupational exposure to airborne toxic substances." World Health Organ Tech Rep Ser **415**: 5-16.

(1974). "TLVs threshold limit values for chemical substances in workroom air adopted by the American Conference of Government Industrial Hygienists for 1973." J Occup Med **16**(1): 39-49.

(1984). "Recommended health-based occupational exposure limits for respiratory irritants. Report of a WHO Study Group." World Health Organ Tech Rep Ser **707**: 1-154.

(1990). "[Proceedings of the Congress on Exposure Limit Values: an instrument of prevention? Desio, 8 February 1991]." G Ital Med Lav **12**(5-6): 181-232.

(1993). Health and safety commission. Advisory committee on toxic substances. Hydrazine: Draft. Criteria document for an occupational exposure limit, 50th ACTS Meeting**:** 1-57.

(1996). Chapter 7-Developing HMIS ratings. HMIS Implementation Manual, Second Edition**:** 59-76.

(1996). "Controlling occupational exposure to hazardous drugs. Occupational Safety and Health Administration." Am J Health Syst Pharm **53**(14): 1669-1685.

Guidelines on the safe management of hazardous drugs (HDs) in the workplace are presented. OSHA published guidelines for the safe management of cytotoxic (antineoplastic) drugs in the workplace in 1986. Those guidelines have been revised in this document to reflect the latest scientific knowledge and expanded to include other potentially hazardous drugs. The guidelines (1) provide criteria for classifying drugs as hazardous, (2) summarize the evidence supporting the management of HDs as an occupational hazard, (3) discuss the equipment and worker education recommended, as well as the legal requirements of standards for the protection of workers exposed and potentially exposed to HDs, (4) update the important aspects of medical surveillance, and (5) list some common HDs currently in use. Revised and expanded work-practice guidelines intended to limit the exposure of workers to HDs are described.

(1996). "Phenol: Health based recommended occupational exposure limit." **90517**(2509).

(2004). "Recommendation of occupational exposure limits (2004-2005)." J Occup Health **46**(4): 329-344.

Abrams, H. K. (1988). "Credibility in the TLV process." Am J Ind Med **13**(5): 609-610.

ACGIH (1998). Threshold Limit Values for Chemical Substances and Physical Agents Biological Exposure Indicies. Cincinnati, OH, American Conference of Governmental and Industrial Hygienists.

ACGIH (2001). Guide to occupational exposure values. Cincinnati, OH, American Conference of Governmental Industrial Hygienists.

Agius, R. (1989). "Occupational exposure limits for therapeutic substances." Ann. Occup. Hyg. **33**(4): 555-562.

Agner, T., J. D. Johansen, et al. (2002). "Combined effects of irritants and allergens. Synergistic effects of nickel and sodium lauryl sulfate in nickel- sensitized individuals." Contact Dermatitis **47**(1): 21-26.

Knowledge of the combined effects of irritants and allergens is of interest with respect to accurate risk assessment. The threshold for elicitation of allergic contact dermatitis in previously sensitized individuals may theoretically be markedly influenced by the simultaneous presence of irritants and allergens. Combined exposures have, however, only been studied infrequently. In the present study, the combined effect of an irritant and an allergen was evaluated in a dose-response designed experimental study. 20 nickel-sensitized subjects were exposed to patch testing with varying concentrations of NiCl2 (nickel chloride) and sodium lauryl sulfate (SLS) alone and in combination. Evaluation of skin reactions was performed by colorimetry, measurement of transepidermal water loss and clinical evaluation, and the data were analyzed by logistic dose-response models. A synergistic effect was found of combined exposure to NiCl2 and SLS, as compared to each of the substances applied separately, as evaluated by colorimetry and clinical scoring. This means that the effect produced by the combined exposure was substantially greater than the effect produced by either of the substances alone. A synergistic effect of combined exposure on skin barrier impairment was not found, since the barrier function is significantly influenced by SLS-exposure only and not by NiCl2. Concentration limits are used by industry and government agencies to protect consumers. The present results clearly illustrate that elicitation thresholds and concentration limits may be influenced considerably by combined exposure to allergens and irritants.

AIHA (1989). Odor thresholds for chemicals with established occupational health standards. Akron, OH, American Industrial Hygiene Association.

AIHA (1997). AMERICAN INDUSTRIAL HYGIENE ASSOCIATION WHITE PAPER ON RISK ASSESSMENT AND RISK MANAGEMENT, American Industrial Hygiene Association.

Aitio, A. (1994). "Reference limits in occupational toxicology." Clin Chem **40**(7 Pt 2): 1385-1386.

Two categories of reference limits can be discerned in biological monitoring: The first category identifies individuals who have been exposed to a toxic agent at work, and is based on the distribution of the concentration of the agent or its metabolite in the population that has not been exposed to the agent at work. The second category, for which the term biological action level (BAL) is proposed, provides a guideline on the level of exposure that is acceptable. These levels may be either directly health-based or derived from good working practices. Thus BAL is a biological equivalent for the generic term occupational exposure limit. BAL should be independent of legal overtones, and implies that workers' exposure should be reduced.

Alarie, Y. (1966). "Irritating properties of airborne materials to the upper respiratory tract." Arch Environ Health **13**(4): 433-449.

Alarie, Y. (1973). "Sensory irritation of the upper airways by airborne chemicals." Toxicol Appl Pharmacol **24**(2): 279-297.

Alarie, Y. (1981). "Bioassay for evaluating the potency of airborne sensory irritants and predicting acceptable levels of exposure in man." Food Cosmet Toxicol **19**(5): 623-626.

Alarie, Y. (1998). "Computer-based bioassay for evaluation of sensory irritation of airborne chemicals and its limit of detection." Arch Toxicol **72**(5): 277-282.

We expanded a previously described rule-based computerized method to recognize the sensory irritating effect of airborne chemicals. Using 2-chlorobenzylchloride (CBC) as a sensory irritant, characteristic modifications of the normal breathing pattern of exposed mice were evaluated by measuring the duration of braking (TB) after inspiration and the resulting decrease in breathing frequency. From the measurement of TB, each breath was then classified as normal (N) or sensory irritation (S). Using increasing exposure concentrations, the classification S increased from < or = 2% (equivalent to sham-exposure) to 100% within a narrow exposure concentration range. The potency of CBC was then evaluated by calculating the concentration necessary to produce 50% of the breaths classified as S, i.e., S50. This approach is easier to use than obtaining RD50 (decrease in respiratory frequency by 50%) when high exposure concentrations are difficult to achieve. Detection limits were also established for this bioassay and experiments were conducted to obtain a level of response just around these limits, in order to delineate the practicality of using this bioassay at low exposure concentrations. Using this approach, sensory irritation was the only effect induced by CBC at low exposure concentrations. However, bronchoconstriction and pulmonary irritation were superimposed on this effect at higher exposure concentrations.

Alarie, Y., G. D. Nielsen, et al. (1998). "A theoretical approach to the Ferguson principle and its use with non-reactive and reactive airborne chemicals." Pharmacol Toxicol **83**(6): 270-279.

The Ferguson principle has been widely used in toxicology to separate or indicate possible mechanisms for acute toxic effects of chemicals. However, this principle has never been adequately tested because of the lack of a database containing a sufficient number of both types of chemicals, non-reactive and reactive, that the Ferguson principle purports to separate. Such a database is now available. In this report a theoretical framework for the Ferguson principle is presented, regarding one of the acute toxicological effects of volatile airborne chemicals: sensory irritation. Previously obtained results on series of non-reactive and reactive chemicals are then used to demonstrate that the Ferguson principle can be extended to reactive chemicals by adding chemical reactivity descriptors to the physicochemical descriptors required by the Ferguson principle. This approach can be successful, provided that specific chemical reactivity mechanisms can be identified for the reactive chemicals of concern. The findings suggest that it is possible to replace the empirical Ferguson principle by formal mechanistic equations which will provide a better foundation for the understanding of the mechanisms by which airborne sensory irritants exert their action.

Alarie, Y., G. D. Nielsen, et al. (1995). "Physicochemical properties of nonreactive volatile organic chemicals to estimate RD50: alternatives to animal studies." Toxicol Appl Pharmacol **134**(1): 92-99.

This article presents the correlations obtained between the results on the potency of nonreactive airborne chemicals as sensory irritants and several of their physicochemical properties. The potency of airborne sensory irritants obtained from a reflexively induced decrease in respiratory frequency has been measured in the past using mice. Typically, their potency has been expressed as the exposure concentration necessary to decrease respiratory frequency by 50% (RD50). A large database of RD50 values is now available and such values are highly correlated with occupational exposure guidelines such as threshold limit values (TLVs). We used the nonreactive volatile organic chemicals from this database, for which relevant physicochemical variables are available or can be calculated. These variables were vapor pressure (P) or Ostwald gas-liquid partition coefficients (L). The liquids used for L values were n-hexadecane, octanol, N-formylmorpholine, tri-(2-ethylhexyl)phosphate, and olive oil. Excellent correlations were found between log RD50 and log P, as well as between log RD50 and log L16, log L(Oct), log L(NFM), log L(EHP), or log L(Oil). It follows that as an alternative to the bioassay, these physicochemical variables can be used to estimate RD50 of nonreactive volatile organic chemicals. Appropriate exceptions to general estimation of RD50 values from physicochemical variables are also presented, as well as the most appropriate estimates which can be obtained within homologous series.

Alarie, Y., M. Schaper, et al. (1996). "Estimating the sensory irritating potency of airborne nonreactive volatile organic chemicals and their mixtures." SAR QSAR Environ Res **5**(3): 151-165.

This article describes the possibility of estimating whether or not a mixture of nonreactive volatile organic chemicals (NRVOC) is likely to elicit complaints of sensory irritation in humans. For this estimation we rely on: a) the sensory irritating potency of individual NRVOC can be estimated from a variety of physicochemical properties of these chemicals, b) at low exposure concentrations, the additivity rule can be applied using the potency of each chemical in a mixture and c) a threshold concentration exists below which no sensory irritation will occur. We used this estimating approach and we compared the results obtained with those obtained experimentally in humans exposed to a well defined mixture. The approach presented can be used to arrive at a decision as to whether or not exposure to a mixture of NRVOC is likely to result in sensory irritation complaints by humans, either in the general indoor air situation or for industrial workers.

Albert, R. E. (1999). "1999 Stokinger Award Lecture. Unifying the standard setting process for carcinogens and non-carcinogens." Appl Occup Environ Hyg **14**(11): 742-747.

Aldridge, W. N. (1995). "Defining thresholds in occupational and environmental toxicology." Toxicol Lett **77**(1-3): 109-118.

When a chemical causes a defined form of toxicity, the threshold is the maximum exposure when this toxicity does not occur. It is an operational parameter and is limited in its interpretation and applicability. The aim of this paper is to consider biological parameters which influence exposure-response relationships. Biomonitoring of dose and effects has much potential for defining thresholds in human exposure; extension of their use in experimental studies on new compounds should help predictions to thresholds for human exposure. Intoxication initiated by both reversible and covalent interactions with targets are discussed and, as exposure is reduced and the time of exposure extended, changes in the shape of the dose-response curves examined for acute and delayed neuropathy (axonopathy) and for carcinogenesis.

Amdur, M. O., J. F. McCarthy, et al. (1983). "Effect of mixing conditions on irritant potency of zinc oxide and sulfur dioxide." Am Ind Hyg Assoc J **44**(1): 7-13.

Measurement of mechanics of respiration in guinea pigs was used to assess the irritant potency of zinc oxide and sulfur dioxide mixed under different conditions of temperature and humidity. Concentrations were 1-2 mg/m3 zinc oxide and 1 ppm sulfur dioxide. Dry conditions of mixing (Chamber RH 30%) either at 24 degrees C in the exposure chamber or at 480 degrees C in a dry furnace gave a biological response which could be completely accounted for by responses to zinc oxide and/or sulfur dioxide alone. Chemical examination of the aerosols did not indicate the formation of particulate sulfur species. Zinc oxide and sulfur

dioxide mixed dry at 480 degrees C and fed into the exposure chamber at 80% RH reacted to produce an irritant aerosol as evidenced by a rapid increase to levels 29% above control; reversal was rapid when exposure ended. Chemical studies indicated the presence of sulfite on these aerosols. Addition of water vapor to the furnace during mixing at 480 degrees C produced a different irritant aerosol. The resistance rose slowly to 19% above control values and remained elevated during the post-exposure hour. Chemical studies indicated the presence of sulfate, sulfite, and adsorbed sulfur trioxide on these aerosols.

American Thoracic Society (1985). "Guidelines as to what constitutes an adverse respriatroy health effect, with special reference to epidemiologic studies of air pollution." Am Rev Respir Dis **131**: 666-668.

American Thoracic Society (1986). "Evaluation of impairment/disability secondary to respiratory disorders." Am Rev Respir Dis **133**: 1205-1209.

American Thoracic Society (1993). "Guidelines for the evaluation of impairment/disability in patients with asthma." Am Rev Respir Dis **147**: 1056-1061.

Amoore, J. E. and E. Hautala (1983). "Odor as an aid to chemical safety: odor thresholds compared with threshold limit values and volatilities for 214 industrial chemicals in air and water dilution." J Appl Toxicol **3**(6): 272-290.

The body of information in this paper is directed to specialists in industrial health and safety, and air and water pollution, who need quantitative data on the odor thresholds of potentially hazardous chemical vapors and gases. The literature, largely unorganized, has been reviewed for 214 compounds and condensed into tables based on consistent units. Data on the volatility, solubility, ionization and water-air distribution ratio at 25 degrees C are included. From the currently recommended threshold limit value (TLV), a safe dilution factor and an odor safety factor are calculated for each compound. The equivalent data are presented for both air and water dilutions of the chemicals. Available data are summarized on the variability of odor sensitivities in the population, and the increased odor concentrations that are required to elicit responses from persons whose attention is distracted, or who are sleeping. This information is reduced to calibration charts that may be used to estimate the relative detectability, warning potential and rousing capacity of the odorous vapors. Each compound has been assigned a letter classification, from A to E, to indicate the margin of safety, if any, that may be afforded by the odor of the compound as a warning that its threshold limit value is being exceeded.

Andersen, I., G. R. Lundqvist, et al. (1983). "Human response to controlled levels of toluene in six-hour exposures." Scand J Work Environ Health **9**(5): 405-418.

The nasal mucus flow, lung function, subjective response, and psychometric performance of 16 young healthy subjects was studied during 6-h exposures to clean air and to 10, 40 or 100 ppm of toluene under controlled conditions. The

toluene exposures did not affect nasal mucus flow or lung function. At 100 ppm irritation was experienced in the eyes and in the nose. There was a significant deterioration in the perceived air quality and a significant increased odor level during all exposures to toluene. The test battery investigated visual perception, vigilance, psychomotor functions, and higher cortical functions and comprised five-choice, rotary pursuit, screw-plate, Landolt's rings, Bourdon Wiersma, multiplication, sentence comprehension, and word memory tests. In these eight tests measuring 20 parameters, no statistically significant effects of the toluene exposure occurred. For three tests (multiplication errors, Landolt's rings, and the screw plate test) there was a borderline significance (0.05% less than p less than 0.10%). The subjects felt that the tests were more difficult and strenuous during the 100-ppm exposure, for which headache, dizziness, and feeling of intoxication were significantly more often reported. The exposures to 10 and 40 ppm did not result in any adverse effects.

Andersen, M. E., M. G. MacNaughton, et al. (1987). "Adjusting exposure limits for long and short exposure periods using a physiological pharmacokinetic model." Am Ind Hyg Assoc J **48**(4): 335-343.

The rationale for adjusting occupational exposure limits for unusual work schedules is to assure, as much as possible, that persons on these schedules are placed at no greater risk of injury or discomfort than persons who work a standard 8 hr/day, 40 hr/week. For most systemic toxicants, the risk index upon which the adjustments are made will be either peak blood concentration or integrated tissue dose, depending on what chemical's presumed mechanism of toxicity. Over the past ten years, at least four different models have been proposed for adjusting exposure limits for unusually short and long work schedules. This paper advocates use of a physiologically-based pharmacokinetic (PB-PK) model for determining adjustment factors for unusual exposure schedules, an approach that should be more accurate than those proposed previously. The PB-PK model requires data on the blood:air and tissue:blood partition coefficients, the rate of metabolism of the chemical, organ volumes, organ blood flows and ventilation rates in humans. Laboratory data on two industrially important chemicals--styrene and methylene chloride--were used to illustrate the PB-PK approach. At inhaled concentrations near their respective 8-hr Threshold Limit Value-Time-weighted averages (TLV-TWAs), both of these chemicals are primarily eliminated from the body by metabolism. For these two chemicals, the appropriate risk indexing parameters are integrated tissue dose or total amount of parent chemical metabolized. Since methylene chloride is metabolized to carbon monoxide, the maximum blood carboxyhemoglobin concentrations also might be useful as an index of risk for this chemical.(ABSTRACT TRUNCATED AT 250 WORDS)

Anderson, R. C. and J. H. Anderson (1999). "Sensory irritation and multiple chemical sensitivity." Toxicol Ind Health **15**(3-4): 339-345.

Many of the symptoms described in Sick Building Syndrome (SBS) and multiple chemical sensitivity (MCS) resemble the symptoms known to be elicited by airborne irritant chemicals. Irritation of the eye, nose, and throat is common to SBS, MCS, and sensory irritation (SI). Difficulty of breathing is often seen with SBS, MCS, and pulmonary irritation (PI). We therefore asked the question: can indoor air pollutants cause SI and/or PI? In laboratory testing in which mice breathed the dilute volatile emissions of air fresheners, fabric softeners, colognes, and mattresses for 1 h, we measured various combinations of SI and PI as well as airflow decreases (analogous to asthma attacks). Air samples taken from sites associated with repeated human complaints of poor air quality also caused SI, PI, and airflow limitation (AFL) in the mice. In previous publications, we have documented numerous behavior changes in mice (which we formally studied with a functional observational battery) after exposure to product emissions or complaint site air; neurological complaints are a prominent part of SBS and MCS. All together, these data suggest that many symptoms of SBS and MCS can be described as SI, PI, AFL, and neurotoxicity. All these problems can be caused by airborne irritant chemicals such as those emitted by common commercial products and found in polluted indoor air. With some chemical mixtures (e.g., emissions of some fabric softeners, disposable diapers, and vinyl mattress covers) but not others (e.g., emissions of a solid air freshener), the SI response became larger (2- to 4-fold) when we administered a series of two or three 1-h exposures over a 24-h period. Since with each exposure the intensity of the stimulus was constant yet the magnitude of the response increased, we concluded that there was a change in the sensitivity of the mice to these chemicals. The response was not a generalized stress response because it occurred with only some mixtures of irritants and not others; it is a specific response to certain mixtures of airborne chemicals. This is one of the few times in MCS research that one can actually measure both the intensity of the stimulus and the magnitude of the response and thus be allowed to discuss sensitivity changes. The changing SI response of the mice might serve as a model of how people develop increasing sensitivity to environmental pollutants. Intensive study of this system should teach us much about how people respond to and change sensitivity to airborne irritant chemicals.

Andresen, B. (1981). "[It is not dangerous says employer: up to fivefold of the limit values of anesthetic gases]." Sygeplejersken **81**(6): 14-16.

Anger, W. K. (1984). "Neurobehavioral testing of chemicals: impact on recommended standards." Neurobehav Toxicol Teratol **6**(2): 147-153.

Historically, the American Conference of Governmental Industrial Hygienists (ACGIH) has served as a major source of information on recommended safe exposure limits (Threshold Limit Values or TLV's) for chemicals most frequently encountered in U. S. industry and of known toxicologic significance. A review of the ACGIH Documentation book, which details the basis for their judgements, has indicated that 167 of the 588 chemicals for which they assigned

recommended standards have, as one of their bases, direct nervous system effects. In order to increase the impact of future behavioral toxicology research on recommended standards, the neurotoxicologist can utilize certain strategies: (a) Focus on established mixtures in the environment of interest or select exposures of particular chemical classes, considering population size and severity of effect; (b) Ensure that the results of the study are referable to the expected route of exposure in the environment of interest; and (c) Select tests with face validity for non-psychologists, using reference substances. Finally, the neurotoxicologist is urged to consider effects related to safety as well as health in developing his/her research.

Apostoli, P., C. Minoia, et al. (1998). "Significance and utility of reference values in occupational medicine." Sci Total Environ **209**(1): 69-77.

Although it is generally accepted that reference values can be included among the instruments of modern occupational medicine, problems arise when applying them from clinical chemistry to the needs of occupational medicine. Here some general aspects regarding reference values beginning from their theoretical basis, their significance and importance and their possible use in occupational medicine are reviewed. Furthermore, their relationship with other more familiar 'guideline values', such as action levels and limit values, is demonstrated.

Apostoli, P., S. Porru, et al. (1990). "[The evaluation of occupational exposure to carcinogenic substances: limit values and risk assessments]." G Ital Med Lav **12**(5-6): 201-207.

Considering that nowadays there is no unanimity about the possibility of adopting environmental and/or biological limit values in occupational exposure to carcinogens, some aspects are discussed about the mechanism of action of carcinogens, their metabolism and problems deriving from the possible multiple exposures, interactions and speciation of the different compounds. After the analysis of the results obtained by means of two different approaches by the American Conference of Governmental Industrial Hygienist and the Environmental Protection Agency of the United States, the authors examine some aspects of the qualitative and as far as possible quantitative comparison for the 16 substances included in both lists and they discuss how the mathematical models are used in the process of carcinogenic risk evaluation. Finally, it is considered the possible application even in occupational carcinogenesis of a model such as the one of the EPA.

Arble, J. (2004). "Toxicology primer: understanding workplace hazards and protecting worker health." Aaohn J **52**(6): 254-261; quiz 262-253.

Hazardous substances are ubiquitous in the environment and common in industrialized societies. Serious harm can occur with sufficient exposures under certain conditions. However, much harm can be avoided if hazardous substances are handled with respect and appreciation for their use and potential. Occupational health nurses must be aware of potential hazards to employees in

the work environment and apply scientific principles to their practice of promoting worker safety and health.

Aresini, G. A. (1993). "[A new proposal of the EEC Directorate for the protection of workers against the risks related to chemical agent exposure]." Med Lav **84**(4): 334-336.

Army, U. (2000). Evaluation of airborne exposure limits for sulfur mustard: Occupational and general exposure criteria. Aberdeen Proving Ground, MD, US Army**:** 1-122.

Arts, J. H., J. Mojet, et al. (2002). "An analysis of human response to the irritancy of acetone vapors." Crit Rev Toxicol **32**(1): 43-66.

Studies on the irritative effects of acetone vapor in humans and experimental animals have revealed large differences in the lowest acetone concentration found to be irritative to the respiratory tract and eyes. This has brought on much confusion in the process of setting occupational exposure limits for acetone. A literature survey was carried out focusing on the differences in results between studies using subjective (neuro)behavioral methods (questionnaires) and studies using objective measurements to detect odor and irritation thresholds. A critical review of published studies revealed that the odor detection threshold of acetone ranges from about 20 to about 400 ppm. Loss of sensitivity due to adaptation and/or habituation to acetone odor may occur, as was shown in studies comparing workers previously exposed to acetone with previously unexposed subjects. It further appeared that the sensory irritation threshold of acetone lies between 10,000 and 40,000 ppm. Thus, the threshold for sensory irritation is much higher than the odor detection limit, a conclusion that is supported by observations in anosmics, showing a ten times higher irritation threshold level than the odor threshold found in normosmics. The two-times higher sensory irritation threshold observed in acetone-exposed workers compared with previously nonexposed controls can apart from adaptation be ascribed to habituation. An evaluation of studies on subjectively reported irritation at acetone concentrations < 1000 ppm shows that perception of odor intensity, information bias, and exposure history (i.e., habituation) are confounding factors in the reporting of irritation thresholds and health symptoms. In conclusion, subjective measures alone are inappropriate for establishing sensory irritation effects and sensory irritation threshold levels of odorants such as acetone. Clearly, the sensory irritation threshold of acetone should be based on objective measurements.

Association, A. M. P. (1998). Quantification of cancer risk due to occupational exposure to acrylamide. Rome, Italy.

Austin, H., E. Delzell, et al. (1988). "Benzene and leukemia. A review of the literature and a risk assessment." Am J Epidemiol **127**(3): 419-439.

Benzene is widely recognized as a leukemogen, and the Occupational Safety and Health Administration is currently attempting to limit exposure to it more

strictly. The proposed new regulation is a limit of an eight-hour time-weighted average of 1 ppm in place of the current limit of 10 ppm. The fundamental rationale for the change is a perception that the current standard is associated with an inordinate excess of leukemia. The epidemiologic literature on benzene and leukemia supports the inference that benzene causes acute myelocytic leukemia. However, the available data are too sparse, or suffer other limitations, to substantiate the idea that this causal association applies at low levels (i.e., 1-10 ppm) of benzene. Nonetheless, under the assumption that causation does apply at such low levels, a number of authors, including ourselves, have performed risk assessments using similar data but different methodologies. The assessments that we consider acceptable suggest that, among 1,000 men exposed to benzene at 10 ppm for a working lifetime of 30 years, there would occur about 50 excess deaths due to leukemia in addition to the baseline expectation of seven deaths. However, this estimate is speculative and whether or not enough confidence can be placed in it to justify a lower occupational benzene standard remains a decision for policy makers.

Baelum, J. (1991). "Human solvent exposure. Factors influencing the pharmacokinetics and acute toxicity." Pharmacol Toxicol **68 Suppl 1**: 1-36.

The purpose of this review has been to discuss human and environmental factors which may influence the acute irritative and neurotoxic effects of organic solvents. The review is based on a field study and on four human experimental studies. Several studies have shown that printers and other workers exposed to mixtures of solvents experience an increased frequency of work related irritative and neurological symptoms although the exposure has been far below the occupational exposure limits. A series of controlled human exposure studies was carried out. Different groups of persons were exposed to the most frequent solvent, toluene. Toluene in alveolar air and the urinary excretion of the metabolites were measured and the acute effects of toluene were assessed by the performance in a series of test of the perceptual and psychomotor functions as well as a standardized registration of annoyance and symptoms. The pharmacokinetics of toluene is complex and there is a large individual variation in the excretion of the metabolites. This variation can only to a limited extend be related to known variables. Intake of alcohol during exposure inhibits the metabolism of toluene and increases the internal dose. Normal therapeutic doses of cimetidine or propranolol have no measurable effect on toluene metabolism. Exposure to 100 ppm during 7 h causes irritation in the eyes and airways as well as feeling of intoxication, dizziness, and headache. There are signs of impairment in the performance in test concerning visual perception, colour vision, vigilance as well as the psychomotor functions. However, the influence on the performance tests was not seen in all studies. Variations in the air concentration of toluene with peaks op to 300 ppm causes fluctuation in the alveolar concentrations, but no acute effect of these peaks or of increased physical activity during exposure could be detected. However, the importance of peek concentrations and of workload for the development of chronic solvent

encephalopathy is still unknown. The influence of a 9-25 years occupational exposure to solvents was investigated. A group of printers occupationally exposed to mixtures of solvents were compared with a matched unexposed control group. There was no difference between printers and controls in the performance in the psychological test, but in two of the tests there were tendencies to increased sensitivity to toluene in the group of printers. It is concluded that exposure to toluene corresponding to the occupational limit in several countries cause irritative and prenarcotic symptoms and possibly a lowered performance.(ABSTRACT TRUNCATED AT 400 WORDS)

Baelum, J., G. R. Lundqvist, et al. (1990). "Human response to varying concentrations of toluene." Int Arch Occup Environ Health **62**(1): 65-71.

Thirty two males and 39 females aged 31-50 were exposed for 7 h to one of the three following conditions: (1) Clean air, (2) constant exposure to 100 ppm toluene, or (3) a varying exposure with the same time-weighted average, but with peaks of 300 ppm every 30 min. During exposure the subjects exercised in three 15-min periods with a load of 50 to 100 W. Exposure to toluene caused significant (P less than 0.05) complaints about poor air quality, altered temperature and noise perception, increased irritation in the nose and the lower airways, feeling of intoxication, and there were tendencies (P less than 0.1) towards irritation in the throat, headache and dizziness. In the four performance tests there was a tendency towards a lower score in a vigilance test while no effect of toluene exposure was seen in a peg board test, a five choice serial reaction test, or a colour test, indicating only minimal if any effect on the psychomotor or visual performance. There was no difference in the acute effects caused by the exposure containing peak concentrations and by the constant exposure.

Balmes, J. R. (2002). "Occupational airways diseases from chronic low-level exposures to irritants." Clin Chest Med **23**(4): 727-735, vi.

Short-term, high-level exposures to dusts, gases, mists, fumes, and smoke that are irritating to the respiratory tract are capable of inducing asthma, the so-called reactive airways dysfunction syndrome. Such exposures, however, do not occur frequently; chronic or recurrent exposures to lower levels of irritants are much more common. This article reviews the evidence that supports the concept that low-level exposures to respiratory tract irritants can contribute to the development of chronic obstructive pulmonary disease and asthma.

Bartsch, R., S. Forderkunz, et al. (1998). "Maximum workplace concentration values and carcinogenicity classification for mixtures." Environ Health Perspect **106 Suppl 6**: 1291-1293.

In Germany, the Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (MAK Commission) generally sets maximum workplace concentration values (i.e., a proposed occupational exposure level [OEL]) for single substances, not for mixtures. For mixtures containing

substances with a genotoxic and carcinogenic potential, the commission considered it scientifically inappropriate to establish a safe threshold. This approach is currently under discussion. Carcinogenic mixtures are categorized according to either the carcinogenicity of the mixture or the classification of the carcinogenic substances included. In regulating exposure to mixtures, an approach similar to that used by the American Conference of Governmental Hygienists is proposed: For components with the same target organ and mode of action or interfering metabolism, synergistic effects must be expected and the respective OELs must be lowered. However, if there is proof that the components act independently, the OELs of the individual compounds are not considered to be modified. In the view of the commission, calculating OELs for solvent mixtures according to their liquid phase composition is not justified, and the setting of scientifically based OELs for complex mixtures is not possible.

Bauer, S., I. Wolff, et al. (1992). "Health hazards in the semiconductor industry. A review." Pol J Occup Med Environ Health **5**(4): 299-314.

The development of semiconductor production has been accompanied by an increased use of toxic production materials and an increased release of potential toxic wastes, which are harmful to health and environment. This paper gives an overview of occupational health hazards resulting from production materials in the microelectronics industry and from waste products originating as gases from plasma etching processes in photolithography during semiconductor production. The paper proposes methods for using experimental toxicology to investigate the occupational risks from complex mixtures of chemicals in the semiconductor industry.

Baur, X. (2003). "I are we closer to developing threshold limit values for allergens in the workplace?" Ann Allergy Asthma Immunol **90**(5 Suppl 2): 11-18.

OBJECTIVE: To define threshold limit values and legally binding occupational exposure limits. DATA SOURCES: Review of suitable literature. STUDY SELECTION: Studies based on detailed descriptions and/or measurements of airborne allergenic dust, total allergens, or even key allergens were selected. RESULTS: Prevalences of IgE-mediated sensitization and occupational asthma are related to the aeroallergen load in workplaces. Data to set threshold limit values for flour, latex, a-amylase, and isocyanates are already sufficiently available. CONCLUSIONS: To optimize primary prevention in workplaces,health-based occupational exposure limits should be set for major occupational allergens.

Baur, X., Z. Chen, et al. (1998). "Can a threshold limit value for natural rubber latex airborne allergens be defined?" J Allergy Clin Immunol **101**(1 Pt 1): 24-27.

BACKGROUND: Recent studies have shown that systemic or respiratory occupational responses to latex can be induced by inhalation of latex aeroallergens. OBJECTIVE: Our objectives were to study the relationship between exposure to different latex aeroallergen levels and type I allergic

reactions in subjects with occupational contact with latex and to assess a threshold value for latex airborne allergens required for sensitization and symptom elicitation. METHODS: We screened 145 subjects working in 32 hospitals or operating rooms with different latex aeroallergen levels. The quantified latex aeroallergen concentrations in the 32 rooms were compared with latex-related allergic symptoms. RESULTS: Different latex aeroallergen concentrations could be detected in rooms where powdered latex gloves were used and no effective ventilation systems were installed. In environments with latex aeroallergen levels of 0.6 ng/m3 or greater, the reported workplace-related symptoms were significantly increased ($p < 0.02$). All 22 subjects with latex-specific IgE antibodies worked in rooms contaminated with latex aeroallergens ($p < 0.05$). CONCLUSIONS: Our results demonstrate that symptoms and presence of latex-specific IgE antibodies in subjects are significantly associated with measurable levels of latex aeroallergens. A latex aeroallergen level of 0.6 ng/m3 is a critical threshold, especially for health care workers who are sensitized to natural rubber latex.

Bechtold, W. E., J. K. Willis, et al. (1992). "Biological markers of exposure to benzene: S-phenylcysteine in albumin." Carcinogenesis **13**(7): 1217-1220.

Results of experiments in our laboratory have shown that benzene is metabolized by animals in part to an intermediate that binds to cysteine groups in hemoglobin to form the adduct S-phenylcysteine (SPC). These results suggested that SPC in hemoglobin may be an effective biological marker for exposure to benzene. However, we could not detect SPC in the globin of humans occupationally exposed to benzene concentrations as high as 28 p.p.m. for 8 h/day, 5 days/week. As another approach, we examined the binding of benzene to cysteine groups of a different blood protein, albumin. To facilitate the process, a new method for the precipitative isolation of albumin from plasma was also developed. The isolated albumin was analyzed for SPC by isotope dilution GC-MS. We used this approach to measure SPC in the albumin of F344/N rats exposed by gavage to 0-10,000 mumol/kg benzene. Amounts of albumin-associated SPC increased as a function of dose, followed by a leveling off in the amount of SPC seen at doses greater than 1000 mumol/kg. Levels of SPC were measured in humans occupationally exposed to average concentrations of 0, 4.4, 8.4 and 23 p.p.m. benzene 8 h/day, 5 days/week. Of nine controls, seven had levels of SPC below the limit of detection (0.1 pmol SPC/mg albumin). SPC increased in the exposed groups linearly, giving a statistically significant slope (P less than 0.001) of 0.044 +/- 0.008 pmol/mg albumin/p.p.m. with an intercept of 0.135 +/- 0.095 pmol/mg albumin. From this study, we conclude that SPC in albumin may prove useful as a biomarker for benzene exposure.

Bello, D., S. R. Woskie, et al. (2004). "Polyisocyanates in occupational environments: a critical review of exposure limits and metrics." Am J Ind Med **46**(5): 480-491.

BACKGROUND: Determination of polyisocyanates is important because they are a major contributor of exposure to the isocyanate functional group in many

workplace environments and are capable of inducing sensitization and asthma. However, with multiple different measurement metrics in use, comparison of isocyanate exposure data between studies and development of occupational exposure limits (OELs) for polyisocyanates is difficult. METHODS: An analysis of existing problems in the measurement and regulation of isocyanates is presented based on the published analytical, toxicological, and regulatory literature, and the authors' own analytical data and experience with isocyanates. RESULTS: This analysis supports a need for standardization of isocyanate measurement metrics and provides a framework for the development of an OEL for polyisocyanates. CONCLUSIONS: The total isocyanate group (microg NCO/m(3)) is recommended as the most feasible and practical metric (unit) by which to express polyisocyanate exposures for research, control, and regulatory purposes. The establishment of a comprehensive isocyanate OEL that simplifies the current agent-by-agent approach and expands coverage to polyisocyanates is also recommended.

Bender, J. (2002). "The use of noncancer endpoints as a basis for establishing a reference concentration for formaldehyde." Regul Toxicol Pharmacol **35**(1): 23-31.
Published studies involving formaldehyde were selected for quality and relevance for determining whether noncancer endpoints could be used to derive a reference concentration for formaldehyde. Chamber studies provided the highest quality data for determining the presence of eye, nose, or throat irritation at a known level of formaldehyde. Some individuals begin to sense irritation at about 0.5 ppm, 5-20% report eye irritation at 0.5 to 1 ppm, and greater certainty for sensory irritation appears at 1 ppm or greater. These levels of formaldehyde do not appear to impact asthmatics even though these individuals are thought to be more sensitive to irritants. Mild, reversible changes in pulmonary function (forced expiratory volume at 1 s and midexpiratory flow) can occur in sensitized individuals at levels approaching 2 ppm. Studies in the manufacturing setting, while confounded by multiple exposures, provide useful information for setting boundaries for sensory irritation or changes in pulmonary function. Community surveys do not provide the specificity nor sensitivity needed to establish a reference concentration. Histological studies of the nasal mucosa suffer significant methodological and technological shortcomings in addition to issues commonly associated with the design of residential and workplace studies. Based on the review of chamber, community, and workplace studies of human exposures to formaldehyde, it is not possible to identify a specific no observed adverse effect level or lowest observed adverse effect level for formaldehyde. Ranges of exposures associated with acute sensory irritation can be derived and do include sensitive subpopulations. However, given the quality and variability of the data, human studies alone, especially those involving sensory irritation, are not adequate to serve as a reference concentration for estimating risk, or lack thereof, for a lifetime of exposure to formaldehyde. Alternative approaches, such as modeling cellular changes observed in animal studies, may be more useful for

quantitative risk assessment of noncancer endpoints and should be used as an adjunct to interpreting human sensory studies.

Berger, M. R. (1994). "Conference on carcinogenic risk factors in the occupational environment (Krebserzeugende Gefahrstoffe in der Arbeitsumwelt). Frankfurt/Main, October 1993." J Cancer Res Clin Oncol **120**(8): 498-501.

In this summary, J. Konietzko (Mainz) stressed the exceptional position of occupational cancer, which is due to the long latent period between exposure to specific carcinogens and cancer manifestation. Obviously, this long latent period of years to decades poses problems in the search for the etiology of occupational cancer. Three methodological areas are instrumental in overcoming these problems. They include epidemiological investigations, in vitro experiments and animal experiments, which have to complement each other. A highly important area within the aetiological research is the field of syncarcinogenesis. Up to now, some research on combined effects has been done, but this field urgently needs further efforts and promotion since the threat of more than additive carcinogenic effects can be ruled out or prevented only after the necessary knowledge has been gathered from properly conducted basic research. Within the discussion of occupational cancer, three areas have to be discriminated; they relate to cancer as an occupational disease, as a problem within the insurance laws, and as a risk that requires preventive measures. Its acknowledgement as an occupational disease is based on strict legal preconditions that limit any generosity. Such a procedure is too reserved, however, as far as preventive measures are concerned. In this area, more generous criteria are required, which do not only result from scientific procedures. Prevention is subject to a clear ranking; primary prevention, i.e. the elimination of carcinogens from the workplace, has priority. If the elimination of occupational hazards is impossible, a quantitative risk assessment that takes account of synergistic carcinogenic effects can help to set priorities. The impossibility of a complete primary prevention necessitates secondary and tertiary prevention, which correspond to early diagnosis and follow-up management of occupational cancer. Each of these areas needs continued attention.

Bhambhani, Y., R. Burnham, et al. (1997). "Effects of 10-ppm hydrogen sulfide inhalation in exercising men and women. Cardiovascular, metabolic, and biochemical responses." J Occup Environ Med **39**(2): 122-129.

This study examined the acute effects of 10-ppm hydrogen sulfide (H2S) inhalation, a concentration equal to its occupational exposure limit, on the cardiovascular, metabolic, and biochemical responses in healthy volunteers. Fifteen men and 13 women completed two 30-minute exercise sessions at 50% of their maximal oxygen uptake, during which they inhaled medical air or 10 ppm H2S in a blind manner. Arterial and finger-prick blood samples were obtained before and during the final minute of exercise. Muscle biopsies were withdrawn from the right vastus lateralis immediately after exercise. Cardiorespiratory measurements were monitored using an automated metabolic cart interfaced

with an electrocardiogram and blood pressure apparatus. A significant decrease in oxygen uptake (VO2), with a concomitant increase in blood lactate, was observed in men and women as a result of H2S exposure. No significant changes were observed in arterial blood parameters and the cardiovascular responses under these conditions. Muscle lactate, as well as the activities of lactate dehydrogenase, citrate synthase, and cytochrome oxidase, were not significantly altered by H2S exposure. However, there was a tendency for muscle lactate to increase and citrate synthase activity to decrease in both genders in the presence of H2S. It appeared that 10-ppm H2S inhalation reduced VO2 during exercise, most likely by inhibiting the aerobic capacity of the exercising muscle. These findings question the scientific validity of the current occupational exposure limit for H2S.

Bhambhani, Y., R. Burnham, et al. (1996). "Effects of 10-ppm hydrogen sulfide inhalation on pulmonary function in healthy men and women." J Occup Environ Med **38**(10): 1012-1017.

This study examined the acute effects of oral inhalation of 10-ppm hydrogen sulfide (H2S) inhalation (a concentration equal to its occupational exposure limit) on the pulmonary function in healthy men and women. Nine men and ten women consented to inhale medical air or 10 ppm H2S for 15 minutes each during cycle exercise at 50% of their maximal aerobic power. Routine pulmonary function tests were administered at rest and immediately after the two exposure conditions. The results indicated no significant changes in any of the variables derived from the flow volume loop, maximum ventilation volume, and diffusion capacity of the lung for carbon monoxide in both genders. None of the subjects experienced any signs and symptoms as a result of H2S exposure. It was concluded that oral inhalation of 10 ppm H2S at an elevated metabolic and ventilation rate does not significantly alter pulmonary function in healthy men and women.

Bigelow, P., D. Moore, et al. (2004). "Assessing the health implications for healthcare workers of regulatory changes eliminating locally developed occupational exposure limits in favor of TLVs: an evidence-based bipartite approach." Int J Occup Environ Health **10**(4): 433-444.

In response to the intention of the Workers' Compensation Board of British Columbia (WCB of BC) to eliminate made-in-BC occupational exposure limits (OELs) and adopt threshold limit values (TLVs), this study assessed the potential health impacts on healthcare workers (HCWs) of the proposed change, by (1) reviewing the processes used to establish the OELs and TLVs, (2) selecting of substances of health concern for HCWs, (3) identifying chemicals with discordances between existing OELs and the 2002 TLVs, and 4) reviewing the discordances and assessing the potential health implications. Differences in philosophies, policies and processes that influenced the setting of OELs and TLVs were substantial. The TLV process involves U.S. and international priorities; in BC, a tripartite committee determined OELs taking into consideration

how OELs should be interpreted in the local context. 47 chemicals of concern to BC HCWs were discordant, with significant discordances totalling 57; 15 compounds had BC 8-hour OELs lower than their respective TLVs and three TLVs were lower than the 8-hour BC OELs. Review of six chemicals with discordances suggested a potential for increased risks of adverse health effects. Eliminating the local capacity and authority to set OELs is unlikely to cause major health problems in the short run, but as chemicals in use locally may not have up-to-date TLVs, eliminating the capacity for local considerations should be undertaken with great caution. While the WCB of BC did implement the change, the present report resulted in procedural changes that will provide better protection for the workforce.

Binks, S. P. (2003). "Occupational toxicology and the control of exposure to pharmaceutical agents at work." Occup Med (Lond) **53**(6): 363-370.

BACKGROUND: The pharmaceutical industry employs >350 000 people worldwide in operations including research and development (R&D), manufacturing, sales and marketing. Workers employed in R&D and manufacturing sectors are potentially exposed to drug substances in the workplace that are designed to modify physiology and also to chemical precursors that are potentially hazardous to health. Pharmaceutical workers are at risk from adverse health effects, including occupational asthma, pharmacological effects, adverse reproductive outcomes and dermatitis. AIM: This study aimed to describe the approaches taken by pharmaceutical companies for identifying and communicating potential adverse health effects that may result from workplace exposures and in setting 'in-house' exposure control limits and to highlight the challenges in controlling workplace exposures to increasingly potent compounds. METHOD: The literature was reviewed by searching the Medline and HSELine databases. RESULTS: The findings are presented in five sections, covering: test methods and approaches to occupational toxicology; hazard communication; approaches to setting health-based occupational exposure limits for pharmaceutically active agents; recent approaches to risk control; and occupational hygiene and exposure controls. CONCLUSION: Significant efforts have been directed at predicting and evaluating potential occupational health hazards in the pharmaceutical industry. The pharmaceutical industry has provided leadership in controlling exposure to hazardous substances. Much of this work has been driven by a real need to control occupational exposures to substances that can have profound adverse health effects in exposed employees and that are becoming increasingly more potent.

Boeniger, M. F. and H. W. Ahlers (2003). "Federal government regulation of occupational skin exposure in the USA." Int Arch Occup Environ Health **76**(5): 387-399.

There are at least 14 federal regulations and three agencies that are involved in the regulation of occupational skin exposures in the USA. The Environmental Protection Agency (EPA) requires the reporting of health effects information on

chemicals, and such information is used to assess the risks of human and environmental exposure. The health effects information and any resulting risk assessments are generally available to the public. A fair amount of this information relates to skin irritation, sensitization, and dermal absorption. The EPA can require the submission of new data necessary for it to carry out its risk assessments, and has the authority to ban hazardous chemicals for certain uses. The Food and Drug Administration (FDA) regulates the correct labeling of cosmetics and requires safety and efficacy data on new products that are claimed to have preventive or health benefits. Commercial distribution of topical skin-care and protection products, therefore, can be potentially scrutinized by the FDA, which can control the use of hazardous chemicals in such products. The Occupational Safety and Health Administration (OSHA) has the most direct contact with workplaces through its field inspection compliance activity, which is directed at the reduction of workplace injuries and illnesses. Our analysis suggests that although considerable amounts of health effects information is generated and available, such information may not always be adequately conveyed to the end users of chemical products. In addition, the most effective and practical means of preventing exposure is often not apparent or generally known. Current regulations may have created a reliance on use of chemical protective equipment that may not always be the best approach to protecting workers. Lack of performance criteria that are measurable has hampered industry from objectively assessing skin exposures. This lack of performance criteria or guidance has also hindered the implementation of prevention strategies and a critical assessment of their effectiveness. Better guidance from regulatory agencies directed at performance-based control of occupational skin hazards is presently needed.

Bogadi-Sare, A., R. Turk, et al. (1995). "Medical surveillance studies of workers exposed to low level benzene." Arh Hig Rada Toksikol **46**(4): 391-398.

The paper presents th results of an investigation of haematotoxicity in workers exposed to low benzene concentrations. Forty-seven female workers in the shoemaking industry, exposed to solvent mixture and twenty-seven non-exposed controls were examined. Benzene concentrations in the working atmosphere ranged from 1.9 to 14.8 ppm. Significant differences in the levels of benzene in blood and phenols in pre- and post-shift urine between the exposed and control groups confirmed benzene exposure. Haemoglobin level and mean corpuscular haemoglobin concentration were significantly lower, and mean corpuscular volume was higher in the shoemaking workers than in controls. In the subgroup of shoemaking workers exposed to benzene concentrations of 5 ppm or lower, no differences in haematological parameters were found. In conclusion, exposure to a benzene concentration lower than 5 ppm does not appear to produce an increased level of abnormal haematological outcomes detectable in routine medical surveillance. The results of the study corroborate the present maximum permissible concentrations (5 ppm) as a protective limit preventing the onset of haematotoxic non-leukemogenic effects of chronic benzene exposure.

Bohlin, G., K. Eliasson, et al. (1986). "Pace variation and control of work pace as related to cardiovascular, neuroendocrine, and subjective responses." Biol Psychol **23**(3): 247-263.

Two studies of paced and self-paced arithmetic performance are reported. Heart rate and blood pressure were recorded and ratings of subjective arousal obtained. In one of the studies, plasma levels of catecholamines and cortisol were determined. Under externally paced experimental conditions pace variation was found to be quantitatively related to changes in systolic and diastolic blood pressure, as well as to ratings of stress and irritation. This was not the case for heart rate or positively evaluated aspects of subjective arousal. Performance was better and ratings of stress and irritation were lower during self-paced than during paced work at a comparable work pace. In one of the studies the diastolic blood pressure increased less when subjects controlled the pace. Plasma catecholamines did not increase significantly during either externally or self-paced work, but adrenaline tended to increase during paced work. Our findings give partial support to the suggestion that personal control may attenuate sympathoadrenal activation and cardiovascular reactivity.

Bois, F. Y. and D. G. Paxman (1992). "An analysis of exposure rate effects for benzene using a physiologically based pharmacokinetic model." Regul Toxicol Pharmacol **15**(2 Pt 1): 122-136.

A new physiological pharmacokinetic model was used to explore the effect of exposure rate on the rate of formation of several crucial metabolites of benzene. Metabolite formation was compared following exposure to benzene over the course of an 8-hr workday and following a single exposure for 15 min. These exposures were based on the permissible exposure limit and short-term exposure limit of the benzene standard set by the Occupational Safety and Health Administration. The model was parametrized using in vitro and in vivo experimental data on benzene toxicokinetics and metabolism. Ranges, rather than fixed values, were assigned to the parameters. Model predictions show that the amounts of hydroquinone, catechol, and muconaldehyde formed in the body following a peak exposure to 32 ppm of benzene over 15 min are on average 20% higher than those formed following an equivalent dose of 1 ppm over an 8-hr period. The health consequences of these findings and the implications for policy concerning short-term exposure limits are discussed.

Bolt, H. M., H. Foth, et al. (2004). "Carcinogenicity categorization of chemicals-new aspects to be considered in a European perspective." Toxicol Lett **151**(1): 29-41.

Existing systems of classification of carcinogens are a matter of discussion, world-wide. There is agreement that it should be distinguished between genotoxic and non-genotoxic chemicals. The risk assessment approach used for non-genotoxic chemicals is similar among different regulatory bodies: insertion of an uncertainty (safety) factor permits the derivation of permissible exposure levels at which no relevant human cancer risks are anticipated. For genotoxic

carcinogens, case studies of chemicals point to a whole array of possibilities. Positive data of chromosomal effects only, in the absence of mutagenicity, may support the characterization of a compound that produces carcinogenic effects only at high, toxic doses. Non-DNA-reactive genotoxins, such as topoisomerase inhibitors or inhibitors of the spindle apparatus are considered in this respect. In such cases, arguments are in favour of the existence of "practical" thresholds. Taking existing concepts together, it is proposed to basically distinguish between "perfect" and "practical" thresholds. There is a wide consensus that for non-DNA-reactive genotoxins such as aneugens (aneuploidy, chromosome loss, non-disjunction) thresholds should be defined. It is being discussed as to whether the identification of possible threshold effects should also include other mechanisms of genotoxicity, in addition to aneugenic effects. Specific mechanisms of clastogenicity have been repeatedly addressed as also having thresholds, such as topoisomerase II poisons or mechanisms based on reactive oxygen. Oxidative stress as an important mechanism is triggered by exposure to exogenous factors such as ultraviolet (UV) and ionizing radiation, anoxia and hyperoxia, and by chemicals producing reactive oxygen species. The idea is receiving increased support that reactive oxygen species (ROS)-mediated processes of carcinogenesis have practical thresholds. Since reactive oxygen species are genotoxic in principle, questions arise whether chemicals that increase ROS production will superimpose to an endogenously produced background level of DNA lesions, related to mechanisms that may result in non-linear dose-effect relationships. The existence of "endogenous" DNA adducts has been generally accepted, and possible regulatory implications of the presence of endogenous carcinogens have been discussed. It is now becoming evident that a diversity of methods of carcinogenic risk extrapolation to low doses must be considered, dependent on the mode of action. Although there is an increasing international awareness of these developments, the system of classification of carcinogens of the European Union still remains static. This should be changed, as the philosophy of separation of a strictly sequential "hazard assessment" and "risk assessment" appears out-of-date.

Borak, J. (1994). "ACGIH's threshold limit values useful, but formulas are still controversial. Toxicologic methods in determining TLVs, scientific adequacy and political factors questioned." Occup Health Saf **63**(8): 26-27.

Borgert, C. J., M. A. Strauss, et al. (1994). Reproductive toxicology and occupational exposure. Occupational Medicine. C. Zenz, O. B. Dickerson and E. P. Horvath. St. Louis, Mosby-Year Book**:** 836-869.

Borm, P. J., T. H. Jorna, et al. (1990). "Setting acceptable exposure limits for toluene diisocyanate on the basis of different airway effects observed in animals." Regul Toxicol Pharmacol **12**(1): 53-63.

Little epidemiological data are available to enable the development of a dose-response relationship for the effects of isocyanates, powerful sensitizing agents

in humans. Remarkably, most classes of effects have been reproduced in some animal models and parallels between animals and man are impressive. In this paper animal data concerning different effects of TDI on the respiratory system were used to calculate acceptable exposure levels for humans. Animal data on respiratory irritation, sensitization, airway hyperresponsiveness, and gradual loss of pulmonary function are discussed. Two different approaches for extrapolation to man were applied to these data. The two models used to extrapolate animal data to man gave similar results. The extrapolations lead to acceptable exposure varying from 6 to 46 ppb. Most international acceptable levels for occupational airborne TDI exposure are within this range. Interestingly, the lowest standard is obtained using the data on respiratory irritation. It is, however, concluded that there is no critical (adverse) effect to define acceptable toluene diisocyanate exposure since the data were obtained from different studies and the accuracy of the applied extrapolation approach might depend on the biological effect considered. We recommend prior testing of "alternative" diisocyanates in one of the animal models described and calibrated for TDI.

Bos, P. M., D. H. Brouwer, et al. (1998). "Proposal for the assessment of quantitative dermal exposure limits in occupational environments: Part 1. Development of a concept to derive a quantitative dermal occupational exposure limit." Occup Environ Med **55**(12): 795-804.

Dermal uptake of chemicals at the workplace may contribute considerably to the total internal exposure and so needs to be regulated. At present only qualitative warning signs--the "skin notations"--are available as instruments. An attempt was made to develop a quantitative dermal occupational exposure limit (DOEL) complementary to respiratory occupational exposure limits (OELs). The DOEL refers to the total dose deposited on the skin during a working shift. Based on available data and experience a theoretical procedure for the assessment of a DOEL was developed. A DOEL was derived for cyclophosphamide and 4,4-methylene dianiline (MDA) according to this procedure. The DOEL for MDA was tested for applicability in an actual occupational exposure scenario. An integrated approach is recommended for situations in which both dermal and respiratory exposures contribute considerably to the internal exposure of the worker. The starting point should be an internal health based occupational exposure limit--that is, the maximum dose to be absorbed without leading to adverse systemic effects. The proposed assessment of an external DOEL is then either based on absorption rate or absorption percentage. The estimation of skin penetration seems to be of crucial importance in this concept. If for a specific substance a maximal absorption rate can be estimated a maximal skin surface area to be exposed can be assessed which may then serve the purpose of a DOEL. As long as the actual skin surface exposed is smaller than this maximal skin surface area the internal OEL will not be exceeded, and therefore, no systemic health problems would be expected, independent of the dermal dose/unit area. If not, the DOEL may be interpreted as the product of dermal dose/unit area (mg/cm2) and exposed skin surface area (cm2). The proposed concept for a DOEL is

relevant and can be made applicable for health surveillance in the occupational situation where dermal exposure contributes notably to the systemic exposure. Further research should show whether this concept is more generally applicable.

Bos, P. M., M. Busschers, et al. (2002). "Evaluation of the sensory irritation test (Alarie test) for the assessment of respiratory tract irritation." J Occup Environ Med **44**(10): 968-976.

Within the framework of risk assessment of existing substances in the EC the irritating properties on the respiratory tract should be considered. Since no standardized test is available it was studied whether the Alarie test could be used for this purpose, as proposed by the Technical Guidance Document for new and existing substances. The available literature on respiratory tract irritation, seen as a local inflammatory response and/or tissue damage, after single and repeated (few-day) exposure was evaluated and compared with data on sensory irritation. No relation was found between the sensory irritation potential (as measured by the Alarie test) and local tissue damage (histopathological changes) in the respiratory tract after single or repeated exposure. It was concluded that the Alarie test is inappropriate to evaluate respiratory tract irritation. In addition, the available data do not support a quantitative potency ranking for man based on the RD50 obtained with experimental animals.

Bos, P. M., A. Zwart, et al. (1991). "Evaluation of the sensory irritation test for the assessment of occupational health risk." Crit Rev Toxicol **21**(6): 423-450.

Many occupational exposure limits (OELs) are based on irritation. A sensory irritation test has been developed based on trigeminal nerve stimulation in the nasal mucosa of rodents which results in a decreased respiratory frequency. The RD50, the concentration inducing a 50% decrease in the respiratory rate, was proposed for the assessment of OELs. The reproducibility within one laboratory appeared to be satisfactory, but interlaboratory differences may be larger. Intra- and interspecies differences were inconsistent. Other effects (pulmonary irritation, toxicity) may interfere with trigeminal nerve stimulation. The effects of mixed and repeated exposures (the occurrence of "sensitization" and "(cross-)tolerance") are evaluated. Severe toxicity was observed in animals exposed below the RD50 for some compounds. A quantitative evaluation with respect to human data was not possible. The suitability of the test for the assessment of an OEL is doubted. The best purpose will be as an upper range-finding study for subacute or chronic toxicity experiments.

Bos, P. M. J., A. Zwart, et al. (1992). "Evaluation of the sensory irritation test for the assessment of occupational health risk." Critical Reviews inToxicology **21**(6): 423-450.

Bowman, J. P., R. S. Berger, et al. (2003). "The 21-day human cumulative irritation test can be reduced to 14 days without loss of sensitivity." J Cosmet Sci **54**(5): 443-449.

The 21-day cumulative irritation test for assessing the irritancy of topical products and chemicals is a venerable procedure that appears to have become the gold

standard for manufacturers. Berger and Bowman in 1982 (1) showed that reducing the exposure to 14 days was less traumatic to the volunteers, less costly, less arduous, and did not affect reliability or the capacity to place the test agents in the proper rank order of irritancy. In the current study we compared (a) the 21-day cumulative irritation test, (b) the 14-day cumulative irritation test, and (c) the 14-day test with every-other-day patching. Additionally, ten-day, seven-day and four-day data from the 21-day test were compared. Forty-one subjects completed this study of six test materials. Two sets of patches were applied to each subject' lower back. One set had 21 consecutive applications of the test articles. The second set was applied, and removal of the test articles occurred Monday, Wednesday, and Friday for 14 days. The 21-day test fully differentiated the test materials from each other. Using only the first 14 days of the 21-day test also fully differentiated the test materials. Every-other-day patching rank ordered the test materials the same as the everyday patching, but full differentiation of the test materials was not obtained. We conclude that the 14-day cumulative irritancy test is as reliable and sensitive as the 21-day test, along with the obvious advantages in time, cost, and minimization of trauma to the test subjects.

Breysse, P. A. (1991). "ACGIH TLVs: a critical analysis of the documentation." Am J Ind Med **20**(3): 423-430.

Brief, R. S. and R. A. Scala (1975). "Occupational exposure limits for novel work schedules." Am Ind Hyg Assoc J **36**(6): 467-469.

Work schedules other than 7 to 8 hr/day and 40 hr/week are being introduced in many industrial operations. Novel work schedules, such as four 10-hour workdays per week or three 12-hour workdays per week for three weeks followed by four 12-hour workdays for three weeks and several other plans are presently being used. The Threshold Limit Values (TLV) do not apply to such novel schedules. Modified occupational limits, which are calculable from the methods suggested in this report, estimate the needed reduction in the TLV to provide protection for exposed workers. A simple system is suggested, but should be cautiously applied with good medical surveillance. Industrial hygiene experience with novel work schedules will ultimately provide the real requirements for acceptable exposures under such work conditions.

Brodeur, J., A. Vyskocil, et al. (2001). "Adjustment of permissible exposure values to unusual work schedules." Aihaj **62**(5): 584-594.

Research activities sought development of a method to adjust exposure limits for 694 substances for unusual work schedules. A consensus was established on the basic toxicological principle for adjustment; criteria for adjustment were selected by a panel of scientists coordinated by a committee of international experts and supported by toxicokinetic modeling; and a group of toxicologists attributed primary health effects and related adjustment category to each substance. A consensus among scientists and employers' and workers' representatives was established on the protocol of the application, in the field, of

the adjusted exposure limits. The guiding toxicological principle for adjusting exposure standards to unusual work schedules is to guarantee an equivalent degree of protection for workers with unusual schedules as for workers with a conventional schedule of 8 hours per day, 5 days per week. The process of the adjustment is inspired from the Occupational Safety and Health Administration logic for attribution of primary health effects and adjustment categories ranging from no adjustment to daily or weekly adjustments. The adjusted exposure limits are calculated according to Haber's rule. Decisions on attribution of adjustment categories for the following toxicological effects were reached: respiratory sensitizers (asthma); skin sensitizers; tissue irritants versus tissue toxicants; methemoglobinenia-causing agents; cholinesterase inhibitors; and reproductive system toxicants and teratogens. A simple procedure is presented to facilitate the calculation, application, and interpretation of the adjusted exposure limits.

Brondeau, M. T., A. Hesbert, et al. (1999). "To what extent are biomonitoring data available in chemical risk assessment?" Hum Exp Toxicol **18**(5): 322-326.

1. Chemical risk assessment integrates the identification of hazards and the human exposure levels which can be established from external and/or internal exposure data. 2. The availability of biomonitoring and metabolism animal data, the skin penetration ability, and the existence of atmospheric threshold limit values were examined for twelve substances of the European first list of priority existing substances. This investigation was focused on workplace exposures and on urinary biomarkers of exposure. Appropriate biomonitoring data appeared to be available for two substances: styrene and trichloroethylene. Some biomonitoring research has been conducted on acrylonitrile, buta-1,3-diene, cyclohexane, 1,4-dichlorobenzene, hydrogen fluoride, 2-(2-methoxyethoxy)ethanol, however additional studies could be usefully carried out. No biomonitoring data are available for alkanes, C10-13, chloro; benzene, C10-13-alkyl derivatives; bis(pentabromophenyl)ether; diphenylether, octabromo-derivative. 3. It was concluded that in some cases, biomonitoring data are either lacking or scarce. This is rather surprising since the selection of the substances of the priority list was based on high tonnage, widespread use, extent of human exposure, and toxicological concern. The development of biomonitoring information could be helpful in assessing individual or population chemical exposure whatever the source and route, and would result in both more realistic and more accurate risk assessments.

Brooke, I. M. (1998). "A UK scheme to help small firms control health risks from chemicals: toxicological considerations." Ann Occup Hyg **42**(6): 377-390.

The UK has developed a simple scheme to provide practical control advice to small and medium-sized enterprises (SMEs), to assist them in their risk assessments and risk management decisions. This scheme makes use of toxicological hazard information indicated by R-phrases assigned under the European Union (EU) classification system, to assign substances to hazard bands. In the UK scheme, the allocation of substances to hazard bands

according to R-phrases has taken into account three key factors: whether or not the toxicological endpoint has an identifiable dose threshold; the seriousness of the resultant health effect; and the relative exposure levels at which toxic effects occur. Based on all these considerations, R-phrases have been allocated to hazard bands within the scheme. An evaluation exercise has been undertaken, to compare the output of the scheme with established health-based occupational exposure limits, for more than 100 substances. The results of this exercise demonstrate that as far as possible, the scheme recommends control strategies which should provide adequate control. This scheme is potentially a very powerful means of helping SMEs adequately control chemical health risks in the workplace. Since it utilises the EU-agreed classification system, the scheme can be applied to any substance supplied and used in the workplace and it may also be used internationally.

Brophy, M. O. (2002). "Comments: implications of hormesis for industrial hygienists." Hum Exp Toxicol **21**(7): 391-393.

Quantitative health risk assessment is based on extrapolating from the high-dose end of the dose-response curve to points close to the origin or the threshold where the dose levels are closer to the lower environmental or occupational exposures. Hormesis is demonstrated in chronic toxicological studies where the animals treated at the lowest experimental dose appear to be healthier than the controls, as evidenced by longer life spans, less disease and/or increased body weight. If the occupational exposure limit (OEL) or environmental exposure limit (EEL) is in the range of the hormetic effect, or lower than the hormetic effect, then a case could be made that exposure at the OEL or EEL is 'safe.' This idea is controversial because it challenges some of the basic assumptions of quantitative health risk assessment as it has been practiced during the past 50 years. De-emphasis of the dose-response curve in determining OELs and EELs will occur not because of hormesis, but because the emerging sciences of genomics and proteomics will shift the focus from statistical methods to individuals as genetic and protein engineering becomes more sophisticated and powerful.

Brouwer, D. H., N. A. De Pater, et al. (2005). "An Experimental Study to Investigate the Feasibility to Classify Paints According to Neurotoxicological Risks: Occupational Air Requirement (OAR) and Indoor Use of Alkyd Paints." Ann Occup Hyg.

The concept of occupational air requirement (OAR), representing the quantity of air required to dilute the vapor concentration in the work environment resulting from 1 l product to a concentration below the occupational exposure limit (OEL), was considered to have potential to discriminate between paints that can and cannot be used safely. The OAR is a simple algorithm with the concentration of volatile organic compound (VOC) in the paint, a discrete evaporation factor and the neurotoxicological effects-based OEL. Conceptually, OAR categories of paints for construction and maintenance applications could be identified that can be applied manually without exceeding OELs with no appreciable room

ventilation. Five painters volunteered in an exposure study aimed at testing the OAR approach in practice. Total exposure to VOC was assessed in 30 experiments during the application of 0.5 l of paint in a defined 'standard indoor paint job'. Fifteen paints were prepared, reflecting differences in solvents (percentage, volatility, toxicity) with a range of OAR levels from 43 to 819 m(3)/l. Exposure was assessed by personal air sampling (PAS). In addition, real-time air monitoring was performed. All tests were conducted at minimum ventilation rate (</=0.33 h(-1)). PAS results were expressed as percentage of the nominal OEL and ranged from 8 to 93% for high solids and from 38 to 168% for conventional paints. In general, higher VOC contents resulted in higher exposure. High volatile paints showed a statistically significant faster increase of VOC concentration with time compared with paints containing low volatile solvents. A significant relationship between OAR value and exposure was observed (R(2) = 0.73). The experiments indicate that OAR-based classification of paints predicts and discriminates risk levels for exposure to neurotoxic paint-solvents in indoor painting fairly well.

Brouwer, D. H., L. Hoogendoorn, et al. (1998). "Proposal for the assessment to quantitative dermal exposure limits in occupational environments: Part 2. Feasibility study for application in an exposure scenario for MDA by two different dermal exposure sampling methods." Occup Environ Med **55**(12): 805-811.

OBJECTIVE: To evaluate two different techniques for assessing dermal exposure to 4,4'-methylene dianiline (MDA) in a field study. The results were used to test the applicability of a recently proposed quantitative dermal occupational exposure limit (DOEL) for MDA in a workplace scenario. METHODS: For two consecutive weeks six workers were monitored for exposure to MDA in a factory that made glass fibre reinforced resin pipes. Dermal exposure of the hands and forearms was assessed during week 1 by a surrogate skin technique (cotton monitoring gloves) and during week 2 by a removal technique (hand wash). As well as the dermal exposure sampling, biological monitoring, measurement of MDA excretion in urine over 24 hours, occurred during week 2. Surface contamination of the workplace and equipment was monitored qualitatively by colorimetric wipe samples. RESULTS AND CONCLUSIONS: Geometric means of daily exposure ranged from 81-1762 micrograms MDA for glove monitoring and from 84-1783 micrograms MDA for hand washes. No significant differences, except for one worker, were found between exposure of the hands in weeks 1 and 2. Significant differences between the mean daily exposure of the hands (for both weeks and sampling methods) were found for all workers. The results of the colorimetric wipe samples indicated a general contamination of the workplace and equipment. Excretion of MDA in 24 hour urine samples ranged from 8 to 249 micrograms MDA, whereas cumulative MDA excretion over a week ranged from 82 to 717 micrograms MDA. Cumulative hand wash and MDA excretion results over a week showed a high correlation (R2 = 0.94). The highest actual daily dermal exposure found seemed to be about 4 mg (hand wash worker A on day 4), about 25% of the external

DOEL. Testing of compliance by means of a biological limit value (BLV) led to similar results for the same worker. It is concluded that both dermal exposure monitoring methods were applicable and showed a compatible performance in the present exposure scenario, where the exposure relevant to dermal absorption is considered mainly restricted to hands. The concept for a DOEL seemed to be relevant and applicable for compliance testing and health surveillance in the situation under investigation.

Brown, S. L. (2002). "Comments on "Implications of Hormesis for Industrial Hygiene"." Hum Exp Toxicol **21**(7): 397-398.

Although demonstrated evidence for hormesis of an agent could be important in setting occupational exposure limits (OELs) for industrial hygiene, several practical problems may limit the utility of toxicologic testing for hormesis. This commentary responds to the lead article of this section, in which Jayjock and Lewis propose using the results of tests for hormesis to guide the establishment of OELs. The principal difficulties may include: a different mechanism or even a different effect leading to the conclusion of hormesis; distinction between a threshold for a health effect and a crossover point in the dose response relationship; estimation of threshold or crossover point from limited test data and estimation of slope at this point; sensitivity of tests for hormesis; and cost of testing. Nevertheless, the proposals of Jayjock and Lewis have considerable merit, and exploratory testing could be useful.

Bruckner, J. V., D. A. Keys, et al. (2004). "The Acute Exposure Guideline Level (AEGL) program: applications of physiologically based pharmacokinetic modeling." J Toxicol Environ Health A **67**(8-10): 621-634.

The primary aim of the Acute Exposure Guideline Level (AEGL) program is to develop scientifically credible limits for once-in-a-lifetime or rare acute inhalation exposures to high-priority, hazardous chemicals. The program was developed because of the need of communities for information on hazardous chemicals to assist in emergency planning, notification, and response, as well as the training of emergency response personnel. AEGLs are applicable to the general population, including children, the elderly, and other potentially susceptible subpopulations. AEGLs are the airborne concentrations of chemicals above which a person could experience notable discomfort or irritation (AEGL-1); serious, long-lasting health effects (AEGL-2); and life-threatening effects or death (AEGL-3). AEGLs are determined for five exposure periods (10 and 30 min and 1, 4, and 8 h). Physiologically based pharmacokinetic (PBPK) models can be very useful in the interspecies and time scaling often required here. PBPK models are used for the current article to predict AEGLs for trichlorethylene (TCE), based on the time course of TCE in the blood and/or brain of rats and humans. These AEGLs are compared to values obtained by standard time-scaling methods. Comprehensive toxicity assessment documents for each chemical under consideration are prepared by the National Advisory Committee for AEGLs, a panel comprised of representatives of federal, state, and local

governmental agencies, as well as industry and private-sector organizations. The documents are developed according to National Research Council (NRC) guidelines and must be reviewed by the NRC Subcommittee on Acute Exposure Guideline Levels before becoming final. AEGLs for 18 chemicals have been published, and it is anticipated that 40 to 50 chemicals will be evaluated annually.

Buckley, L. A., X. Z. Jiang, et al. (1984). "Respiratory tract lesions induced by sensory irritants at the RD50 concentration." Toxicol Appl Pharmacol **74**(3): 417-429.

Exposure of mice to airborne sensory irritants causes a concentration-dependent depression of respiratory rate. The RD50 concentration (that concentration which elicits a respiratory rate decrease of 50%) has been predicted to be an unacceptable occupational exposure concentration due to intolerable sensory irritation and possible respiratory tract injury in humans. The purpose of this study was (1) to determine whether lesions occur in the respiratory tract of Swiss-Webster mice after exposure to the RD50 concentrations of ten sensory irritants and (2) to compare these changes with respect to type and severity. The RD50 values (ppm) of the chemicals studied are as follows: 2,4-toluene diisocyanate (0.4), acrolein (1.7), formaldehyde (3.1), chloropicrin (8.0), chlorine (9.3), sulfur dioxide (117), ammonia (303), hydrogen chloride (309), dimethylamine (511), and epichlorohydrin (687). After exposure of mice for 6 hr/day for 5 days, the respiratory tract was examined for histopathologic changes. All irritants produced lesions in the nasal cavity with a distinct anterior-posterior severity gradient. There was considerable variation in the extent, and nature of the lesions. The lesions ranged from slight epithelial hypertrophy or hyperplasia to epithelial erosion, ulceration, and necrosis with variable inflammation of the subepithelial tissues. Only chlorine, chloropicrin, and epichlorohydrin induced lesions in the lower respiratory tract. These findings give additional support to the potential value of the RD50 model for setting occupational exposure guidelines and predicting the risk of injury to the respiratory tract from exposure to airborne sensory irritants.

Budarina, O. V. (2002). "[Occupational health issues related to maximum allowable content of aromatic substances in the air]." Gig Sanit(4): 49-51.

Buringh, E. and R. Lanting (1991). "Exposure variability in the workplace: its implications for the assessment of compliance." Am Ind Hyg Assoc J **52**(1): 6-13.

Day-to-day variations of occupational exposures have important implications for the industrial hygienist trying to assess compliance with an occupational exposure limit. As only a limited number of samples are taken during an observation period, extrapolations are required to estimate exposures over the unsampled period. Compliance may be evaluated using estimates of the geometric mean (GM) and the geometric standard deviation (GSD) to calculate a confidence interval around the mean exposure and compare this interval to a limit value, assuming a lognormal distribution of exposures over time. These confidence intervals are very sensitive to the estimate of GSD. Hence, the

questions of when to sample and how many samples to take for a reliable assessment of exposure variability (GSD) are the focus of this paper. Analyses of simulated exposure-time series and 420 data sets of personal exposures with three or more measurements obtained from actual workplaces demonstrate that the small number of samples usually collected during surveys leads to biased estimates of the variance of the exposure distribution. There is a high likelihood of an underestimate of variance, which rapidly increases if 8-hr time-weighted average samples are collected on consecutive days or within a week. The results indicate that in 80% of the within-week exposure-time series, the estimated GSD may be too low, even up to a factor of 2. Evidence is presented that autocorrelation is a likely explanation for the bias observed.(ABSTRACT TRUNCATED AT 250 WORDS)

Burroughs, G. E. and W. J. Woodfin (1995). "On-site screening for benzene in complex environments." Am Ind Hyg Assoc J **56**(9): 874-882.

A technique is described for on-site screening of workplace atmospheres for benzene in the presence of many potentially interfering substances. The technique allows benzene monitoring with reasonable specificity at the part per million (ppm) level in confined spaces. A commercially available portable gas chromatograph (GC), shown in the laboratory to be capable of resolving benzene from a complex mixture of hydrocarbons, was compared in the field with other portable GCs, sorbent tube samples, and detector tubes. During three field evaluations samples were collected in Tedlar bags, which allowed replicate, on-site analyses by up to three portable gas chromatographs and three types of detector tubes. Additionally, replicate samples were collected from each bag onto charcoal tubes for subsequent laboratory analysis by capillary column flame ionization gas chromatography and by gas chromatography/mass spectrometry. The portable GCs resolved samples to the extent that an integratable response with the retention time of benzene was seen. In some samples this response was not due solely to the presence of benzene, but such instances would overestimate the concentration and provide a more conservative result. The portable GCs had a total analysis time of less than 10 minutes and detected concentrations of benzene below the Occupational Safety and Health Administration's permissible exposure limit of 1 ppm (in most samples, below 0.1 ppm, although the limit of quantitation was matrix dependent). While benzene concentration measurements using detector tubes were less precise, they agreed in almost every instance with the other techniques regarding whether the space was within the 1 ppm "safe for entry" concentration.

Cain, W. S. and J. E. Cometto-Muniz (1995). "Irritation and odor as indicators of indoor pollution." Occup Med **10**(1): 133-145.

Both irritation and odor figure prominently in complaints about indoor air. Irritation poses the greater problem since it arguably represents an adverse health effect per se and since its sources are often difficult to locate. There exist various potential assays for irritation, some better for validation of symptoms and some

better for research on structure-activity relations. One animal assay, the respiratory depression technique, has produced measures of irritant potency in good accord with sensory psychophysical measurements in humans. Both the animal and human data point toward common physicochemical determinants of potency, especially for the weak irritants that often exist in indoor environments. For the foreseeable future, the assessment of odors in indoor environments will need to proceed as in the past, as a psychophysical measurement rather than as a chemical measurement. Methodologies for odor measurement continue to evolve. The evaluation of their usefulness in field settings must ultimately stand against a criterion of validity that has to date proved elusive to establish.

Cain, W. S., A. A. Jalowayski, et al. (2004). "Sensory and associated reactions to mineral dusts: sodium borate, calcium oxide, and calcium sulfate." J Occup Environ Hyg **1**(4): 222-236.

Occupational exposure limits (OELs) for irritant dusts have had no quantifiable bases. This study (1) charted chemosensory feel, denoted chemesthesis here, to dusts of calcium oxide (1 to 5 mg/m(3)), sodium tetraborate pentahydrate [sodium borate] (5 to 40 mg/m(3)), and calcium sulfate (10 to 40 mg/m(3)); (2) examined correlates of the chemesthetic sensations; and (3) sought to illuminate the basis for potency. Twelve screened men exercised against a light load while they breathed air in a dome fed with controlled levels of dust for 20 min. Measured parameters included nasal resistance, nasal secretion, minute ventilation, heart rate, blood oxygenation, mucociliary transport time, and chemesthetic magnitude, calibrated to pungency of carbon dioxide. Subjects registered time-dependent feel from exposures principally in the nose, secondarily in the throat, and hardly in the eyes. Calcium oxide had the greatest potency, followed by sodium borate, with calcium sulfate a distant third. Of the physiological parameters, amount of secretion showed the best association with chemesthetic potency. That measure, as well as mucociliary transport time and minute ventilation, went into calculation of mass of dust dissolved into mucus. The calculations indicated that the two alkaline dusts increased in equal molar amounts with time. At equal molar concentrations, they had, to a first approximation, equal chemesthetic magnitude. On the basis of mass concentration in air or dissolved into mucus, calcium oxide and sodium borate differed in potency by a factor just above five, equal to the difference in their molecular weights. This relationship could inform the setting of OELs for a critical effect of irritation.

Candura, F. (1990). "[On the limits of "limit values"]." G Ital Med Lav **12**(5-6): 185-187.

Caplan, K. J. and J. Lynch (1996). "A need and an opportunity: AIHA should assume a leadership role in reforming risk assessment." Am Ind Hyg Assoc J **57**(3): 231-237.

Caravati, E. M. (1988). "Acute hydrofluoric acid exposure." Am J Emerg Med **6**(2): 143-150.

Significant local and systemic toxicity may occur from hydrofluoric acid by all routes of exposure. Prompt decontamination by removal from the source and copious irrigation of eyes and skin are essential to reduce morbidity and mortality. Ingestion of small amounts of HF can lead to rapid systemic poisoning and death. Calcium gluconate therapy has become the preferred method of detoxifying the fluoride ion, although its efficacy is based mainly on anecdotal reports and poorly controlled clinical studies. Therefore, more basic research is needed to elucidate the pathophysiology of local toxicity and the best therapeutic modalities to limit injury. All significant exposures should be evaluated by health care personnel familiar with the potential toxicity of this compound.

Carelli, G., I. Iavicoli, et al. (2002). "Hormesis and industrial hygiene: a new hypothesis for low-dose response in occupational risk assessment." Hum Exp Toxicol **21**(7): 401-403.

The study of Jayjock and Lewis, 'Implication of Hormesis for Industrial Hygiene', represents a challenge for the scientific community to consider hormesis as a possible working hypothesis for redefining risk assessment strategy for low-dose exposures in the realm of industrial hygiene. This invited commentary aims at examining some aspects of the study for which no proven and conclusive scientific evidence has yet been found, such as the limited nature of some statistical tests, the calculation of the safety factor, the place occupied by hormesis in industrial hygiene and, finally, the impact that scarce knowledge of this phenomenon and rejection by part of the scientific community has on the possibility of using hormesis in the safeguarding of workers' health.

Carlton, G. N. (2003). "The impact of a change to inhalable occupational exposure limits: strontium chromate exposure in the U.S. Air Force." AIHA J (Fairfax, Va) **64**(3): 306-311.

The American Conference of Governmental Industrial Hygienists has announced its intention to replace all total particulate threshold limit values (TLVs) with size-selective TLVs. Because the U.S. Air Force has adopted the TLVs as its occupational exposure limits, the impact of this change is of interest, specifically for hexavalent chromium. This article reviews historical strontium chromate sampling data in the Air Force and the impact of its reinterpretation in comparison to an inhalable TLV. Based on the measured conversion factor between the 37-mm cassette and the IOM inhalable sampler, inhalable strontium chromate exposures will continue to exceed the TLV during all aircraft priming and most sanding procedures. In addition, inhalable exposures are expected to exceed 1000 times the TLV, greater than the highest currently assigned protection factor for airline respirators, during 25% of priming procedures. Without a change in the value of the current TLV time-weighted average of 0.5 microg/m(3), the Air Force will need to reduce strontium chromate levels, either by incorporating work practices that decrease worker productivity or considering a change to nonchromated primers.

Carnevale, F., R. Montesano, et al. (1987). "Comparison of regulations on occupational carcinogens in several industrialized countries." Am J Ind Med **12**(5): 453-473.

Regulations controlling the manufacture and use of carcinogens in the industrial setting of various countries are examined. In addition, the occupational exposure limits (OEL) of chemicals known or suspected to be carcinogenic in humans are listed, and criteria for the establishment of OELs are discussed. It is also stressed that control measures should not be confined to a few developed countries, and it is hoped that attracting attention to their unevenness will contribute to the implementation of a more efficient primary prevention of cancer.

Carter, J. T. (1989). "Indicative criteria for the new occupational exposure limits under COSHH." Ann Occup Hyg **33**(4): 651-652.

Castleman, B. (1997). "How threshold limits for lead were established in the 1950s." Am J Ind Med **32**(6): 702-703.

Castleman, B. I. and G. E. Ziem (1988). "Corporate influence on threshold limit values." Am J Ind Med **13**(5): 531-559.

Investigations into the historical development of specific Threshold Limit Values (TLVs) for many substances have revealed serious shortcomings in the process followed by the American Conference of Governmental Industrial Hygienists. Unpublished corporate communications were important in developing TLVs for 104 substances; for 15 of these, the TLV documentation was based solely on such information. Efforts to obtain written copies of this unpublished material were mostly unsuccessful. Case studies on the TLV Committee's handling of lead and seven carcinogens illustrate various aspects of corporate influence and interaction with the committee. Corporate representatives listed officially as "consultants" since 1970 were given primary responsibility for developing TLVs on proprietary chemicals of the companies that employed them (Dow, DuPont). It is concluded that an ongoing international effort is needed to develop scientifically based guidelines to replace the TLVs in a climate of openness and without manipulation by vested interests.

Castleman, B. I. and G. E. Ziem (1994). "American Conference of Governmental Industrial Hygienists: low threshold of credibility." Am J Ind Med **26**(1): 133-143.

Castranova, V., D. G. Frazer, et al. (2002). "Pulmonary alterations associated with inhalation of occupational and environmental irritants." Int Immunopharmacol **2**(2-3): 163-172.

Many gases, vapors, or particles found in occupational and/or environmental settings can act as irritants. In the present study, sensory irritants are characterized by the stimulation of neuropeptide release from sensory nerves in the nasal mucosa, while pulmonary irritants are characterized by recruitment of PMN into bronchoalveolar airspaces, elevation of breathing frequency, and neuropeptide release from sensory fibers innervating the epithelium of the

conducting airways. A review of data from our laboratory as well as results from others indicate that asphalt fume is a sensory irritant; toluene diisocyanate (TDI), methyl isocyanate, and machining fluid act as both sensory and pulmonary irritants; while cotton dust, agricultural dusts, microbial products, leather conditioner, and ozone exhibit responses characteristic of pulmonary irritants.

Cavalini, P. M. (1994). "Industrial odorants: the relationship between modeled exposure concentrations and annoyance." Arch Environ Health **49**(5): 344-351.

In a series of epidemiologic studies, the relationship between objective exposure to odorant concentrations emitted by several industrial plants was investigated, as was the relationship between odor annoyance and subjective health complaints. Exposure was determined with a dispersion model of odorants, in which meteorological data and industrial emissions were used as input. Long-term averaged exposure was related to odor annoyance measured with a questionnaire. In addition, the influence of several other factors (demographic variables and variables emanating from the coping theory) on odor annoyance was studied. Among others, it appears that the dispersion model performs moderately well in predicting annoyance (correlations between odorant concentrations and odor annoyance were about 0.35). The extent to which people regard mal-odor as a threat to their health is a relatively strong predictor of annoyance. Moreover, the effects of long-term low exposure are similar to the effects of temporary high exposure.

CDC, N. (1974). Criteria for a recommended standard.... occupational exposure to chloroform, US Dept of Health, Education, and Welfare. Public Health Service. CDC. NIOSH**:** 1-56.

CDC, N. (1978). Criteria for a recommended standard... occupational exposure to benzyl chloride, US Dept of Health, Education, and Welfare**:** 1-25.

Checkoway, H. and C. H. Rice (1992). "Time-weighted averages, peaks, and other indices of exposure in occupational epidemiology." Am J Ind Med **21**(1): 25-33.

Dose surrogates commonly used in occupational epidemiology are exposure intensity, exposure duration, and cumulative exposure. The appropriateness of any of these measures as dose indicators depends on the nature of the induction process for the disease under consideration. Peak exposure intensity is often associated with acute health outcomes, whereas cumulative exposure is generally more relevant for diseases with long induction times, i.e., "chronic" diseases. However, there may be situations where peak exposure is etiologically relevant in chronic disease induction, such as might occur with nonlinear rates of damage during brief intervals of very high exposure. An approach is described for evaluating the effect of peak exposures in which peaks may be defined on a relative basis for each worker, or with respect to an absolute value, such as the permissible occupational exposure limit. The analytic strategy is illustrated with data from a case-control study of silicosis in relation to quantitative estimates of

silica exposure. In this example, relative peak exposures and average non-peak exposures appear to be better predictors of silicosis risk than cumulative exposure.

Clewell, H. J., G. A. Lawrence, et al. (2003). "Determination of an occupational exposure guideline for manganese using the benchmark method." Risk Anal **23**(5): 1031-1046.

An occupational risk assessment for manganese (Mn) was performed based on benchmark dose analysis of data from two epidemiological studies providing dose-response information regarding the potential neurological effects of exposure to airborne Mn below the current Occupational Safety and Health Administration (OSHA) Permissible Exposure Level (PEL) of 5 mg Mn/m3. Based on a review of the scientific evidence regarding the toxicity of Mn, it was determined that the most appropriate measure of exposure to airborne Mn for the subclinical effects measured in these studies is recent (rather than historical or cumulative) concentration of Mn in respirable (rather than total) particulate. For each of the studies analyzed, the individual exposure and response data from the original study had been made available by the investigators. From these two studies benchmark concentrations calculated for eight endpoints ranged from 0.09 to 0.27 mg Mn/m3. From our evaluation of these results, and considering the fact that the subtle, subclinical effects represented by the neurological endpoints tested in these studies do not represent material impairment, we believe an appropriate occupational exposure guideline for manganese would be in the range of 0.1 to 0.3 mg Mn/m3, based on the respirable particulate fraction only, and expressed as an 8-hour time-weighted average.

Colato, O. (1990). "[The introducibility of the Italian regulation of TLVs: the viewpoint of a judge]." G Ital Med Lav **12**(5-6): 213-215.

Colato, O. (1991). "[The admissibility into Italian regulations of the TLV. The paragraph on occupational carcinogens]." Med Lav **82**(1): 65-70.

Collins, J. F., G. V. Alexeeff, et al. (2004). "Development of acute inhalation reference exposure levels (RELs) to protect the public from predictable excursions of airborne toxicants." J Appl Toxicol **24**(2): 155-166.

Uniform guidelines have been developed for the derivation of 1-h acute inhalation reference exposure levels (RELs) applicable to the general public exposed routinely to hazardous substances released into the environment. Existing acute exposure guidance values developed by other organizations have been examined, and strengths and weaknesses in these existing guidelines have been identified. The results of that examination have led to the development of a reproducible and resource-intensive methodology to calculate acute inhalation RELs for 41 prioritized chemicals. Approaches to estimating levels protective against mild and severe acute effects are discussed in this report. The default methodology is the no-observed-adverse-effect level (NOAEL)/uncertainty factor

(UF) approach using mainly reports in the peer-reviewed toxicological and medical literature. For two well-studied chemicals, ammonia and formaldehyde, the data allowed a benchmark dose (or concentration) methodology, as a departure from the default options, to be used. However, better human dose-response data from, for example, improved workplace monitoring correlated with symptoms, and more extensive epidemiological studies are needed before the departure from default approaches can be expanded to more substances.

Cometto-Muniz, J. E. and W. S. Cain (1992). "Sensory irritation. Relation to indoor air pollution." Ann N Y Acad Sci **641**: 137-151.

All mucosae of the body possess chemical sensitivity provided by the CCS. Airborne chemicals can stimulate the CCS through the ocular, nasal, and respiratory mucosae, evoking different pungent sensations, for example, stinging, irritation, burning, piquancy, prickling, freshness, and tingling. Pungent sensations elicited in the nose differ from odor sensations in various characteristics. They are achieved at considerably higher concentrations than those necessary to elicit odor, but they increase with the concentration of the stimulus in a steeper fashion than odor. Pungent sensations from mixtures of compounds show a higher degree of addition--relative to the pungency of the individual components--than that of odor sensations. Pungency is more resistant to adaptation than odor, and, unlike it, displays considerable temporal integration with continuous stimulation. Measurement of a reflex, transitory apnea produced upon inhalation of pungent chemicals holds promise as an objective indicator of the functional status of the CCS. Results from the measurement of this reflex have agreed quantitatively with sensory data in a number of studies, and have shown higher common chemical sensitivity in nonsmokers (compared to smokers), in females (compared to males), and in young adults (compared to the elderly). Research issues mentioned here include the following: 1. We can rarely validate the symptoms putatively caused by indoor air pollution objectively. Without such means, we will always have the potential problem of overreporting and embellishment. Although one person may seem more sensitive than another, the difference may lie in a greater proclivity to complain. 2. Studies of anosmic persons offer a simple means to understand the functional characteristics of the nasal CCS. Studies of chemical series in such subjects should eventually allow construction of quantitative structure-activity models for human pungency perception. The human data can be compared with relevant animal data when possible. 3. The rules of additivity of pungency in mixtures need explication. Regarding the possible role of VOCs in the creation of irritation, we need to ask whether subthreshold levels add up or even amplify each other to produce noticeable irritation. Do repetitive or continuous exposures to subthreshold concentrations increase sensitivity to those substances, so that they evoke pungency when they otherwise would not? Do the various mucose--ocular, nasal, throat--differ in their sensitivity? 4. Modulation of CCS sensitivity by long-term and short-term inhalation of various agents (for example, environmental tobacco smoke) would seem a suitable topic for further research.

Cometto-Muniz, J. E. and W. S. Cain (1998). "Trigeminal and olfactory sensitivity: comparison of modalities and methods of measurement." Int Arch Occup Environ Health **71**(2): 105-110.

OBJECTIVE: The principal objective was to chart sensitivity for human nasal irritation by alternative psychophysical methods, namely, a common detection procedure versus a nasal lateralization procedure that required the subject to indicate whether a vapor had stimulated the left or right nostril. This objective relates to the broader issues as to (a) whether subjects with normal olfaction (normosmics) can yield, through novel methodology, an index of sensitivity to nasal irritation comparable with that obtained from subjects without olfaction (anosmics) and (b) whether both types of subjects have similar irritation sensitivity in general. This study sought to gauge interconvertability both between types of subjects and between modes of stimulus presentation for irritative and, where appropriate, olfactory stimulation. METHODS: Static dilution series of four n-aliphatic alcohols, chosen to represent volatile organic compounds (VOCs), provided the source of calibrated olfactory and irritative vapors emitted from their squeezable containers into the nose or eye either by a mechanical device or by hand. Standard psychophysical methodology (forced-choice; ascending strength of stimulation) served to chart detection thresholds for irritation and odor and an analogous procedure served to chart the threshold for localization of stimulation. RESULTS: Within the limits of resolution, detection thresholds and nasal localization thresholds yielded comparable indices of the potency of the VOCs to evoke nasal irritation. The thresholds agreed well with those for detection of eye irritation, though only the eyes proved to be capable of detecting irritation from l-octanol. The method of emitting the stimulus had little material effect on measures of either irritative or olfactory detection. CONCLUSIONS: The threshold for nasal localization offers a suitable way to measure nasal irritation in normosmic persons. Olfactory stimulation does not interfere with the measure since subjects cannot localize on that basis. Anosmic and normosmic persons have comparable sensitivity to nasal and ocular irritation. If anosmic persons have any lower sensitivity, as sometimes claimed, it would seem to have only trivial consequences for estimates of the irritative potency of VOCs.

Cometto-Muniz, J. E., W. S. Cain, et al. (2003). "Quantification of chemical vapors in chemosensory research." Chem Senses **28**(6): 467-477.

Studies of olfaction and chemesthesis often rely on nominal, liquid-phase dilutions to quantify the chemicals tested, even though the associated vapor concentrations constitute the actual stimuli. For more than a decade now, our systematic studies of the olfactory and chemesthetic potency of members of homologous chemical series have routinely included quantification of vapors via gas chromatography. This article depicts the relationships between liquid- and vapor-phase concentrations for 60 volatile organic compounds and summarizes the theoretical and technical factors influencing these relationships. The data presented will allow other investigators working with these materials to express

them as vapor concentrations even when they lack the resources to perform the analytical measurements. The paper represents a step toward creation of a practical archive for vapor quantification in chemosensory science.

Cometto-Muniz, J. E., W. S. Cain, et al. (2002). "Psychometric functions for the olfactory and trigeminal detectability of butyl acetate and toluene." J Appl Toxicol **22**(1): 25-30.

We measured psychometric (i.e. concentration-response) functions for the detection of odor, nasal pungency and eye irritation from butyl acetate and toluene. Olfactory detection was measured in subjects with normal olfaction (i.e. normosmics) for whom nasal trigeminal detection does not interfere because it requires much higher concentrations. Nasal trigeminal detection, called nasal pungency, was measured only in subjects lacking olfaction (i.e. anosmics) in order to avoid odor interference. Ocular trigeminal detection, called eye irritation, was measured in both groups. The method employed entailed a two-alternative, forced-choice procedure with presentation of increasing concentrations. The outcome showed, for both chemicals, similar ocular trigeminal chemosensitivity in normosmics and anosmics and similar overall ocular and nasal trigeminal chemosensitivity. Olfactory sensitivity was much higher than both forms of trigeminal sensitivity by concentration differences of six and four orders of magnitude for butyl acetate and toluene, respectively. Detectability plots (i.e. detection performance vs log concentration) for the three sensory endpoints followed an S-shaped function with a middle range section that showed a robust linear fit ($r > 0.94$) on graphs of z-score vs log concentration. These detectability functions allow the calculation of olfactory and trigeminal thresholds at various levels of performance. At a point half-way between random and perfect detection, trigeminal and olfactory threshold concentrations were, respectively, 0.67 (+/- 0.32) and 2.28 (+/-1.77) log units lower than those measured by us in the past for the same chemicals using an analogous procedure but under just one, fixed, level of performance. The available data suggest that, although considerably laborious, detectability functions provide chemosensory thresholds of closer relevance to environmentally realistic conditions (e.g. whole-body exposures).

Cometto-Muniz, J. E., W. S. Cain, et al. (1998). "Trigeminal and olfactory chemosensory impact of selected terpenes." Pharmacol Biochem Behav **60**(3): 765-770.

In Experiment 1, four normosmics and four anosmics (three congenital, one idiopathic) provided odor and nasal pungency thresholds, respectively, for the following terpenes: delta3-carene, p-cymene, linalool, 1.8-cineole, and geraniol, plus the structurally related compound cumene. Additionally, all subjects provided nasal localization (i.e., right/left) and eye irritation thresholis. Trigeminally mediated thresholds (i.e., nasal pungency, nasal localization, and eye irritation) lay about three orders of magnitude above odor thresholds, which ranged between 0.1 and 1.7 ppm. The results implied uniform chemesthetic sensitivity across tasks and sites of impact. In Experiment 2, normosmics and anosmics provided odor and nasal pungency thresholds, respectively, for three pairs of isomeric terpenes: alpha- and gamma-terpinene, alpha- and beta-pinene,

and R(+)- and S(-)-limonene. Odor thresholds ranged between 1.4 and 19 ppm, that is, about an order of magnitude higher than those of the previous terpenes, with no substantial differences between odor thresholds of members of a pair. Regarding chemesthetic impact, only alpha-terpinene evoked nasal pungency. The overall outcome suggests comparable trigeminal chemosensitivity between nose and eyes and between normosmics and anosmics, as shown before for homologous n-alcohols. It also lends support to a previously derived solvation model of the chemesthetic potency of airborne substances, and indicates the likely importance of certain molecular-size restrictions for effective trigeminal impact.

Cometto-Muniz, J. E., W. S. Cain, et al. (1997). "Agonistic sensory effects of airborne chemicals in mixtures: odor, nasal pungency, and eye irritation." Percept Psychophys **59**(5): 665-674.

Thresholds responses of odor, nasal pungency (irritation), and eye irritation were measured for single chemicals (1-propanol, 1-hexanol, ethyl acetate, heptyl acetate, 2-pentanone, 2-heptanone, toluene, ethyl benzene, and propyl benzene) and mixtures of them (two three-component mixtures, two six-component mixtures, and one nine-component mixture). Nasal pungency was measured in subjects lacking a functional sense of smell (i.e., anosmics) to avoid interference from olfaction. Various degrees of stimulus agonism (additive effects) were observed for each of the three sensory channels when testing mixtures. As the number of components and the lipophilicity of such components in the mixtures decreased, so did the degree of agonism. Synergistic stimulus agonism characterized the eye-irritation response for the most complex (the nine-component) and the most lipophilic (one of the six-component) mixtures. Physicochemical properties play a large role in the determination of sensitivity to airborne chemicals, particularly to their ability to evoke irritation. While this has revealed itself previously with respect to single chemicals, it seems to have relevance to mixtures as well.

Cook, W. A. (1989). "Occupational exposure limits for carcinogens--variant approaches by different countries." Am Ind Hyg Assoc J **50**(9): A680-684.

The differences in treatment of occupational exposure limits for carcinogens by 24 countries is described along with a discussion of the American Conference of Governmental Industrial Hygienists (ACGIH) threshold limit values (TLV) treatment, the similar treatment of the new Occupational Safety and Health Administration (OSHA) standard, and the treatment by provinces of Canada. The unique listing by the Federal Republic of Germany of so-called technical guiding concentrations of a group of carcinogens is discussed with the note that Austria used this same system. Publications on justification for establishing occupational exposure limits for certain carcinogens are discussed also.

Cook, W. A. (1992). "1990 Henry F. Smyth, Jr. Award Lecture. Criteria for occupational exposure limits by selected countries." Am Ind Hyg Assoc J **53**(6): 395-397.

Costigan, M. G. (2003). "Hydrogen sulfide: UK occupational exposure limits." Occup Environ Med **60**(4): 308-312.

Cox, G. V. (1988). "Threshold limit values: a balanced report." Am J Ind Med **14**(2): 233-234.

Craig, M. H. Feuston, et al. (?). "A method for estimating safe levels of exposure to reproductive and developmental toxins in the occupational setting." Teratolgy Abstracts: 415-416.

Craig, D. K., J. S. Davis, et al. (2000). "Derivation of temporary emergency exposure limits (TEELs)." J Appl Toxicol **20**(1): 11-20.

Short-term chemical concentration limits are used in a variety of applications, including emergency planning and response, hazard assessment and safety analysis. Development of emergency response planning guidelines (ERPGs) and acute exposure guidance levels (AEGLs) are predicated on this need. Unfortunately, the development of peer-reviewed community exposure limits for emergency planning cannot be done rapidly (relatively few ERPGs or AEGLs are published each year). To be protective of Department of Energy (DOE) workers, on-site personnel and the adjacent general public, the DOE Subcommittee on Consequence Assessment and Protective Actions (SCAPA) has developed a methodology for deriving temporary emergency exposure limits (TEELs) to serve as temporary guidance until ERPGs or AEGLs can be developed. These TEELs are approximations to ERPGs to be used until peer-reviewed toxicology-based ERPGs, AEGL or equivalents can be developed. Originally, the TEEL method used only hierarchies of published concentration limits (e.g. PEL- or TLV-TWAs, -STELs or -Cs, and IDLHs) to provide estimated values approximating ERPGs. Published toxicity data (e.g. lc(50), lc(LO), ld(50) and ld(LO) for TEEL-3, and tc(LO) and td(LO) for TEEL-2) are included in the expanded method for deriving TEELs presented in this paper. The addition here of published toxicity data (in addition to the exposure limit hierarchy) enables TEELs to be developed for a much wider range of chemicals than before. Hierarchy-based values take precedence over toxicity-based values, and human toxicity data are used in preference to animal toxicity data. Subsequently, default assumptions based on statistical correlations of ERPGs at different levels (e.g. ratios of ERPG-3s to ERPG-2s) are used to calculate TEELs where there are gaps in the data. Most required input data are available in the literature and on CD ROMs, so the required TEELs for a new chemical can be developed quickly. The new TEEL hierarchy/toxicity methodology has been used to develop community exposure limits for over 1200 chemicals to date. The new TEEL methodology enables emergency planners to develop useful approximations to peer-reviewed community exposure limits (such as the ERPGs) with a high degree of confidence. For definitions and acronyms, see Appendix.

Criteria group for occupational, s. (1985). "Scientific basis for Swedish Occupational Standards. VI. Consensus report for phenol." Arbete och H lsa **32**(1985).

Cross, H. J., S. P. Faux, et al. (1997). "Establishing an occupational exposure limit for hexavalent chromium in the European Union." Reg. Tox. Pharm. **26**: S72--S76.

Crump, K. S. (1994). "Risk of benzene-induced leukemia: a sensitivity analysis of the pliofilm cohort with additional follow-up and new exposure estimates." J Toxicol Environ Health **42**(2): 219-242.

This report updates the risk assessment by Crump and Allen (1984) for benzene-induced leukemia that was used by OSHA (1987) to support its reduction of the permissible exposure limit (PEL) to 1 ppm and that also was the basis for EPA's (1985) interim "unit risk" for benzene. The present study derives new risk estimates using data from follow-up through 1987 (whereas the earlier assessment only had follow-up available through 1978), and using new exposure estimates for this cohort developed by Paustenbach et al. (1992) that account for a number of factors that were unknown or not fully evaluated in earlier exposure assessments. There was a significant excess of acute myelocytic or acute monocytic leukemia (AMML, the only forms of acute nonlymphatic leukemia observed) in this cohort, and this end point also exhibited a strong dose-response trend. AMML was the only hematopoietic or lymphatic cancer that was clearly linked to benzene exposure. However, quantitative estimates of risk based on modeling either AMML or all leukemia differed by only 20%. Differences between the two Pliofilm plant locations in the occurrence of AMML were not statistically significant (.12 < or = p < or = .21) after differences in levels of benzene exposure were taken into account. The Paustenbach et al. exposures predicted a quadratic dose response, based on a measure of exposure that weighted intensity of exposure more heavily than duration of exposure. The best-fitting quadratic models predicted an additional lifetime risk of a benzene-related death from 45 yr of exposure to 1 ppm of between 0.020 and 0.036 per thousand. Statistical confidence intervals (90%) on these estimates were barely wide enough to include risk estimates based on linear dose response models. These linear models predicted risks of between 1.6 and 3.1 per thousand.

Cunningham, E. A., J. J. Todd, et al. (1998). "Was there sufficient justification for the 10-fold increase in the TLV for silica fume? A critical review." Am J Ind Med **33**(3): 212-223.

In 1992, the Threshold Limit Value (TLV) for amorphous silica fume produced as a by-product of metallurgical processes was revised upwards from 0.2 mg/m3 (respirable dust) to 2.0 mg/m3. Comparison of the documentation justifying the lower TLV published by the ACGIH in 1989, with the subsequent documentation justifying the higher value published in 1992, does not support this increase. Following an outline of the problem areas existing in interpretational difficulties of experimental and review material in the silica fume bibliography, this paper provides a detailed examination of the six additional references cited in the 1992 documentation. All additional material suggests a need for extra caution,

particularly with respect to recent experimental work in Australia on the sizing of silica fume. This paper concludes that the health evidence supports a TLV for silica fume closer to 0.3 mg/m3 rather than the current 2.0 mg/m3 now adopted in the U.S. and Australia.

Czerczak, S., J. A. Indulski, et al. (1993). "Current principles of hygienic standards setting (Part II)." Pol J Occup Med Environ Health **6**(3): 245-261.

The paper presents general principles of setting the hygienic standards for substances of threshold effect and nonthreshold agents. The authors introduced the mathematical models used for quantitative risk assessment and models for assessment of the dose-response relationship according to the physiological principles.

Czerczak, S., J. A. Indulski, et al. (1993). "Current principles of hygienic standards setting. Part I." Pol J Occup Med Environ Health **6**(2): 117-126.

A critical analysis of the present situation with respect to hygienic standard setting is presented. The authors introduce requirements for developing scientifically based exposure limits for chemicals as well as differences between documentation of recommended exposure limits for the agents occurring in the working environment and in the communal environmental medicine.

Czerczak, S., J. A. Indulski, et al. (1993). "Occupational exposure standards. Historical outline and present state." Pol J Occup Med Environ Health **6**(1): 1-18.

The paper presents the history of hygienic standards setting in various countries, as well as the current situation in this respect. Methodological approaches to hygienic standards setting in the USA and USSR have been analysed and compared. The paper shows also the contribution of international organizations to unification of both the definition and the approach to MAC setting. The authors present systems of MAC setting in such countries as USA (ACGIH, NIOSH, OSHA), former USSR, Germany, Scandinavian countries, Hungary and Poland. The paper comprises also classification of substances and carcinogenic agents adopted by IARC as well as the classifications in those countries which publish lists of carcinogens.

Czerczak, S., J. A. Indulski, et al. (1994). "[Methods of establishing occupational and environmental hygienic norms]." Med Pr **45**(3 Suppl 2): 1-88.

Dalton, P. (2001). "Evaluating the human response to sensory irritation: implications for setting occupational exposure limits." Aihaj **62**(6): 723-729.

Although animal models of sensory irritation have led to the development of useful assays for evaluating the potency of chemical irritants, the importance of conducting human exposure studies to model and understand the human response to sensory irritants cannot be minimized. In recent years a series of tests have been developed for humans that can be safely conducted and that can provide excellent data on which to base occupational exposure limits. This

article delineates the major issues involved in the evaluations of sensory irritation in humans. Among these issues are the differences between odor and irritation, irritation and slight toxicity, adaptation and habituation, as well as personal expectation about discomfort and the reported irritation. The article also describes psychophysiological and electrophysiological methods for assessing sensory irritation. Some of the possible confounders that can influence the results of human tests involving sensory irritants are addressed.

Dalton, P. (2001). "Psychophysical methods in the study of olfaction and respiratory tract irritation." Aihaj **62**(6): 705-710.

This article describes the fundamentals of olfaction and irritation perception and the dominant psychophysical methods for the assessment of olfaction and respiratory tract irritation. It also discusses factors that determine the olfactory and irritant response (ranging from the physicochemical properties of the stimulus to the physiological and cognitive characteristics of the individual). Because the vast majority of volatile chemicals stimulate the olfactory system at concentrations well below that at which they will elicit trigeminal activation, the evaluation of irritation from volatiles is often confounded by the perception of odor. Several methods have been used for studying the perception of irritation, without the influence of olfaction. The perception and reports of acute adverse effects of odor, annoyance, and irritation from volatile chemicals have multiple determinants. Understanding the perceptual impact of chemicals under environmentally realistic conditions requires attending to both the sensory and the psychological impact of those exposures. The review, which is largely based on presentations given by Dr. Richard Doty and Dr. William Cain, concludes by discussing the importance of the psychophysical approach, which considers physiochemical, subject, experimental, and cognitive/ psychological factors, for research in the chemical senses.

Dalton, P. (2002). "Odor, irritation and perception of health risk." Int Arch Occup Environ Health **75**(5): 283-290.

OBJECTIVES: Understanding the potential for volatile chemicals to elicit chemosensory irritation in the upper respiratory tract is critical to setting occupational exposure limits that are protective of comfort and well-being for the majority of workers. However, the determination of irritant potency for any volatile chemical has been limited by the lack of reliable and non-invasive assays for studying sensory irritation in humans and a failure to appreciate the many non-sensory factors that can influence the reactions to an odor or an irritant in the workplace. METHODS: This paper reviews the issues involved in distinguishing and measuring sensations of odor and irritation from volatile chemicals, and describes recent developments in psychophysical methods for evaluating chemical irritancy in humans, and discusses some of the many non-sensory factors such as exposure history, attitudes and expectations and personality variables that can significantly alter the perception of odor, irritation and health risk following exposure to a volatile chemical. RESULTS: The availability of safe,

non-invasive assays to measure directly odor and irritant responses in the species of interest, humans, can both simplify and improve accuracy in the process of developing appropriate occupational exposure guidelines. CONCLUSIONS: Objective measures of irritation onset obtained in conjunction with subjective responses can lend valuable input to the decision process for determining occupational exposure limits but should always account for other factors (e.g., cognitive or emotional) that may be modulating the subjective response.

Dalton, P. (2003). "Upper airway irritation, odor perception and health risk due to airborne chemicals." Toxicol Lett **140-141**: 239-248.

Chemosensory irritation associated with the manufacture and use of volatile materials has been a public and employee health concern for many years. Because odor properties can often be detected at much lower concentrations than those capable of eliciting upper respiratory tract irritation, confusion between odor and irritation coupled with variability in odor sensitivity and response can produce significant obstacles for evaluating the potential for adverse effects or annoyance from worker and community exposures. Although rigorous research methods have been developed to accurately quantify chemosensory irritation in human evaluations, several important considerations should be included in the design and interpretation of such studies. Specifically, research studies evaluating chemosensory irritation from volatile materials should be capable of (1) distinguishing between the annoyance or concern elicited by odor sensation and that elicited by true sensory irritation, (2) evaluating exposure-related factors that affect odor or irritancy responses, and (3) separating true adverse health effects from those mediated via psychosocial factors. Objective measures of upper respiratory tract irritation onset obtained in conjunction with subjective reports can lend valuable input to the decision process for determining occupational exposure limits. Subjective reports of irritation at low levels that cannot be reconciled with objective measures should prompt a careful investigation into the other factors (e.g. cognitive or emotional) that may be modulating the sensory response. Distinguishing between the exposure that elicits local effects of sensory irritation in the upper respiratory tract and the exposure that elicits self-reports of irritation is a key component in establishing occupational exposure limits that are protective of exposed workers.

Dalton, P. and T. Hummel (2000). "Chemosensory function and response in idiopathic environmental intolerance." Occup Med **15**(3): 539-556.

This chapter reviews the current literature on the possible role of olfactory and trigeminal chemosensory function in idiopathic environmental intolerances (IEI). Two general points emerge from the review. First, studies of chemosensory function in IEI patients indicate that, despite their self-reported "heightened sensitivity" and enhanced responsivity to environmental odors, when compared to healthy controls they generally are found to be equally or even less sensitive to odors as measured by objective psychophysical and electrophysiological

measures of olfactory function. These studies point towards alterations in the cognitive processing of olfactory information as the major characteristic of IEI. Second, studies of the role of sensitivity and bias in olfactory and trigeminal chemosensory functioning indicate that nonsensory factors (e.g., attention, bias, personality) can dramatically alter the self-reported impact of exposure to volatile chemicals. Together, these general points suggest a perspective on IEI that views many symptoms of the disorder to primarily reflect the influence of nonsensory, cognitive processes on responses to environmental odors.

Dalton, P., C. J. Wysocki, et al. (1997). "The influence of cognitive bias on the perceived odor, irritation and health symptoms from chemical exposure." Int Arch Occup Environ Health **69**(6): 407-417.

OBJECTIVE: Responses to volatile chemicals are often subjective and variable, both over time and across individuals. Although variability can derive from differences in individual olfactory sensitivity, the response to a chemical stimulus is also influenced by the complex environment surrounding the exposure, which can include the perceiver's cognitive state. To explore the role of cognitive bias in chemical exposures, we evaluated whether information about the consequences of exposure to acetone could influence ratings of odor and irritation during exposure and/or the frequency or intensity of reported health symptoms following exposure. METHODS: Ninety adults (mean age 33.7, range 25-64) with no history of occupational exposure to solvents, were exposed to 800 ppm acetone in a chamber for 20 min. To control for non-specific responses to the odor of acetone, the subjects were also exposed for 20 min to 200 ppm phenylethyl alcohol (PEA), a non-irritant volatile chemical that produces a distinct odor but does not elicit irritation in the vapor phase. Subjects were assigned to one of three groups (n = 30/group); each group was given either a positive, negative or neutral bias towards the consequences of exposure to the chemicals in the study. During exposure, subjects rated the intensity of odor and irritation; following exposure, they completed symptom questionnaires. RESULTS: During the 20-min exposure to acetone, the positive bias group exhibited the most adaptation to its odor and the lowest perceived irritation; following exposure they reported the fewest health symptoms. In contrast, the negative bias group rated higher levels of odor intensity and, on average, reported the most over-all irritation; following exposure they reported significantly more health symptoms than the other groups, None of the demographic variables studied (e.g., age, gender, race, smoking status) were predictive of the response to odor or irritation. The perceived irritancy of acetone was well predicted by a linear combination of the perceived odor of acetone and perceived irritation for PEA (the nonirritant), r2 = 0.73. CONCLUSIONS: The results provide strong evidence that both the perceived odor and cognitive expectations about a chemical can significantly affect how individuals respond to it. Moreover, because naive control subjects appear to exhibit extreme variation in their cognitive evaluations of chemical effects, there may be limited value in using non-exposed controls to assess the irritancy of chemicals for worker populations.

Dalton, P., C. J. Wysocki, et al. (1997). "Perceived odor, irritation, and health symptoms following short-term exposure to acetone." Am J Ind Med **31**(5): 558-569.

The subjectivity of irritancy judgments can bias attempts to establish exposure guidelines that protect individuals from the sensory irritation produced by volatile chemicals. At low to moderate chemical concentrations, naive and occupationally exposed individuals often show considerable variation in the reported levels of perceived irritation. Such variation could result from differences in exposure history, differences in the perceived odor of a chemical, or differences in generalized response tendencies to report irritation, or response bias. Thus, experimental evaluation of sensory irritancy must dissociate sensory irritation from response bias. To this end, judgments of perceived irritation from 800 ppm acetone were obtained from acetone-exposed workers and age- and gender-matched naive controls. To assess the role of response bias during exposure to odorants, subjects were also exposed to phenylethyl alcohol (PEA), an odorant that does not produce sensory irritation. Following exposure, subjects completed a subjective symptom survey that included symptoms that have been associated with long-term solvent exposures and symptoms that have not. Acetone-exposed workers and naive controls reported large differences in the perceived intensity of odor and irritation from acetone, yet no differences in the perception of PEA. However, for both groups, the most significant factors mediating reported irritancy and health symptoms from acetone were the perceived intensity of its odor and an individual's bias to report irritation from PEA. The perception of odor intensity and degree of response bias will differ between and within groups of exposed and naive individuals; hence, an assessment of the influence of these factors in experimental and workplace studies of chemical irritancy is warranted.

Dalton, P. H., D. D. Dilks, et al. (2000). "Evaluation of odor and sensory irritation thresholds for methyl isobutyl ketone in humans." Aihaj **61**(3): 340-350.

Odor and irritation sensitivity for methyl isobutyl ketone (MIBK) was evaluated by obtaining olfactory detection thresholds and irritation (lateralization) thresholds, as well as perceived odor intensity and irritation ratings for three predetermined concentrations of MIBK, acetone, and phenylethyl alcohol. Subsequently, perceived annoyance ratings for the three concentrations were measured for 25 of the 40 volunteers. The mean odor detection threshold for MIBK was 10 ppm, and mean lateralization threshold was 8874 ppm. Calculating the fifth percentile for lateralization thresholds revealed that 95% of the sample population did not experience sensory irritation at or below 1802 ppm. Thus, while odor thresholds were well below the current recommended exposure limits (50 ppm, threshold limit value; 75 ppm short-term exposure limit, American Conference of Governmental Industrial Hygienists), irritation thresholds were significantly higher. Odor and irritation intensity ratings for the chemicals increased with increasing concentrations and were higher for MIBK than for acetone. However, when the affective component of the irritation response (annoyance) was rated separately from the sensory component (perceived irritation), no significant

differences were found between the irritancy of MIBK and acetone, suggesting that negative hedonic evaluations of MIBK (perhaps based on odor unfamiliarity) contributed to ratings of perceived irritation. These results validate coupling affective and sensory ratings to more effectively examine the human response to volatile stimuli. Results indicate that intranasal sensory irritation from MIBK will not be experienced at or near current exposure levels. Notably, the best predictors of perceived irritation to high concentrations of MIBK were those measures related to its odor, not to the threshold for sensory irritation, suggesting that negative responses to MIBK involve reactions to olfactory properties.

Danuser, B. (2001). "Candidate physiological measures of annoyance from airborne chemicals." Chem Senses **26**(3): 333-337.

Annoyance due to short-term exposure to airborne chemicals is a key factor in modern environmental research. Unpleasant odors or those that are believed harmful can annoy us. Since annoyance is modulated by the psychological and physiological states of the exposed persons, it is essential that we understand how these factors interact with environmental stimuli to yield a given level of this response. A potentially fruitful approach in this effort may be to treat annoyance as an emotion induced by the odor, and possibly irritation, resulting from chemical exposures. In this way, methods applied to assess induced emotions will likely be of value in elucidating annoyance. A rationale is presented for use of the startle reflex to elucidate the motor component of annoyance, which is manifest as a redirecting of attention towards the annoying odor (or irritant). Although evidence supporting the use of breathing changes to assess the vegetative component of annoyance is somewhat more scattered and indirect, this approach seems likely to be the most fruitful for future research. Experiments to enhance our understanding of annoyance using these two non-verbal end-points are outlined.

Davis, J. M. (1988). "Corporate influence on threshold limit values." Am J Ind Med **13**(5): 615.

de Ceaurriz, J. C., J. C. Micillino, et al. (1981). "Sensory irritation caused by various industrial airborne chemicals." Toxicol Lett **9**(2): 137-143.

A short inhalation experiment was performed on mice using 22 industrial airborne irritants. The parameter chosen as an index of sensory irritation was the reflex decrease in respiratory rate. For each compound, systematic determination of the concentration associated with a 50% decrease in the respiratory rate (RD50) permitted, on the basis of the same end point, a comparison of their relative potencies. The possibility of using the obtained data as initial guidelines to establish acceptable Threshold Limit Values (TLVs) in the workplace was examined.

De Fruyt, F., E. Thiery, et al. (1998). "Neuropsychological effects of occupational exposures to carbon disulfide and hydrogen sulfide." Int J Occup Environ Health **4**(3): 139-146.

In the framework of an extensive health survey of viscose rayon workers in Belgium, 187 workers underwent a neuropsychological examination. Of these, 120 had been exposed for at least a year to carbon disulfide (CS&inf2;) and hydrogen sulfide (H2S), and 67 served as a non-exposed control group. Measurements showed that many of the 17 jobs in the factory involved exposures to CS&inf2; ranging from 3 mg/m(3) (centrifuge operator) to 147 mg/m(3) (spinning cake regulator), far in excess of the threshold limit value (TLV) of 31 mg/m(3); H2S exposures remained below the recommended TLV of 14 mg/m(3). The neuropsychological investigation included subtests of the Wechsler Adult Intelligence Scale, the entire Wechsler Memory Scale, the Bourdon-Wiersma Test, the Santa Ana Dexterity Test, the Gibson Spiral Maze, and the Bimanual Sinusoidal Movement Test. Specific questions were included to account for the effects of age, educational level, eye complaints, alcohol consumption, medication intake, and test motivation. Only the group exposed to values exceeding three times the recommended TLV for CS2; had significant impairments in both the speed and the quality of psychomotor performance. Exposure to CS2; and H2S had no significant effect on memory and attention. Covariance analysis revealed the confounding influences of educational level and eye complaints for explaining observed "differences" in memory and attention tasks found by univariate analysis.

de Raat, W. K., H. Stevenson, et al. (1997). "Toxicological risk assessment of worker exposure to pesticides: Some general principals." Reg. Tox. Pharm. **25**: 204-210.

de Raat, W. K., H. Stevenson, et al. (1997). "Toxicological risk assessment of worker exposure to pesticides: some general principles." Reg. Toxicol. Pharmacol. **25**: 204-210.

DECOS, D. E. C. o. O. S. (1992). Health-based recommended occupational exposure limits for crystalline forms of silicon dioxide(free silica). The Hague, Ministry of Social Affairs and Employment.

DECOS, D. E. C. o. O. S. (1998). Chromium and its inorganic compounds. Rijswijk, Health Council of the Netherlands.

DECOS, D. E. C. o. O. S. (1998). Quartz: Evaluation of the carcinogenicity and genotoxicity. Rijswijk, Health Council of the Netherlands.

Dedhia, H. V., R. J. Rando, et al. (2000). "Can We protect workers from developing the adverse respiratory effects of isocyanate exposure?" Occup Med **15**(2): 399-410.

In this review, the authors have attempted to present the difficulty in defining a permissible exposure limit (PEL) to agents that act as sensitizers and may induce

asthma-even at exposure levels less than the PEL. One approach to this relatively unaddressed problem may be to define the separate aspects of exposure to the specific sensitizing agent. The first effect is an accelerated rate of decline in lung function in nonsensitized individuals who are exposed to the agent (in this case the model used is isocyanates). The second effect is sensitization. Rules for developing a PEL might take this sensitizing effect into account, and this group of agents with such dual effects may be defined as "sensitizers." Exposure to agents with this designation would require special educational and surveillance initiatives to facilitate early detection. The elimination of sensitization may be a greater challenge. An important form of prevention is medical screening of exposed workers, yet it is unclear which screening approach best identifies workers with early isocyanate asthma.

Demers, P. A., K. Teschke, et al. (1997). "What to do about softwood? A review of respiratory effects and recommendations regarding exposure limits." Am J Ind Med **31**(4): 385-398.

Wood dust has been classified as a human carcinogen by the International Agency for Research on Cancer with a footnote that the evaluation was based on a marked excess of sino-nasal cancer among workers exposed primarily to hardwood dusts. Because the epidemiologic data on the carcinogenic effects of softwoods are weaker than for hardwoods, standard setting for softwood dust presents a greater dilemma. Unfortunately, the studies of wood dust and cancer do not have the quantitative exposure data necessary for standard setting for either hardwoods or softwoods. Asthma, non-asthmatic airflow obstruction, and both upper and lower respiratory symptoms have been associated with exposure to both 'allergenic' and 'non-allergenic' softwood dusts, and an association with increasing intensity of exposure has been observed in multiple studies. The available evidence seems to indicate that to prevent these nonmalignant effects, the level of exposure to all softwood dust should be at least as low 2 mg/m3. A standard of 1 mg/m3 may be more appropriate to provide a safety margin to protect more sensitive workers. It may be that some of the health effects observed are due to the natural components of wood, such as resin acids or monoterpenes, or to molds.

DesRoches, P. (2003). "Cytotoxic drug handlers--monitoring in the occupational health setting." Aaohn J **51**(3): 106-108.

Many advances have been made in the area of cytotoxic drug handling among health care workers. The publication of technical guidelines in the late 1980s and early 1990s have served a fundamental role in increasing awareness of the potential risk to health care workers exposed to cytotoxic agents. The OSHA and ASHP guidelines have greatly assisted occupational health professionals in developing appropriate policy for their hospital institution. However, with their use during the years, the guidelines have been criticized as impractical and not very useful. Occupational health professionals welcome the changes on the horizon as research uncovers new and better ways to monitor high risk employees.

Devillers, J., D. Domine, et al. (1997). "Occupational exposure modelling with ease." Sar And Qsar In Environmental Research **6**: 1-2.

Devriese, S., W. Winters, et al. (2004). "Perceived relation between odors and a negative event determines learning of symptoms in response to chemicals." Int Arch Occup Environ Health **77**(3): 200-204.

BACKGROUND: We investigated the effects of worrying information about chemical pollution on subjective symptoms in response to an odor that was previously associated with symptom episodes. METHODS: Ammonia and butyric acid in harmless concentrations were used as odor cues, and 10% CO2-enriched air was used to induce symptoms. One of two odors was consistently mixed with CO2-enriched air while the other odor was presented in room air during 80 s breathing trials (three trials of each). Next, information framing the experiment in the context of possible health-damaging effects of chemical pollution of our environment was presented to half the participants, whereas no information was given to the other half. Finally, both odor cues were presented with room air. Symptom scores were used as the dependent variable. RESULTS: Unexpectedly, participants reported more symptoms in response to the odor previously presented with air than to the odor previously presented with CO2-enriched air. Post-hoc analyses suggested a crucial role for perceived rather than actual contingencies between odor and symptom episodes. Information manipulation had no effect. CONCLUSIONS: Believing that a specific odor cue was associated with a symptom episode was more important than the actual association in order to provoke symptoms in response to harmless odor cues.

DFG, D. F. (2001). List of MAK and BAT values 2000: Maximum concentrations and biological tolerance values at the workplace. Weinheim.

Diaper, J. (1987). "Odour potential and annoyance." Dev Toxicol Environ Sci **15**: 147-152.

Dick, R. B. (1988). "Short duration exposures to organic solvents: the relationship between neurobehavioral test results and other indicators." Neurotoxicol Teratol **10**(1): 39-50.

Short duration exposure to solvents at even low concentrations can induce signs of mild toxicity such as mucous membrane irritation, tearing, nasal irritation, headache, and nausea. These irritant effects are often used as warning properties for potential solvent toxicities and have frequently been classified in the literature as pre-narcotic effects. With higher exposures the toxic effects are more pronounced and can include intoxication, incoordination, exhilaration, sleepiness, stupor, and the beginning stages of anesthesia. Collectively these effects are taken as indicators of narcosis. Offering recommendations for safe exposure limits for these shorter term exposures is made difficult because, (1) the mild toxic effects are often reported subjectively and tolerance usually

develops, (2) the solvent concentration(s) cannot be documented in all cases, and (3) the effects are reversible when individuals are removed from exposure. Laboratory experiments involving controlled exposures to solvents using neurobehavioral performance tests represent one form of investigation that can provide meaningful information in this instance. The results can be viewed in two ways with reference to issues of safe exposure limits. One is to ensure that performance functions that can compromise safety are not affected by the exposure limits prescribed. The second is to consider performance changes due to short-term exposures as possible precursors of similar but more severe effects given longer term exposures. Thus, setting exposure limits to protect against these performance changes could possibly prevent the development of more serious cases of chronic solvent neurotoxicity. This paper compares solvent concentrations from short-duration exposure studies using neurobehavioral tests with the concentrations producing irritant and narcotic effects, as documented by the two main standards recommending bodies, the National Institute for Occupational Safety and Health and the American Conference of Governmental Industrial Hygienists. Comparisons are also made with the regulatory exposure limits established by the Occupational Safety and Health Administration. In general, the neurobehavioral changes which occur following short-duration exposures are reported at concentrations between those which produce irritant effects and narcosis. For the chemicals which have been tested, the performance changes measured by the present day neurobehavioral tests in use rarely occur at or below those limits recommended by the standards recommending bodies.

Dick, R. B., J. V. Setzer, et al. (1984). "Effects of acute exposure of toluene and methyl ethyl ketone on psychomotor performance." Int Arch Occup Environ Health **54**(2): 91-109.

Organic solvents are used frequently in industry and workers are often exposed to various combinations of these chemicals. Several are CNS depressants, and the purpose of this experiment was to assess the behavioral effects of 4-hour inhalation exposures to two solvents, toluene and methyl ethyl ketone (MEK) alone and combined. Ethanol at 0.08% blood levels was used as a positive control. A total of 144 paid volunteers were randomly assigned to one of eight treatment combinations in a series of four two-group between subjects studies. Testing was carried out in an exposure chamber, and participants were tested before, during, and after the treatment or control condition on three performance tasks. The tasks measured alertness and psychomotor function and produced a total of 28 measures on each individual over the approximate 8 h of testing. Results indicated that toluene at 100 ppm produced a small but significant impairment on one measure of a visual-vigilance task by lowering the percentage of correct hits. MEK at 200 ppm produced no interpretable significant effects on any of these measures. Additivity was not evident when individuals were exposed to MEK (100 ppm) and toluene (50 ppm) in combination, as no significant performance differences were noted. Ethanol, at 0.08%, affected both the visual-vigilance and a choice-reaction time task at statistically significant

levels on two measures, confirming the sensitivity of these two tasks to CNS depressants.

Djerassi, L. (1988). "Time to reconsider TLVs." Am J Ind Med **13**(5): 611-612.

Djuric, D. (1988). "Comments on the article by Castleman and Ziem." Am J Ind Med **13**(5): 613-614.

Doty, R. L., Gregor, Thomas, and Monroe, Carl (1986). "Quantitative Assessment of Olfactory Function in an INdustrial Setting." Journal of Occupational Medicine **28**(6): 457-460.

Doty, R. L., J. E. Cometto-Muniz, et al. (2004). "Assessment of upper respiratory tract and ocular irritative effects of volatile chemicals in humans." Crit Rev Toxicol **34**(2): 85-142.

Accurate assessment of upper respiratory tract and ocular irritation is critical for identifying and remedying problems related to overexposure to volatile chemicals, as well as for establishing parameters of irritation useful for regulatory purposes. This article (a) describes the basic anatomy and physiology of the human upper respiratory tract and ocular mucosae, (b) discusses how airborne chemicals induce irritative sensations, and (c) reviews practical means employed for assessing such phenomena, including psychophysical (e.g., threshold and suprathreshold perceptual measures), physiological (e.g., cardiovascular responses), electrophysiological (e.g., event-related potentials), and imaging (e.g., magnetic resonance imaging) techniques. Although traditionally animal models have been used as the first step in assessing such irritation, they are not addressed here since (a) there are numerous reviews available on this topic and (b) many rodents and rabbits are obligate nose breathers whose nasal passages differ considerably from those of humans, potentially limiting generalization of animal-based data to humans. A major goal of this compendium is to inform the reader of procedures for assessing irritation in humans and to provide information of value in the continued interpretation and development of empirical databases upon which future reasoned regulatory health decisions can be made.

Douglas, R. B. and J. E. Coe (1987). "The relative sensitivity of the human eye and lung to irritant gases." Ann Occup Hyg **31**(2): 265-267.

Drake-Lee, A., R. Ruckley, et al. (2002). "Occupational rhinitis: a poorly diagnosed condition." J Laryngol Otol **116**(8): 580-585.

The civil claim of occupational rhinitis may be difficult to prove on the balance of probabilities and is the responsibility of the claimant. There are two types of occupational rhinitis, an allergic rhinitis or a rhinitis due to irritation. Occupational rhinitis can be likened to occupational asthma. Particular attention must be paid to the relationship to alleged exposure and symptoms. Irritation causes symptoms during exposure that cease afterwards unless clinically obvious

damage has occurred. Tobacco smoke and nicotine may also cause symptoms. A full examination, both externally and internally of the nose, mouth and eyes should be undertaken. The presence of squamous metaplasia is important. The validity of a claimant's symptoms must be checked against the medical records. Details of all occupations, compounds and protection should be noted. Manufacturing data on the compounds should also be obtained. The Health and Safety Executive publish occupational exposure limits for many industrial chemicals. Allergen-specific IgE may be raised when an allergy is considered to cause the occupational rhinitis. Nasal challenge tests have been used in Scandinavia to diagnose allergic occupational rhinitis. The sense of smell should be tested. There are two approaches, detecting threshold or recognition, which is suprathreshold. When present, three degrees of social effect occur: impairment, disability and handicap. The degree depends on the occupation of the individual.

Dravnieks, A. and H. J. O'Neill (1979). "Annoyance potentials of air pollution odors." Am Ind Hyg Assoc J **40**(2): 85-95.

The various parameters of odor sensation can be evaluated to yield their relative potential to cause annoyance. The effect of prolonged exposure to odors on the human sense of smell is not clear, but circumstantial evidence points to the possibility of deleterious changes.

Drexler, H. (1998). "Assignment of skin notation for MAK values and its legal consequences in Germany." Int Arch Occup Environ Health **71**(7): 503-505.

Dror, K. (1988). "TLVs--a personal opinion." Am J Ind Med **13**(5): 617-618.

Droz, P. O., M. Berode, et al. (1999). "Biological monitoring of tetrahydrofuran: contribution of a physiologically based pharmacokinetic model." Am Ind Hyg Assoc J **60**(2): 243-248.

A seven-compartment physiologically based pharmacokinetic (PBPK) model was developed to predict biological levels of tetrahydrofuran under various exposure scenarios. Affinities for the tissue were estimated from measurements of liquid-gas partition coefficients for water, olive oil, and blood. Metabolism was assumed to follow a rapid first order reaction. urinary excretion was simulated considering passive reabsorption of tetrahydrofuran in the tubules. The validity of the model was tested by comparison with available experimental and field data. Agreement was satisfactory with all studies available except one, which showed much higher results than expected. The source of this difference could not be identified, but cannot be explained by different exposure conditions, such as duration, concentration, or physical work load. However, it is recommended that this particular study not be used in the establishment of a biological exposure index. Simulation of repeated occupational exposure with the PBPK model allowed the prediction of biological levels that would be reached after repeated exposure at the American Conference of Governmental Industrial Hygienists' threshold limit value, time-weighted average of 200 ppm. For samples taken at the end of the

shift, the PBPK model predicts 5.1 ppm for breath, 57 mumol/L (4.1 mg/L) for venous blood, and 100 mumol/L (7.2 mg/L) for urine.

Dube, D., M. Puruckherr, et al. (2002). "Reactive airways dysfunction syndrome following metal fume fever." Tenn Med **95**(6): 236-238.

Metal fume fever (MFF) is an acute response to the inhalation of heavy metals used in industry. The patient typically experiences symptoms of cough, fever, chills, malaise, and myalgia that are self-limited and of short duration. Wheezing may occur and pulmonary function may be acutely impaired with a decrease in lung volumes and diffusing capacity of carbon monoxide. Nevertheless, respiratory function quickly returns to normal, and persistent pulmonary insufficiency is unusual. Irritant-induced asthma is a non-immunogenic form of airway injury that may be associated with industrial inhalation exposure. In this situation, the direct toxic effect on the airways causes persistent airway inflammation and bronchial hyperreactivity. The two conditions are considered distinct entities, but we report a previously healthy worker who had classic MFF and was left with irritant-induced asthma or reactive airways dysfunction syndrome (RADS).

Duncan, K. P. (1988). "Standard setting." Am J Ind Med **13**(5): 619-620.

Echeverria, D., L. Fine, et al. (1989). "Acute neurobehavioural effects of toluene." Br J Ind Med **46**(7): 483-495.

An acute inhalation chamber study of 42 college students was performed to investigate the relation between exposure to 0, 75, and 150 ppm of toluene and changes in central nervous system function and symptoms. Paid subjects were exposed for seven hours over three days. Verbal and visual short term memory (Sternberg, digit span, Benton, pattern memory); perception (pattern recognition); psychomotor skill (simple reaction time, continuous performance, digit symbol, hand-eye coordination, finger tapping, and critical tracking); manual dexterity (one hole); mood (profile of mood scales (POMS]; fatigue (fatigue checklist); and verbal ability were evaluated at 0800, 1200, and 1600 hours. Voluntary symptoms and observations of sleep were collected daily. An analysis of variance and test for trend was performed on the difference and score for each concentration reflecting an eight hour workday where each subject was their own control. A 3 x 3 Latin square study design evaluated toluene effects simultaneously, controlling for learning across the three days and the solvent order. Intersubject variation in solvent uptake was monitored in breath and urine. A 5-10% decrement in performance was considered significant if it was consistent with a linear trend at p less than 0.05. Adverse performance at 150 ppm toluene was found at 6.0% for digit span, 12.1% for pattern recognition (latency), 5.0% for pattern memory (number correct), 6.5% for one hole, and 3.0% for critical tracking. The number of headaches and eye irritation also increased in a dose response manner. The greatest effect was found for an increasing number of observations of sleep. Overall, no clear pattern of

neurobehavioural effects was found consistent with the type 1 central nervous system as classified by the World Health Organisation. Subtle acute effects, however, were found just below and above the ACGIH TLV of 100 ppm toluene, supporting the position that the guideline be lowered since the biological threshold of behavioural effects may be comparable with the TLV.

Echeverria, D., L. Fine, et al. (1991). "Acute behavioural comparisons of toluene and ethanol in human subjects." Br J Ind Med **48**(11): 750-761.

A comparison of toluene and ethanol (EtOH) induced changes in central nervous system (CNS) function and symptoms were evaluated in two studies, and when possible the effects of toluene were expressed in EtOH equivalent units. The toluene concentrations were 0, 75, and 150 ppm, bracketing the American Conference of Governmental Industrial Hygienists threshold limit value (ACGIH TLV) of 100 ppm. The socially relevant EtOH doses were 0.00, 0.33, and 0.66 g EtOH/kg body weight, equivalent to two and four 3.5% 12 ounce beers. Forty two paid college students were used in each study. In the first study, subjects were exposed to toluene and an odour masking agent menthol (0.078 ppm) for seven hours over three days. In the second study EtOH or a placebo was administered at 1530 across three days also in the presence of menthol. Verbal and visual short term memory (Sternberg, digit span, Benton, pattern memory), perception (pattern recognition), psychomotor skill (simple reaction time, continuous performance, symbol-digit, hand-eye coordination, finger tapping, and critical tracking), manual dexterity (one hole), mood (profile on mood scales (POMS), fatigue (fatigue checklist), and verbal ability were evaluated at 0800, 1200, and 1600. Voluntary symptoms and observations of sleep were collected daily. A 3 x 3 latin square design evaluated solvent effects simultaneously controlling for learning and dose sequence. An analysis of variance and test for trend were performed on am-pm differences reflecting an eight hour workday and on pm scores for each solvent, in which subjects were their own control Intersubject variation in absorbance was monitored in breath. A 5 to 10% decrement was considered meaningful if consistent with a linear trend at p less than 0.05. At 150 ppm toluene, losses in performance were 6.0% for digit span, 12.1% for pattern recognition (latency), 5% for pattern memory (number correct), 6.5% for one hole, and 3% for critical tracking. The number of headaches and eye irritation also increased in a dose-response manner. The greatest effect was found for an increasing number of observations of sleep. A range of 2 to 7% decrements suggest the ACGIH TLV of 100 ppm toluene may be a good estimate of the biological threshold supporting a re-evaluation of the TLV. At 0.66 g EtOH/kg body weight symptoms and performance decrements were 6.6% for digit span, 9.2% for pattern recognition, 4.0% for continuous performance, 7.9% for symbol-digit, 16.5% for finger tapping, 6.2% for critical tracking, and 5.2% for the one hole test. The EtOH equivalents at 150 ppm toluene for digit span (0.56g EtOH/kg/body weight), the latency for pattern recognition (0.66 g EtOH kg body weight), and the one hole element "move" (0.37 g EtOH kg body weight) show that the first two measures would be affected at or above the 50 mg% blood

alcohol concentration. This concentration is recognised as the lowest alcohol concentration associated with increased numbers of automobile accidents. The results suggest that EtOH may be a useful acute standard to compare the effects of various industrial solvents and support investigating an association between exposure to solvents and increased risk to safety in industry.

Eckardt, R. E. (1991). "In defense of TLVs." J Occup Med **33**(9): 945, 947-948.

Edling, C. and P. Lundberg (2000). "The significance of neurobehavioral tests for occupational exposure limits: an example from Sweden." Neurotoxicology **21**(5): 653-658.

The setting of OELs is part of risk management. It should, however, be kept in mind that not only scientific data affects the outcome of an OEL but also cost-benefit and technical feasibility. During the last decades, neurobehavioral methods have been used increasingly in human studies to investigate the effects of neurotoxic chemicals on the nervous system. Since exposure levels in the workplace are becoming lower and lower, traditional epidemiology will face difficulties in revealing any effects. Therefore authorities regulating chemicals must rely more and more on toxicological data and on results from experimental human studies. It will then be crucial that sound criteria for the validity of human neurobehavioral studies of neurotoxicity are established if the results from neurobehavioral studies are to be used in regulatory risk assessment. Because of the variation in individuals response to chemical exposures, exposure limits might not be possible to set with a view toward this range of susceptibility and the avoidance of any neuropathic effects. This paper discuss the Swedish experience when using neurobehavioral data in deciding effects on the nervous system as the critical effect.

Egilman, D. S., S. Bagley, et al. (2003). "The beryllium "double standard" standard." Int J Health Serv **33**(4): 769-812.

Brush Wellman, the world's leading producer and supplier of beryllium products, has systematically hidden cases of beryllium disease that occurred below the threshold limit value (TLV) and lied about the efficacy of the TLV in published papers, lectures, reports to government agencies, and instructional materials prepared for customers and workers. Hypocritically, Brush Wellman instituted a zero exposure standard for corporate executives while workers and customers were told the 2 microgram standard was "safe." Brush intentionally used its workers as "canaries for the plant," and referred to them as such. Internal documents and corporate depositions indicate that these actions were intentional and that the motive was money. Despite knowledge of the inadequacy of the TLV, Brush has successfully used it as a defense against lawsuits brought by injured workers and as a sales device to provide reassurance to customers. Brush's policy has reaped an untold number of victims and resulted in mass distribution of beryllium in consumer products. Such corporate malfeasance is perpetuated by the current market system, which is controlled by an organized

oligopoly that creates an incentive for the neglect of worker health and safety in favor of externalizing costs to victimized workers, their families, and society at large.

Egilman, D. S. and A. A. Reinert (1995). "The origin and development of the asbestos Threshold Limit Value: scientific indifference and corporate influence." Int J Health Serv **25**(4): 667-696.

Several recent articles have critiqued the process employed by the American Conference of Governmental Industrial Hygienists in determining Threshold Limit Values. Criticisms have included inadequate data collection, inadequate research, excessive corporate influence, and slow response to informational changes. In this article, the authors address the historical development of the American Conference of Governmental Industrial Hygienists' asbestos exposure guideline. They demonstrate that the proposed guideline was known to be inadequate when it was first proposed, was severely criticized between 1946 and 1968, but nonetheless was promulgated annually and remained unchanged 1971.

Elkins, H. B. (1988). "Response to "Corporate Influence on Threshold Limit Values"." Am J Ind Med **14**(6): 737-740.

EU (1996). Technical Guidance Documents in support of the Commission Directive 93/67/EEC on Risk Assessment for New Notified Substances and Commission., European Union.

EU, E. U. (2001). European Union Dirctive 2000/39/EC establishing a first list of indicative occupational exposure limit values at European Community level in implementation of council directive 98/24/EC on the protection of the health and safety of workers from the risks related to chemical agents at work, European Union: Health and Safety Commission.

FAIR (2000). Criteria to establish health-based occupational exposure limits for pesticides, European Union: Food, Agriculture and Fisheries Programme.

FAIR (2000). Recommended method for the establishment of acceptable operator exposure levels (AOELs), European Union: Food, Agriculture, and Fisheries Programme.

FAIR (2000). Scientific basis to estblish health-based occupational exposure limits for pesticides. Orta, Italy, Food, Agriculture and Fisheries Programme, European Union.

Fairchild, E. J. (1967). "Tolerance mechanisms. Determinants of lung responses to injurious agents." Arch Environ Health **14**(1): 111-126.

Fairhurst, S. (1995). "The uncertainty factor in the setting of occupational exposure standards." Ann. Occup. Hyg. **39**(3): 375-385.

Fairhurst, S. (2003). "Hazard and risk assessment of industrial chemicals in the occupational context in Europe: some current issues." Food Chem Toxicol **41**(11): 1453-1462.

This paper is about industrial chemicals, the manner in which their toxicity is assessed and the use of such assessments in regulatory decision-making. It begins with general points concerning toxicological data availability and hazard identification, then moves on to risk assessment and occupational exposure limits, and finally looks briefly at three specific toxicological issues, asthma, chronic toxic encephalopathy, and "low toxicity" dust effects on the lung, where the science is far from resolved. The overall purpose of the paper is to raise, or perhaps to act as a reminder of a number of issues of particular relevance to industrial chemicals and the occupational setting, and hopefully to prompt further thinking and perhaps some new initiatives directed at the areas in question.

Farina, G., L. Alessio, et al. (1980). "[Occupational exposure to drugs: antibiotics (author's transl)]." Med Lav **71**(3): 228-234.

FederalRegister (1993 - March 23). Occupational Exposure to 2-Methoxyethanol, 2-Ethoxyethanol and Their Acetates (GlycolEthers); Proposed Rule, OSHA, Dept. of Labor.

Fenske, R. A. and J. J. van Hemmen (1994). "Occupational skin exposure to chemical substances: setting limits." Ann Occup Hyg **38**(4): 333-336.

Ferguson, D. M. (1976). "Short-term exposure limits." Ann Occup Hyg **19**(3-4): 275-284.

Ferguson, W. S., W. C. Koch, et al. (1977). "Human physiological response and adaption to ammonia." J Occup Med **19**(5): 319-326.

Other than anecdoted observations, there are no published reports on the physiological effects of ammonia at concentrations normally encountered industrially or information on whether inurement develops after repeated exposure. Six unacclimated male and female volunteers were exposed six hours per day over a six week period to concentrations of 25, 50, and 100 ppm ammonia in an industrial environment, under strict medical surveillance. Inurement to eye, nose, and throat irritation was demonstrated after two to three weeks in addition to short-term subjective adaption. There were no significant differences between subjects or controls on common biological indicators, in physical examinations, or in performance of normal job duties. After acclimation, continuous exposure to 100 ppm, with occasional excursions to 200 ppm, is easily tolerated and has no observed effect on general health.

Feron, V. J., J. H. Art, et al. (2001). "Approach to setting occupational exposure limits for sensory irritants in The Netherlands." Aihaj **62**(6): 733-735.

This article describes how scientists in the Netherlands set occupational exposure limits (OELs) for sensory irritants. When they tackle this issue, a number of key questions need to be answered. For example, did the studies indeed measure sensory irritation and not cytotoxicity? When the irritant is an odorant, can interference of olfactory stimulation be excluded? In the case of subjective measurements, can psychological irritation be excluded? When adaptation is an issue, did the studies indeed measure adaptation and not habituation? When OELs are established in the Netherlands, each of these issues is carefully addressed before a value is suggested. When setting an OEL in the Netherlands, human data carry more weight than animal data of comparable quality. As in the United States, documentation for the recommended OEL is written and a discussion of all available relevant and reliable data culminating in the selection of the key study for deriving the health-based recommended occupational exposure limit is provided. Special effort is dedicated to reconciling differences between the animal and human data. If the toxicological database is considered to be inadequate, the committee acknowledges this limitation and will not recommend a limit value due to insufficient data.

Feron, V. J., C. Hoeksema, et al. (1994). "A critical appraisal of the setting and implementation of occupational exposure limits in the Netherlands." Indoor Environ **3**: 260-265.

Feron, V. J., C. Hoeksema, et al. (1994). "A critical appraisal of the setting and implementation of occupational exposure limits in the Netherlands." Indoor Environ **3**: 260-265.

Finkelstein, M. M. (2000). "Leukemia after exposure to benzene: temporal trends and implications for standards." Am J Ind Med **38**(1): 1-7.

BACKGROUND: Benzene is a human leukemogen. Risk assessment, and the setting of occupational and environmental standards, has assumed that risk is constant in time after a unit of exposure. Leukemia risk is known to vary with time after exposure to ionizing radiation. METHODS: A matched case-control study of leukemia risk in relation to the temporal pattern of benzene exposures was performed using data from the National Institute of Occupational Safety and Health. RESULTS: Leukemia risk following exposure to benzene varied with time in a manner similar to that following exposure to ionizing radiation. More recent exposures were more strongly associated with risk than were more distant ones. There was no significant relation between leukemia death and benzene exposures incurred more than 20 years previously. CONCLUSIONS: Recent analyses of specific occupational and environmental carcinogens, including benzene and radon, have indicated that cancer risk tends to decline as the time from exposure increases. This suggests that standards for the control of

occupational or public risk must be selected to control exposures over a narrower time frame than the usual lifetime one. In the case of benzene, it would appear that risk is attributable primarily to exposures incurred during the previous 10 to 20 years, with exposures in the most recent 10 years being the most potent. To limit risk, exposures must be controlled during that interval. It is important that epidemiologists explore the temporal pattern of risk in their studies to facilitate the risk assessment of other carcinogens.

Finkelstein, M. M. (2000). "Silica, silicosis, and lung cancer: a risk assessment." Am J Ind Med **38**(1): 8-18.

BACKGROUND: To investigate exposure-response relationships for silica, silicosis, and lung cancer. METHODS: Quantitative review of the literature identified in a computerized literature search. RESULTS: The risk of silicosis (ILO category 1/1 or more) following a lifetime of exposure at the current OSHA standard of 0.1 mg/m(3) is likely to be at least 5-10% and lung cancer risk is likely to be increased by 30% or more. The exposure-response relation for silicosis is nonlinear and reduction of dust exposures would have a greater than linear benefit in terms of risk reduction. Available data suggests that 30 years exposure at 0.1 mg/m(3) might lead to a lifetime silicosis risk of about 25%, whereas reduction of the exposure to 0.05 mg/m(3) might reduce the risk to under 5%. CONCLUSIONS: The lifetime risk of silicosis and lung cancer at an exposure level of 0.1 mg/m(3) is high. Lowering exposures to the NIOSH recommended limit if 0.05 mg/m(3) may have substantial benefit.

Finklea, J. A. (1988). "Threshold limit values: a timely look." Am J Ind Med **14**(2): 211-212.

Fiori, J. M. and R. D. Meyerhoff (2002). "Extending the threshold of regulation concept: de minimis limits for carcinogens and mutagens." Regul Toxicol Pharmacol **35**(2 Pt 1): 209-216.

Risk assessment processes for carcinogens are highly developed but risk assessment processes for mutagens are not well established. In the pharmaceutical industry, risk associated with exposure to carcinogens is tightly controlled. It is desirable to control risk associated with exposure to mutagens also, in spite of the greater uncertainty associated with the risk. In this paper, a published cancer potency database is used to frame the risk and to support risk management decisions. A de minimis exposure for mutagens is proposed and a decision matrix is presented to align available data with risk assessment approaches for carcinogens and mutagens.

Fiserova-Bergerova, V. and J. Vlach (1997). "Exposure limits for unconventional shifts: toxicokinetic and toxicodynamic considerations." Am J Ind Med **31**(6): 744-755.

Adjustment factors (AF) for inhalation exposure to chemical agents during unconventional work schedules were derived on toxicokinetic bases. AFs depend on the half-life of the agent and on the work schedule. Because they are grossly

affected by cumulation, AFs were calculated for steady-state conditions. They were based on the following measures of chemical body burden: (1) end-of-shift biological level as used previously by other investigators; and (2) areas under the curves, AUCexp, AUCday, and AUCweek, which correlate with average biological levels during the shift, work day, and work week, respectively. The dependence of AFs on the half-life was studied on 50 possible work schedules using agents with a half-life of 1 hr to 2 years. Based on the data, simple equations suitable for field conditions were derived for determination of AFs. Since AFs based on individual measures of body burden are not the same, the pharmacodynamics of the toxic endpoint should be considered when selecting the measure of body burden and the half-life for AF determination.

Formisano, J. A., Jr., K. Still, et al. (2001). "Application of statistical models for secondary data usage of the US Navy's Occupational Exposure Database (NOED)." Appl Occup Environ Hyg **16**(2): 201-209.

Many organizations around the world have collected data related to individual worker exposures that are used to determine compliance with workplace standards. These data are often warehoused and thereafter rarely used as an information resource. Using appropriate groupings and analysis of OSHA data, Gomez showed that such stored data can provide additional insight on factors affecting occupational exposures. Using data from the Occupational Exposure Database of the United States Navy, the usefulness of statistical models for defining probabilities of exposure above permissible limits for observed work conditions is examined. Analyses have highlighted worker Similar Exposure Groups (SEGs) with potential for overexposure to asbestos and lead. In terms of grouping data, Rappaport et al. defined the Within-Between Lognormal Model, a scale-independent measure for quantifying between-worker variability within a selected worker group: (B)R.95 = exp[3.92s(sB)], representing the ratio of arithmetic mean exposures received by workers in the 97.5th and 2.5th percentiles. To help search for groups, the Proportional Odds Model, a generalization of the logistic model to ordinal data, can predict probabilities for group exposure above the Occupational Exposure Limit (OEL), or the Action Level (AL), which is one-half of the OEL. Worker SEGs have been identified for asbestos workers removing friable asbestos ((B)R.95 = 11.0) and nonfriable asbestos ((B)R.95 = 6.5); metal cleaning workers sandingspecialized equipment ((B)R.95 = 11.3), and workers at target shooting ranges cleaning up lead debris ((B)R.95 = 10). Estimated probabilities for the categories <AL, AL-OEL, and >OEL support current understanding of work processes examined. Differences in probability noted between tasks and levels of ventilation validate this method for evaluating other available workplace exposure determinants, and for predicting probability of membership in categories that may help further define worker exposure groups, and determinants of excessive exposures. Thus, analyses of retrospective exposure data can help identify work site and work practice factors for efficient targeting of remediation resources.

Frank, A. L. (1988). "Corporate influence on threshold limit values by Castleman and Ziem." Am J Ind Med **13**(5): 607-608.

Fry, R. M. and M. W. Carter (1993). "Should ICRP have prescribed an averaging period for the occupational dose limit in its basic general recommendations?" Health Phys **64**(3): 319-320.

Galer, D. M., H. W. Leung, et al. (1992). "Scientific and practical considerations for the development of occupational exposure limits (OELs) for chemical substances." Reg. Tox. Pharm. **15**: 291-306.

Gao, Y. and B. E. Kanengiser (2004). "Categorical evaluation of the ocular irritancy of cosmetic and consumer products by human ocular instillation procedures." J Cosmet Sci **55**(4): 317-325.

The assessment of ocular irritation potential is an important part of safety testing for cosmetic and consumer products. The purpose of this investigation was to examine ocular irritancy levels elicited in humans by various categories of a specific class of cosmetic and consumer products that have a potential to enter the eye inadvertently during use. Test materials assessed belonged to one of seven categories, which included liquid makeup, shampoo, baby wash, mascara, eye makeup remover, powder eye shadow, and facial cleanser. These test materials were evaluated by human ocular instillation, followed by examinations, for which subjective perceptions of irritation were recorded, and component areas of ocular tissues were individually examined for inflammation and for the area and density of fluorescein staining patterns at 30 seconds and at 5, 15, 60, and 120 minutes post-instillation. Subjective and objective ocular irritation scores of 410 eyes were analyzed by product classification. Average score levels were determined for subjective responses, inflammation, and fluorescein staining patterns. This investigation determined that irritation levels of the evaluated test materials varied markedly with respect to product category, type of ocular irritation, and ocular tissue, demonstrating that these factors are important considerations for the prediction of the ocular irritancy of a test material.

Gardner, R. J. and P. J. Oldershaw (1991). "Development of pragmatic exposure-control concentrations based on packaging regulation risk phrases." Ann Occup Hyg **35**(1): 51-59.

This paper relates United Kingdom and other national Occupational Exposure Limits (OELs) for volatile organic substances to the Risk Phrases (RPs) which they are assigned under EEC Classification, Packaging and Labelling Directives. The OELs for organic volatiles assigned RP 20 ('harmful by inhalation'), RP 23 ('toxic by inhalation') and RP 26 ('very toxic by inhalation') fitted better to the cumulative log-normal distribution than to the cumulative normal distribution and the means for RPs 23 and 26 were not significantly different. The means for RP 20 and RP 23/26 were 100 mg m-3 (or 25 ppm) and 5 mg m-3 (or 1 ppm), respectively. In the absence of any relevant, specific information, it is suggested

that these values may be useful as guidelines for pragmatic exposure-control concentrations (PECCs) for the control of exposure by inhalation in workplaces handling substances labelled with these RPs.

Garrod, A. N. and R. Rajan-Sithamparanadarajah (2003). "Developing COSHH Essentials: dermal exposure, personal protective equipment and first aid." Ann Occup Hyg **47**(7): 577-588.

The 'control banding' approach in COSHH Essentials combines the potential for harm with the potential for exposure by inhalation to band measures to control exposure at source, as generic strategies. These are simply adapted to specific tasks and circumstances to produce specific control advice. Where it is not possible or practical to use this control advice, the control bands can suggest adequate respiratory protective equipment using 'protection factors'. Proposals in the paper enable the user to identify the right level of respiratory protective equipment (RPE), and to begin selecting suitable RPE. Selection is made through a formatted questionnaire, enabling the user to give the right facts to the supplier. COSHH Essentials applies mainly to exposure by inhalation. However, skin exposure is very common and uptake via the skin can be an important contributor to body dose. This paper examines the factors concerning skin exposure, and the options for banding the potential for harm to the skin or via the skin. Proposals have then been made for dermal exposure control. Planning for emergencies is an important facet of risk control. Proposals are outlined to band chemical hazards for emergency planning according to a minimum of information, i.e. the danger symbol on a product label.

Gawkrodger, D. J. (2004). "Occupational skin cancers." Occup Med (Lond) **54**(7): 458-463.

Skin cancer due to occupation is more common than is generally recognized, although it is difficult to obtain an accurate estimate of its prevalence. Over the past two centuries, occupational skin cancers have particularly been due to industrial exposure of men (it seems more so than women) to chemical carcinogens such as polycyclic hydrocarbons (e.g. from coal tar products) or to arsenic. Industrial processes have improved in most Western countries to limit this type of exposure, but those with outdoor occupations are still exposed to solar ultraviolet irradiation without this being widely recognized as an industrial hazard. Ionizing radiation such as X-rays can also cause skin cancer. Occupational skin cancers often resemble skin tumours found in non-occupational subjects, e.g. basal cell carcinoma, squamous cell carcinoma and malignant melanoma, but some pre-malignant lesions can be more specific and point to an occupational origin, e.g. tar keratoses or arsenical keratoses. An uncommon but well-recognized cause of occupational skin cancer is that which results from scar formation following an industrial burn. In the future it will be necessary to focus on preventative measures, e.g. for outdoor workers, the need to cover up in the sun and use sun protective creams and a campaign for earlier

recognition of skin cancers, which are usually curable if treated in their early stages.

Ghittori, S., L. Maestri, et al. (1995). "Evaluation of occupational exposure to benzene by urinalysis." Int Arch Occup Environ Health **67**(3): 195-200.

Urinary phenol determinations have traditionally been used to monitor high levels of occupational benzene exposure. However, urinary phenol cannot be used to monitor low-level exposures. New biological indexes for exposure to low levels of benzene are thus needed. The aim of this study was to investigate the relations between exposure to benzene (A-benzene, ppm), as measured by personal air sampling, and the excretion of benzene (U-benzene, ng/l), trans,trans-muconic acid (MA, mg/g creatinine), and S-phenylmercapturic acid (PMA, micrograms/g creatinine) in urine. The subjects of the study were 145 workers exposed to benzene in a chemical plant. The geometric mean exposure level was 0.1 ppm (geometric standard deviation = 4.16). After logarithmic transformation of the data the following linear regressions were found: log (U-benzene, ng/l) = 0.681 log (A-benzene ppm) + 4.018; log (MA, mg/g creatinine) = 0.429 log (A-benzen ppm) - 0.304; and log (PMA, micrograms/g creatinine) = 0.712 log (A-benzene ppm) + 1.664. The correlation coefficients were, respectively, 0.66, 0.58, and 0.74. On the basis of the equations it was possible to establish tentative biological limit values corresponding to the respective occupational exposure limit values. In conclusion, the concentrations of benzene, mercapturic acid, and muconic acid in urine proved to be good parameters for monitoring low benzene exposure at the workplace.

Gobba, F. (2003). "Occupational exposure to chemicals and sensory organs: a neglected research field." Neurotoxicology **24**(4-5): 675-691.

The effect of industrial chemicals on the sensory perception of exposed workers has received scant attention from the medical community to date, and the scientific literature is mainly limited to some case-reports or isolated studies. Possible explanations for this include the complexity of sensory perception, and the lack of agreement among researchers on methods for testing large groups of subjects. Nevertheless, some published studies showed that vision, hearing and olfactory function can be affected by various industrial metals and solvents, and some data exist also for touch and taste. This review discusses the main industrial chemicals involved. The pathogenesis of the toxicity of chemicals to sensory perception may be related to an action on receptors, nerve fibers, and/or the brain; probably, different pathogenetic mechanisms are involved. One of the main problems in this research field is that most of the studies to date evaluated the effect of a single industrial chemical on a single sense: as an example, we know that styrene exposure can impair smell and also hearing and vision but we have little idea whether different senses are impaired in the same worker, or whether each impairment is independent. In addition, workers are frequently exposed to different chemicals: co-exposure may have no effect, or result in both an increase or a decrease of the effect, as was observed for hearing loss, but

studies on this aspect are largely insufficient. Research shows that both occupational and environmental exposure to industrial chemicals can affect sense organs, and suggests that the decline of perception with age may be, at least partly, related to this exposure. Nevertheless, available evidence is incomplete, and is largely inadequate for an estimation of a "safe" threshold of exposure. Good quality further research in this field is needed. This is certainly complex and demands adequate resources, but is justified by the ultimate result: the possibility to prevent an avoidable part of the decline in sensory function with age.

Goede, H. A., S. C. Tijssen, et al. (2003). "Classification of dermal exposure modifiers and assignment of values for a risk assessment toolkit." Ann Occup Hyg **47**(8): 609-618.

This paper describes how default dermal exposure values can be adjusted with modifier values for specific work situations. The work presented here is supplementary to a toolkit developed for the EU RISKOFDERM project. This toolkit is intended for the assessment and management of dermal risks in small and medium sized enterprises. Potential dermal exposure (on the outer envelope of the body) is estimated with an algorithm whereby modifier values are applied multiplicatively to dermal default exposure values. These exposure modifiers with their assigned factors are intended to increase or decrease the potential (default) dermal exposure accordingly. Default estimates are modified to obtain two modified defaults: potential exposure rate to the hands and to the body. Quantitative exposure data is at present inadequate and insufficient to derive meaningful information that can be used for the selection of independent modifiers and the assignment of appropriate values. Instead, available information from the literature was considered and, in combination with expert judgement, 15 potential dermal modifiers were selected. Modifiers were classified and grouped into non-overlapping groups in order to avoid double scoring. Values were assigned to modifiers in three different exposure routes, i.e. direct contact, surface contact and deposition. Depending on the significance of a modifier, the values assigned to modifiers were weighted in equal steps on a log-scale. The values assigned to modifiers as presented in this paper are open to validation and revision once new data become available.

Goedicke, H. J., E. Thiele, et al. (1990). "[Permissible dermal exposure dose and safety level for herbicide residues as an occupational hygiene standard for the evaluation of exposure]." Z Gesamte Hyg **36**(5): 248-250.

At preparing mixtures for spraying, application of pesticides and entering treated areas workers are subject of potential exposure, more than 90% via skin. The limitation of dermal exposure requires hygiene-toxicological threshold limit values. On the basis of toxicity data from experiments with animals a permissible dermal exposure dose for pesticide residues is determined. For that a safety and a resorption factor are used, which are fixed in dependence on the toxic effects. The permissible dermal exposure dose is the basis of the calculation of a safety value for residues on plant surfaces and reentry time.

Goetz, M. E. and A. Luch (2008). "Reactive species: a cell damaging rout assisting to chemical carcinogens." Cancer Lett **266**(1): 73-83.

Reactive oxygen and nitrogen species (ROS and RNS) are known to contribute as pathogenic factors to the development of chronic progressive diseases at various stages. The present review discusses the role of oxidative stress in chemically induced cancer development and progression. Reactive species are capable of inducing DNA damage that eventually may contribute to cell transformation and tumor initiation. ROS and RNS are also associated with tumor promotion and progression. Both endogenous processes and redox-cycling of xenobiotic compounds have been shown to result in oxidative DNA damage. In addition, several exocyclic DNA adducts represent secondary DNA damage caused by products of lipid peroxidation in the course of oxidative cellular stress. Due to their intrinsic ability to catalyze redox reactions, transition metals, and quinones from various classes of xenobiotics or endogenous compounds are important mediators of oxidative stress and thus likely of being involved in DNA damage, lipid peroxidation, cell transformation, and tumor development.

Gold, L. S., G. M. Backman, et al. (1987). "Ranking the potential carcinogenic hazards to workers from exposures to chemicals that are tumorigenic in rodents." Environ Health Perspect **76**: 211-219.

For 41 chemicals there exist both reasonable data on carcinogenic potency in experimental animals and also a defined Permissible Exposure Level (PEL), which is the upper limit of legally permissible chronic occupational exposure for U.S. workers. These 41 agents are ranked by an index that compares the permitted chronic human exposure to the chronic dose rate that induces tumors in 50% of laboratory animals. This index, the Permitted Exposure/Rodent Potency index, or PERP, does not estimate absolute risks directly, but rather suggests the relative hazards that such substances may pose. The PERP values for these 41 substances differ by more than 100,000-fold from each other. The PERP does not take into account the actual level of exposure or the number of exposed workers. Nevertheless, it might be reasonable to give priority attention to the reduction of allowable worker exposures to substances that appear most hazardous by this index and that some workers may be exposed to full-time near the PEL. Ranked by PERP, these chemicals are: ethylene dibromide, ethylene dichloride, 1,3-butadiene, tetrachloroethylene, propylene oxide, chloroform, formaldehyde, methylene chloride, dioxane, and benzene.

Goldsmith, J. R. (1991). "Perspectives on what we formerly called threshold limit values." Am J Ind Med **19**(6): 805-812.

From the point of view of an epidemiologist with experience in community air quality standards, occupational health standards, radiation standards, and water quality standards, reasons are given for discarding the assumption that occupational health protection should be based on threshold concepts. The

weakness of worker health protection based on prescription of maximal exposure levels is noted, regardless of whose judgement is used for such levels.

Goyal, R., K. Krishnan, et al. (1992). "Assessment of occupational health risk during unusual workshifts: review of the needs and solutions for modifying environmental and biological limit values for volatile organic solvents." Can J Public Health **83**(2): 109-112.

Aspects of occupational health risk assessment for unusual workshifts are discussed in relation to the question of: 1) using a suitable model for adjusting occupational exposure limits, and 2) assessing the influence of altered work schedules on biological exposure limits. The relative importance of two separate approaches, i.e., mathematical and pharmacokinetic, for the adjustment of exposure limits is discussed. Emphasis is placed on the usefulness of a physiologically based pharmacokinetic model for the exposure limits adjustments during prolonged work hours. The influence of prolonged work schedules on biological exposure limits is discussed and it is concluded that the latter do not have to be adjusted for unusual workshifts. Research needs arising as a result of unusual workshifts and pertaining to the practice of industrial hygiene and biological monitoring are suggested.

Greene, G. J. and H. M. Kipen (2002). "The vomeronasal organ and chemical sensitivity: a hypothesis." Environ Health Perspect **110 Suppl 4**: 655-661.

Environmental exposures to very low levels of airborne chemicals are associated with adverse symptoms, often affecting multiple organ systems, in the phenomenon of chemical sensitivity (CS). Recent surveys suggest a significant prevalence of chemically sensitive subjects in the United States, but the mechanism linking exposure to symptoms remains unclear, despite the advancement of a variety of theoretical models. In many of these models, exposure of the nasal respiratory system to an airborne agent is the first step in the pathway leading to symptoms. In this article, we advance the hypothesis that interactions between environmental chemicals and the vomeronasal organ (VNO) may play a role in the etiology of CS. The VNO, a bilateral, tubular organ located in the nose, serves in animals as part of a sensitive chemosensory system; however, evidence suggesting that the VNO retains a functional role in the adult human is controversial. Reported characteristics of the human VNO relevant to CS, including location, prevalence, selective sensitivity to airborne chemical exposure, and capacity to produce systemic effects, are discussed within the context of this ongoing debate. Beyond relevance to CS, the demonstration of an active, adult VNO could have significant impact on environmental toxicology.

Greim, H. and U. Reuter (2001). "Classification of carcinogenic chemicals in the work area by the German MAK Commission: current examples for the new categories." Toxicology **166**(1-2): 11-23.

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (MAK Commission) introduced an extended

classification scheme in 1998. In addition to the traditional three categories still used to date, now called: Category 1 (human carcinogen); Category 2 (animal carcinogen); and Category 3 (suspected carcinogen), two new Categories (4 and 5) were added. Classification of substances into the new Categories 4 and 5 is based on the knowledge of mode of action and the potency of carcinogens. The essential feature of substances classified in the new Categories 4 and 5 is that exposure to these chemicals does not contribute significantly to the risk of cancer to man, provided that an appropriate exposure limit (MAK value) is observed. Chemicals known to act typically by non-genotoxic mechanisms are classified in Category 4. Genotoxic chemicals for which low carcinogenic potency can be assessed on the basis of dose-response relationships and toxicokinetics are classified in Category 5. Since the use of this scheme for 3 years, various chemicals have been classified in one of the new categories. However, in several cases data to sufficiently substantiate a MAK value are missing. Such substances are now classified in a subcategory of Category 3, called Category 3 A, which indicates that further data are required for final classification. Examples are given for classification of dichloromethane into Category 3 A, chloroform and sulfuric acid into Category 4 and ethanol into Category 5.

Greim, H. A. and K. Ziegler-Skylakakis (1997). "Strategies for setting occupational exposure limits for particles." Environ Health Perspect **105 Suppl 5**: 1357-1361.

To set occupational exposure limits (OELs) for aerosol particles, dusts, or chemicals, one has to evaluate whether mechanistic considerations permit identification of a no observed effect level (NOEL). In the case of carcinogenic effects, this can be assumed if no genotoxicity is involved, and exposure is considered safe if it does not exceed the NOEL. If tumor induction is associated with genotoxicity, any exposure is considered to be of risk, although a NOEL may be identified in the animal or human exposure studies. This must also be assumed when no information on the carcinogenic mechanism, including genotoxicity, is available. Aerosol particles, especially fibrous dusts, which include man-made mineral fiber(s) (MMMF), present a challenge for toxicological evaluation. Many MMMF that have been investigated have induced tumors in animals and genotoxicity in vitro. Since these effects have been associated with long-thin fiber geometry and high durability in vivo, all fibers meeting such criteria are considered carcinogenic unless the opposite has been demonstrated. This approach is practicable. Investigations on fiber tumorigenicity/genotoxicity should include information on dose response, pathobiochemistry, particle clearance, and persistence of the material in the target organ. Such information will introduce quantitative aspects into the qualitative approach that has so far been used to classify fibrous dusts as carcinogens. The rationales for classifying the potential carcinogenicity of MMMF and for setting OELs used by the different European committees and regulatory agencies are described.

Gromiec, J. P. (2000). "[Exposure assessment strategies for determination of compliance with ceiling occupational exposure limits]." Med Pr **51**(2): 173-184.

The goal of the assessment of exposure to chemicals is to demonstrate the compliance with occupational exposure limit (OEL). There are numerous publications on recommended air sampling strategies for compliance measurements of time weighted average (TWA) concentrations of chemicals but no clear and unambiguous guidelines for measurements and interpretation of ceiling concentrations can be found. Furthermore, definitions and interpretation of ceiling values in different countries may differ considerably. Systems of establishing ceiling limit values, their definitions and interpretation in Germany, the USA (OSHA, ACGIH and NIOSH), the UK and Poland have been reviewed. In most countries of the European Union and in the USA, continuous monitoring using either self contained instruments, multipoint sampling systems or multiplexed sensors is considered as being the most appropriate approach. Based on the literature review the following air sampling strategies have been proposed:--for substances with both OEL--Ceiling and OEL-TWA values dual sampling: 8-hour samples for time weighted average concentrations, and in parallel short (5-10 min) samples during the expected highest exposure for ceiling concentrations measurements; for substances with OEL--Ceiling as the only exposure limit (which is preferable); continuous monitoring using direct reading instruments, possibly with an alarm device. If such instruments are not available, short time measurements may be performed at regular (30 min) intervals using direct reading gas analysers or detector tubes.

Grosjean, R. (1994). "European standardization: guidance on the assessment of occupational exposure to chemical agents. CEN TC 137." Analyst **119**(1): 9-12.

Working group 1 of CEN TC 137 has produced a draft proposal for the assessment of exposure to chemical agents and measurement strategy. A review of the standard is given. The purpose is to give practical guidance to those who have to carry out these assessments. A systematic approach allows the number of measurements to be reduced. The report of the work done allows communication in an efficient way with interested parties: workers, occupational physicians and the labour inspectorate.

Grossman, E. A. and J. Martonik (1990). "OSHA's approach to risk assessment for setting a revised occupational exposure standard for 1,3-butadiene." Environ Health Perspect **86**: 155-158.

In its 1980 benzene decision [Industrial Union Department, ALF-CIO v. American Petroleum Institute, 448 U.S. 607 (1980)], the Supreme Court ruled that "before he can promulgate any permanent health or safety standard, the Secretary [of Labor] is required to make a threshold finding that a place of employment is unsafe--in the sense that significant risks are present and can be lessened by a change in practices" (448 U.S. at 642). The Occupational Safety and Health Administration (OSHA) has interpreted this to mean that whenever possible, it must quantify the risk associated with occupational exposure to a toxic substance at the current permissible exposure limit (PEL). If OSHA determines that there is significant risk to workers' health at its current standard, then it must quantify the

risk associated with a variety of alternative standards to determine at what level, if any, occupational exposure to a substance no longer poses a significant risk. For rulemaking on occupational exposure to 1,3-butadiene, there are two studies that are suitable for quantitative risk assessment. One is a mouse inhalation bioassay conducted by the National Toxicology Program (NTP), and the other is a rat inhalation bioassay conducted by Hazelton Laboratories Europe. Of the four risk assessments that have been submitted to OSHA, all four have used the mouse and/or rat data with a variety of models to quantify the risk associated with occupational exposure to 1,3-butadiene. In addition, OSHA has performed its own risk assessment using the female mouse and female rat data and the one-hit and multistage models.(ABSTRACT TRUNCATED AT 250 WORDS)

Guillemin, M. (1975). "[The threshold limit values (author's transl)]." Ther Umsch **32**(3): 189-192.

Haber, L. T., J. S. Dollarhide, et al. (2001). Noncancer risk assessment: Principals and practice in environmental and occupational settings. Patty's Toxicology, Fifth Edition. E. Bingham, B. Cohrssen and C. H. Powell, John Wiley & Sons, Inc. **1:** 169-232.

Haber, L. T. and A. Maier (2002). "Scientific criteria used for the development of occupational exposure limits for metals and other mining-related chemicals." Regul Toxicol Pharmacol **36**(3): 262-279.

The scientific approaches employed by selected internationally recognized organizations in developing occupational exposure limits (OELs) for metals and other mining-related chemicals were surveyed, and differences and commonalities were identified. The analysis identified an overriding need to increase transparency in current OEL documentation. OEL documentation should adhere to good risk characterization principles and should identify (1) the methodology used and scientific judgments made; (2) the data used as the basis for the OEL calculation; and (3) the uncertainties and overall confidence in the OEL derivation. At least within a single organization, a consistent approach should be used to derive OELs. Opportunities for harmonization of scientific criteria were noted, including (1) consideration of severity in identification of the point of departure; (2) definition of the minimum data set; (3) approaches for interspecies extrapolation; (4) identification of default uncertainty factors for developing OELs; and (5) approaches for consideration of speciation and essentiality of metals. Potential research approaches to provide the fundamental data needed to address each individual scientific criterion are described. Increased harmonization of scientific criteria will ultimately lead to OEL derivation approaches rooted in the best science and will facilitate greater pooling of resources among organizations that establish OELs and improved protection of worker health.

Hakes, J. K. (1999). "Stringency of workplace air contaminant exposure limits: A case study of OSHA risk management." Risk Analysis **19**(6): 11131125.

Hansen, L. E. (1993). "Occupational exposure limits. Criteria document for phenol." **2985**.

Hansen, L. F. and G. D. Nielsen (1994). "Sensory irritation and pulmonary irritation of n-methyl ketones: receptor activation mechanisms and relationships with threshold limit values." Arch Toxicol **68**(3): 193-202.

Activation of the trigeminal nerve endings in eyes and nose, termed sensory irritation, was determined from the reflexively induced decrease in respiratory rate in mice for methyl propyl ketone, methyl butyl ketone, methyl amyl ketone and methyl hexyl ketone. The relationship between exposure concentration and the decrease in respiratory rate followed Michaelis-Menten equations. Two estimates of each agonist-receptor dissociation constant were obtained, one from the Michaelis-Menten equation and one from the threshold (RD-0) of the log concentration-effect curve. The values were equal and thus one receptor type could account for the activation process. The hydrophobic properties of the receptor biophase were found to approach that of the internal part of the bilayer membrane. It therefore follows that the receptor-air partition coefficients increase with the size of the ketones, thus accounting for the observed increase in potency. Estimates of Threshold Limit Values (TLV) were obtained and compared with established values. Close agreements were found for methyl propyl ketone and methyl amyl ketone, but not for methyl butyl ketone, where the neurotoxic effect constituted a more sensitive endpoint than sensory irritation.

Hansen, L. F. and G. D. Nielsen (1994). "Sensory irritation, pulmonary irritation and structure-activity relationships of alcohols." Toxicology **88**(1-3): 81-99.

Sensory irritation due to inhalation of n-pentanol, n-heptanol, sec-butanol and tert-pentanol was determined from the reflexively induced decrease in respiratory rate in CF-1 mice. The concentration-effect relations followed Michaelis-Menten equations, complying with receptor mediated processes. The relations were transformed into nearly rectilinear relationships in log concentration-effect plots, and the extrapolated threshold concentrations (RD-0) from the lines were 120, 28, 640 and 1210 ppm, respectively, obtained from the first 2 min of the exposure period. These values were comparable to those found in Swiss-Webster mice and to those obtained by electrophysiological experiments in Sprague-Dawley rats. The hydrophobic properties of the receptor biophase were found to approach that of the internal part of the bilayer membrane. Estimates on threshold limit values (TLV) were obtained and were found in reasonable agreement with the established values. The nose has a scrubbing effect, which reduces the concentration in the lungs in normal mice. n-Pentanol, sec-butanol and tert-pentanol decreased tidal volume in normal mice, explained either by an activation of receptors in the upper airways or by a sensitization of the stretch receptors. Two types of pulmonary responses were seen in tracheal-cannulated mice, which could be explained by an effect on stretch receptors and another type of lung receptors.

Hansson, S. O. (1997). "Critical effects and exposure limits." Risk Anal **17**(2): 227-236.
The use of critical effects in the determination of occupational exposure limits (OELs) in Sweden is subjected to a statistical study. Many of the present OELs are high in relation to known no-effect levels and effect levels, and the degree of protection has a surprisingly weak correlation with the seriousness of the adverse effect. Several proposals for improved procedures are put forward. One of these is to supplement the concept of critical effects with that of dominant effects. A dominant effect of a substance is a health effect that is at some concentration the most serious health effect.

Harrison, J. and O. Sepai (2000). "Should control measures be based on air measurements or biological/biological effect monitoring?" Occup Med (Lond) **50**(1): 61-63.
The setting of, and the review of, exposure limits takes into account toxicological, occupational hygiene and epidemiological data. The COSHH Regulations 1994 define a hierarchical approach to controlling workplace exposures with a particular emphasis on the measurement and control of airborne substances. Absorption via the lungs is considered the most important route of entry in the workplace, however, percutaneous absorption must not be overlooked. Biomarkers are used extensively in the surveillance of workers' exposure to metals and organic chemicals. In addition, Genetic polymorphism for xenobiotic metabolism has been widely studied. The selection, validation and application of any biomarker is a complicated process and requires careful consideration prior to any application.

Harssema, H. (1987). "Characterization of exposure in odour annoyance situations." Dev Toxicol Environ Sci **15**: 95-104.

Hartley, C. (1980). "Safety: applying TLVs." Occup Health (Lond) **32**(6): 301-303.

Hatch, T. F. (1972). "The role of permissible limits for hazardous airborne substances in the working environment in the prevention of occupational disease." Bull World Health Organ **47**(2): 151-159.

Hatch, T. F. (1973). "Criteria for hazardous exposure limits." Arch Environ Health **27**(4): 231-235.

Health, N. I. f. O. S. a. (1976). Criteria for a Recommended Standard ... Occupational Exposure to Acrylamide. Stanford Research Institute, Menlo Park, California, NIOSH.

Heederik, D. (2001). "Are we closer to developing threshold limit values for allergens in the workplace?" Curr Opin Allergy Clin Immunol **1**(2): 185-189.
The use of immunoassays has facilitated the measurement of high molecular weight sensitizers, usually protein molecules, in the picogram and nanogram per

cubic meter range. This facilitated the evaluation of exposure response relationships for bakery workers, exposed to wheat allergens and fungal alpha-amylase and other groups exposed to other allergens such as laboratory animal workers. The application for the standard setting is still limited and requires rigorous standardization, but can be expected in the near future.

Heederik, D., P. S. Thorne, et al. (2002). "Health-based occupational exposure limits for high molecular weight sensitizers: how long is the road we must travel?" Ann Occup Hyg **46**(5): 439-446.

In this paper pitfalls in risk assessment for high molecular weight allergens, which can cause typical Type I/IgE-mediated respiratory allergy, are discussed. The major pitfalls seem to be that no agreement exists on the preferential end point that should be used in risk assessment. As a result, it is unclear which exposure-response relationship should be considered. In addition, there is a lack of data on health risks for non-occupationally exposed reference populations, so the baseline risk is often not known and little is known about the shape of exposure-response relationships and the existence of exposure thresholds. The good news is that more and more groups have published exposure-response relationships for several allergens. The possibilities for risk assessment approaches that should lead to occupational exposure standards are explored. Specific consideration is given to situations in which data on exposure-response relationships for humans are available. Considerable progress has been made in this area by use of advanced statistical techniques for exposure-response modelling. The major practical constraint at this moment seems to be the absence of well-standardized measurement techniques (immunoassays) for the evaluation of allergen exposure in the field.

Hellgren, J., G. Karlsson, et al. (2003). "The dilemma of occupational rhinitis: management options." Am J Respir Med **2**(4): 333-341.

Occupational rhinitis is a common heterogeneous group of inflammatory conditions in the nose, caused by exposure to airborne irritants and sensitizers in the occupational environment. The mechanism can be allergic, neurogenic or toxic.Data from several epidemiologic studies indicate that animal dander, organic dusts, latex and chemicals can cause occupational rhinitis, but because of methodological problems as well as weaknesses in the definition of occupational rhinitis, occupational exposure is probably an underestimated cause of rhinitis. The effect of rhinitis on the mental aspects of quality of life and substantial costs due to loss of productivity make it important to diagnose and treat occupational rhinitis. Diagnosis relies on a history of exposure, skin prick testing and, if possible, nasal provoacation. Avoidance of exposure, protective measures at the workplace and medical treatment, with agents such as second generation antihistamines and nasal corticosteroids, can make it possible to avoid progress of the disease from rhinitis to asthma. The efficacies of montelukast, a leukotrienne receptor antagonist, and omalizumab, an anti-

immunoglobulin E monoclonal antibody in the treatment of occupational rhinitis are yet to be evaluated

Hempel-Jorgensen, A., S. K. Kjaergaard, et al. (1997). "Integration in human eye irritation." Int Arch Occup Environ Health **69**(4): 289-294.

Today it is widely known and accepted that indoor air pollution can affect health. To ensure a healthy indoor climate through source control it is necessary to be able to predict how much of a source can be introduced into a building without unacceptable health and comfort effects. This paper describes a study of human eye irritation, which is part of a research program aimed at developing the use of sensory reference scaling in source characterization. In reference scaling the sensory eye irritation caused by exposure to polluted air is measured in terms of a concentration of a reference gas causing equivalent eye irritation intensity. The purpose of this study, therefore, was to estimate a possible difference in the magnitude of perceived sensory irritation between unilateral and bilateral exposure of human eyes. In each of four runs ten subjects were exposed to five progressive concentrations of CO2. In two of the runs the subjects were exposed unilaterally and in the other two runs the subjects were exposed bilaterally. In an analysis of variance no significant difference was found between unilateral and bilateral exposures. As expected, the intensity of the perceived irritation increased significantly with increasing exposure level. The sensitivity decreased slightly but significantly following previous exposures. These results enable us to develop a model for source characterization in which sensory eye irritation is measured by reference scaling. The use of reference scaling has the advantage that an otherwise subjective response (perceived irritation intensity) becomes less biased.

Hempel-Jorgensen, A., S. K. Kjaergaard, et al. (1998). "Cytological changes and conjunctival hyperemia in relation to sensory eye irritation." Int Arch Occup Environ Health **71**(4): 225-235.

In general, irritation is a physiological response to a chemical or physical stimulus involving objective changes (e.g., local redness and edema) and subjective sensations (e.g., pruritus and pain). The perception of an irritating stimulus in the eyes and the upper airways is called sensory irritation. Sensory irritation is a prevalent symptom in relation to complaints about indoor air quality. The intensity of perceived sensory irritation in humans has mainly been evaluated using psychophysical methods. However, perceived sensory irritation is dependent on the subject expressing the symptoms; that is, it is a subjective measure. This is a problem in assessment of irritation effects from air pollution or other factors, since the expression of the irritation symptoms may be biased by, for example, interaction with other people and odors. The subjectivity of the measures is an important complication in several studies dealing with problems regarding indoor air quality. The bias problems make it important to complement the psychophysical measurements of sensory irritation with objective assessments of irritation. In addition, only little is known about the association between sensory

irritation and possible physiological/ pathological changes in the mucosal membranes in relation to studies of indoor air. Two studies (study 1 and study 2) were conducted to investigate changes in conjunctival hyperemia and conjunctival fluid cytology for subjects exposed to volatile organic compounds (VOCs) in their eyes only. Eight subjects participated in study 1. Each subject was exposed to three different mixtures of VOCs. A total of 16 subjects participated in study 2. Half of the subjects were exposed to 1-octene and the other half, to n-butanol. In both studies, photographs of bulbar conjunctiva were taken and conjunctival fluid was sampled before and after exposure. Moreover, the perceived irritation intensities were registered continuously during exposure. Overall, perceived irritation intensity and conjunctival hyperemia increased with increasing exposure concentrations, whereas cytological changes in the conjunctival fluid samples did not seen to be related to exposure concentration, perceived irritation, or changes in conjunctival hyperemia.

Hempel-Jorgensen, A., S. K. Kjaergaard, et al. (1999). "Time course of sensory eye irritation in humans exposed to N-butanol and 1-octene." Arch Environ Health **54**(2): 86-94.

In this study, we investigated the time course effect of sensory eye irritation in 16 subjects exposed (i.e., eye only) to n-butanol and 1-octene. Half the subjects were exposed to n-butanol, and the remaining subjects were exposed to 1-octene. Each subject was studied on 5 different days; during each day each subject was exposed in three runs (i.e., run 1, run 2, and run 3) to a constant concentration of either n-butanol or 1-octene. We performed run 1 and run 3, both of which lasted 15 min each, to evaluate persistence in "sensitization." We performed run 2, which lasted 60 min, to study the time course of sensory irritation. Ratings of ocular irritation intensity were obtained continuously during all three runs. The exposure concentrations for n-butanol were 0 mg/m3, 300 mg/m3, 900 mg/m3, and 3 000 mg/m3, and the exposure concentrations for 1-octene were 0 mg/m3, 6 000 mg/m3, 10 400 mg/m3, and 18 000 mg/m3. During run 2, we observed a slight increase in perceived eye irritation intensity for the lower concentrations of 1-octene and for all exposure concentrations of n-butanol. However, the threshold for irritation was clearly exceeded for only the 1-octene 10 400-mg/m3 and 18 000-mg/m3 exposures. During these two exposures, the response increased 10-fold following 20-40 min of exposure during run 2, after which the response remained constant. We investigated the existence of persistence in "sensitization" by comparing intensity of responses between run 1 and run 3. Persistence in "sensitization" was apparent for only the 1-octene exposure.

Hempel-Jorgensen, A., S. K. Kjaergaard, et al. (1999). "Sensory eye irritation in humans exposed to mixtures of volatile organic compounds." Arch Environ Health **54**(6): 416-424.

Eight subjects participated in a controlled eyes-only exposure study of human sensory irritation in ocular mucosal tissue. The authors investigated dose-

response properties and the additive effects of three mixtures of volatile organic compounds. The dose-response relationships for these mixtures showed increases in response intensity as concentration increased. Replication of exposure did not result in significantly different dose- response relationships. Moreover, the result implied that components of the three mixtures interacted additively to produce ocular irritation, a result referred to as simple agonism. Finally, the authors addressed the comparability of two methods to measure sensory irritation intensity (visual analogue scale and a comparative scale). The results indicated that the two rating methods produced highly comparable results.

Henderson, P. T., D. H. Brouwer, et al. (1993). "Risk assessment for worker exposure to agricultural pesticides: Review of a workshop." Ann. Occup. Hyg. **37**(5): 499-507.

Henderson, R. E. and E. J. Willwerth (2003). "Coping with the new TLV for diesel fuel." Occup Health Saf **72**(2): 28-30, 32-23.

Henschler, D. (1984). "Exposure limits: history, philosophy, future developments." Ann Occup Hyg **28**(1): 79-92.

Henschler, D. (1990). "1990 Yant memorial award lecture. Science, occupational exposure limits, and regulations: a case study on organochlorine solvents." Am Ind Hyg Assoc J **51**(10): 523-530.

Henschler, D. (1991). "The concept of occupational exposure limits." Sci Total Environ **101**(1-2): 9-16.

Germany was the first country to introduce occupational exposure limits (OEL) in 1886. A theoretical consideration for the existence of toxicological thresholds has been provided. Prerequisites for OELs are seen in: reversibility, existence of a threshold, deviation of (physiological) functions from normal to be regarded as "safe", knowledge about mechanism of toxic effect; and for the decision process: complete transparency of decision making, and combination with intensive health surveillance in the workplace. A variety of additional provisions has been introduced into the German MAK-list: a system for limitation of peak exposures; notification of sensitization and skin absorption, and of reproductive hazards; no satisfactory regulation of exposure to mixtures has been established. Occupational carcinogens constitute a special case because of identification of a threshold and the establishment of health-based standards has not yet been demonstrated justifiably. At present, strategies are elaborated for the quantification of cancer risk from a given compound. Despite many shortcomings and criticism. OELs continue to be an important and valid instrument for the protection of workers' health.

Henschler, D. (1992). "Evaluation of adverse effects in the standard-setting process." Toxicol Lett **64-65 Spec No**: 53-57.

Occupational exposure limits (OELs) were first introduced more than a century ago in Germany [1]. They were based on observations of people exposed at the workplace, and on experimental exposures of humans and animals, all accompanied by analytical determination of airborne occupational toxicants. The "acceptable concentrations for short-term and long-term exposure" were derived using crude subjective criteria (humans), or gross pathological alterations (animals). Over the years considerable refinement of these criteria has been achieved, both in their type and number, starting from overt histological derangements, going on to the physiological and biochemical level, and even to subtle psychological parameters. This development has taken place in parallel with, and has been considerably influenced by changes in the definition of health and the perception of effects detrimental to health. Differences in the elementary philosophy of health and in the activities aimed at preventing damage to health in different societies have complicated all the efforts to harmonize standard-setting processes at the international level.

Heron, R. J. and F. C. Pickering (2003). "Health effects of exposure to active pharmaceutical ingredients (APIs)." Occup Med (Lond) **53**(6): 357-362.

BACKGROUND: Workers involved in the manufacture of pharmaceutical products are exposed in the course of their work to the active pharmaceutical ingredient (API) in the products. Such APIs are designed to produce biological change in the human body, which is an unacceptable outcome in the pharmaceutical worker. AIM: To review the evidence for the presence of the health effects of APIs in the pharmaceutical industry. METHOD: The study employed a literature review based on a systematic search of the MEDLINE database. RESULTS: Studies have shown that such biological effects can be produced, particularly in personnel working with potent compounds such as steroids, compounds with capacity to cause cumulative damage such as cytotoxic anti-cancer drugs and antibiotics, unless careful risk assessment and appropriate control measures are implemented. CONCLUSION: There is limited epidemiological evidence for increased mortality and morbidity in this population, but adverse effects on health from exposure to potent agents, such as corticosteroids, sex hormones and antibiotics, can occur. The protection of workers from the potential harmful effects of APIs poses a significant challenge for the pharmaceutical industry.

Hewett, P. (1996). "Interpretation and use of occupational exposure limits for chronic disease agents." Occup Med **11**(3): 561-590.

Hewett, P. (2001). "Misinterpretation and misuse of exposure limits." Appl Occup Environ Hyg **16**(2): 251-256.

Users of occupational exposure limits (OELs) often fail to distinguish between the complementary processes of risk assessment and exposure (risk) management. The former refers to those activities that lead to the selection of a reasonably protective exposure limit and often includes an analysis of exposure databases

and an evaluation of group-based risk. The latter focuses on individual risk, and refers to those actions required of employers to ensure that each employee is unlikely to incur harm to health. This presentation focuses on how this failure to distinguish leads to misinterpretation and misuse of OELs. A typical OEL definition consists of at least three components: a concentration, an averaging time, and a target (usually the individual worker). OELs are occasionally improperly applied, resulting in a reduction of the expected level of protection. For example, sampling strategies proposed by the American Industrial Hygiene Association (AIHA) and Comite Europeen de Normalisation (CEN) permit workers to be aggregated into exposure groups. Under certain circumstances this practice can leave some workers unevaluated and unprotected. Protection is also reduced when the averaging time is extended from a single shift to multiple shifts. Frequently, OELs are misinterpreted as upper limits to exposures averaged over weeks, months, or even years, rather than a single shift. Much of this confusion can be traced to the desire of some to reconcile research (epidemiology) sampling strategies with compliance sampling strategies. But the two have fundamentally different goals and objectives. Others are simply attracted to alternative OEL interpretations that permit frequent overexposures (i.e., measurements that exceed the OEL), thus making compliance easier. Given the current limitations of industrial hygiene and occupational epidemiology, and the general unwillingness of employers to routinely collect exposure data, OELs should continue to be defined as upper limits for single shift exposures. The current OEL model, which permits the use of proximate risk management goals to realize long-range objectives, should be retained. There are, however, valid reasons for augmenting this model to include criteria for evaluating compliance with long-range objectives. The augmented OEL model would be applicable to future new and revised OELs. The author suggests that OEL setting organizations consider harmonizing definitions and statistical interpretations for both existing and new OELs, thus minimizing future misinterpretation and misuse.

Hewitt, P. J. and J. T. Sanderson (1993). "The role of occupational hygiene in exposure assessment by biological indices. A position paper from the Occupational Hygiene Committee of the International Congress on Occupational Health." Ann Occup Hyg **37**(5): 579-581.

Hickey, J. L. and P. C. Reist (1977). "Application of occupational exposure limits to unusual work schedules." Am Ind Hyg Assoc J **38**(11): 613-621.

A one-compartment exponential models is described which predicts "equal protection", based on biological uptake rates, for unusual air contaminant exposure situations as compared to a "normal" exposure of five 8-hour days per week. This is done by equating peak body burdens resulting from a normal and an unusual exposure, in terms of an adjustment factor applied to the normal exposure limit for an air contaminant. This factor predicts the highest allowable concentration in an unusual exposure situation which will not result in a higher-

than normal body accumulation of the inhaled substance. Graphs and formulae are provided for determining adjustment factors for anticipated unusual exposure schedules. The model's predictions and published data are compared.

Hill, C. (1988). "Control limits of MELs?" Occup Health (Lond) **40**(4): 513-514.

Hlawiczka, S. (1987). "[Smell threshold levels of substances as a criterion for evaluating the maximum permissible exposure levels]." Med Pr **38**(4): 307-312.
Compared in the paper are the threshold limit values (TLV) and odour threshold concentrations (OTC) of 85 substances. As so far the generally accepted methods of odour nuisance measurements have been missing; the TLV/OTC ratio was adopted as a criterion of possible appearance of odour discomfort. The substances were divided into groups according to their feasibility of odorous nuisance. It was demonstrated that the odour discomfort might appear even with concentrations below TLVs. This particularly refers to styrene, naphthalene, CS2, pyridine and H2S.

Hofmann, A. (1995). "Fundamentals and possibilities of classification of occupational substances as developmental toxicants." Int Arch Occup Environ Health **67**(3): 139-145.
It is now widely accepted that describing and labeling of chemicals as developmental toxicants on a purely qualitative basis does not make sense. Agents possessing the potential to induce reproductive or developmental toxicity present a risk of human harm only under certain conditions. This critical fact cannot be properly communicated with a simple designation as "positive" or "negative". Rather, a number of parameters that deal with dose or concentration, frequency, duration and route of exposure must also be conveyed. Unsubstantiated blacklisting is equally counterproductive for preventive medicine as downplaying of the toxicity of chemicals. Gender-based restrictions on exposure at workplaces of women of child-bearing age are neither socially acceptable nor scientifically justifiable. Therefore, the German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area published in 1983 a quantitatively based classification concept, which became effective in 1985 and was modified in the following years. The present contribution summarizes what is required for an integrated judgment on the relevance of laboratory and epidemiological data for predicting the potential risk associated with exposure at workplaces to occupational chemicals. Methyl mercury, carbon disulfide, dimethylformamide, ethanol, toluene, N,N-dimethyl acetamide, nitrous oxide, methanol, ethyl benzene, and phosphorus pentoxide will be described as examples of classified substances.

Hofmann, H. T. (1972). "[Problem of "harmless" threshold limit values for work materials]." Offentl Gesundheitswes **34**(5): 241-254.

Holmberg, B. and M. Winell (1977). "Occupational health standards. An international comparison." Scand J Work Environ Health **3**(1): 1-15.

The background for establishing standards for toxic agents is reviewed, and the standards of 14 different countries, including Sweden, are compared with special reference to criteria and organizational aspects. The differences among countries in the numerical limit values for toxic substances are largely due to differences in definitions, biomedical criteria, technical feasibility and sociopolitical judgements.

Hooper, K., J. LaDou, et al. (1992). "Regulation of priority carcinogens and reproductive or developmental toxicants." Am J Ind Med **22**(6): 793-808.

In California, 370 carcinogens and 112 reproductive/developmental toxicants have been identified as a result of the State's Safe Drinking Water and Toxic Enforcement Act of 1986. They include pesticides, solvents, metals, industrial intermediates, environmental mixtures, and reactive agents. Occupational, environmental, and consumer product exposures that involve these agents are regulated under the Act. At levels of concern, businesses must provide warnings for and limit discharges of those chemicals. The lists of chemicals were compiled following systematic review of published data, including technical reports from the U.S. Public Health Service--National Toxicology Program (NTP), and evaluation of recommendations from authoritative bodies such as the International Agency for Research on Cancer (IARC) and the U.S. Environmental Protection Agency (USEPA). Given the large number of chemicals that are carcinogens or reproductive/developmental toxicants, regulatory concerns should focus on those that have high potential for human exposure, e.g., widely distributed or easily absorbed solvents, metals, environmental mixtures, or reactive agents. In this paper, we present a list of 33 potential priority carcinogens and reproductive/developmental toxicants, including alcoholic beverages, asbestos, benzene, chlorinated solvents, formaldehyde, glycol ethers, lead, tobacco smoke, and toluene.

Hotz, P., P. Carbonnelle, et al. (1997). "Biological monitoring of vehicle mechanics and other workers exposed to low concentrations of benzene." Int Arch Occup Environ Health **70**(1): 29-40.

It has been suggested that the threshold limit value (TLV) for the time-weighted average (TWA), of benzene be lowered because of its possible leukemogenic effect at low exposure concentrations. This requires the development of new methods of biological monitoring. In this cross-sectional study the diagnostic power of blood and breath benzene and of urinary phenol, catechol, hydroquinone, S-phenylmercapturic acid, and muconic acid were compared in a population of 410 male workers exposed to benzene in garages, in two coke plants, and in a by-product plant. Benzene exposure was assessed by personal air sampling (charcoal tube and passive dosimeter). In all, 95% of the workers were exposed to less than 0.5 ppm benzene. According to the multiple regression equation, the muconic acid and S-phenylmercapturic acid concentrations detected in nonsmokers exposed to 0.5 ppm benzene were 0.3 mg/g and 6 micrograms/g, respectively (range 0.2-0.6 mg/g and 1.2-8.5 micrograms/g, respectively). With muconic acid very few false-positive test

results were found, and this determination remained reliable even around a cutoff level of 0.1 ppm benzene. Moreover, the diagnostic power of this test proved to be good even when diluted or concentrated urine samples were not excluded. S-Phenylmercapturic acid (S-PMA) also performed fairly well. Blood and breath benzene as well as urinary phenol (PH) and hydroquinone (HQ) were clearly less suitable biomarkers than muconic acid (MA). Catechol (CA) was not associated with occupational benzene exposure. According to the results of biological monitoring, the skin resorption of benzene from gasoline or other fuels seems negligible. Correlation, multiple regression, and likelihood ratios consistently showed that MA and S-PMA concentrations were fairly good indicators of benzene exposure in the 0.1- to 1-ppm range, even in a population comprising both smokers and nonsmokers. PH, HQ, CA, and blood and breath benzene were less suitable, if at all, in the same exposure range.

Hu, X., D. H. Wegman, et al. (1993). "Application of an event marker in the occupational epidemiologic study of acute irritant symptoms." Epidemiology **4**(3): 266-270.

Field studies of occupational exposure to airborne irritants have predominantly relied on symptom surveys of study participants. As part of a new approach to the study of acute irritant symptoms, subjects exposed to sodium borate dusts recorded their symptom responses at hourly interviews as well as instantaneously on an electronic device called an event marker. Overall, the unprompted marks indicated fewer irritant events than the interviews. Marks were more frequent in the presence of more than one type of symptom and also appeared to reflect more severe symptoms. A proportion of the marked events occurred in time intervals when no symptoms were recalled during the interview. The exposure-response relations were similar regardless of whether they were based on the interview reports or the electronically marked symptoms. The event marker provided a means to examine the time of onset of the acute symptom event. It also made it possible to examine directly the timing profiles of symptom response in relation to changes in exposure levels in a field setting. Despite some inconsistencies, the finding suggests that the event marker may provide an alternative to frequent interviews of exposed workers to obtain irritant symptom responses for exposure-response modeling.

Hu, X., D. H. Wegman, et al. (1992). "Dose related acute irritant symptom responses to occupational exposure to sodium borate dusts." Br J Ind Med **49**(10): 706-713.

A repeated measurement design was employed in the study of acute symptoms of eye and respiratory tract irritation resulting from occupational exposure to sodium borate dusts. The symptom assessment of the 79 exposed and 27 unexposed subjects comprised interviews before the shift began and then at regular hourly intervals for the next six hours of the shift, four days in a row. Exposures were monitored concurrently with a personal real time aerosol monitor. Two different exposure profiles, a daily average and short term (15 minute) average, were used in the analysis. Exposure-response relations were evaluated by linking incidence rates for each symptom with categories of

exposure. Acute incidence rates for nasal, eye, and throat irritation, and coughing and breathlessness were found to be associated with increased exposure levels of both exposure indices. Steeper exposure-response slopes were seen when short term exposure concentrations were used. Results from multivariate logistic regression analysis suggest that current smokers tended to be less sensitive to the exposure to airborne sodium borate dust. There was no indication that anhydrous sodium borate was more potent than the other sodium borates in this work environment.

Hudnell, H. K., D. A. Otto, et al. (1992). "Exposure of humans to a volatile organic mixture. II. Sensory." Arch Environ Health **47**(1): 31-38.

Time-course functions for symptoms of the sick building syndrome were derived from 66 healthy males who, during separate sessions, were exposed to clean air and to a volatile organic compound (VOC) mixture. The mixture contained 22 VOCs (25 mg/m3 total concentration) commonly found airborne in new or recently renovated buildings. Subjects rated the intensity of perceived irritation, odor, and other variables before, and twice during, 2.75-h exposure periods. Eye and throat irritation, headache, and drowsiness increased or showed no evidence of adaptation during exposure, whereas odor intensity decreased by 30%. These results indicate that irritation intensity and other symptoms are not related in any simple way to odor intensity, which suggests that the symptoms may not be a psychosomatic response to the detection of an aversive odor. Instead, subthreshold levels of VOCs may interact additively or hyperadditively and stimulate trigeminal nerve receptors. Also, air quality ratings improved by 18% during exposure, which suggests that both odor and irritation intensity may influence assessments of air quality.

Hursidic-Radulovic, A., J. Mustajbegovic, et al. (2002). "Gender related differences of low level exposure to occupational irritants--a three-year follow-up of chemical industry workers." Coll Antropol **26 Suppl**: 109-118.

The authors followed changes in the ventilatory function in a group of 102 chemical workers over a three year period to evaluate gender related differences on respiratory effects of low concentrations of occupational irritants. Measurements were performed annually and the results of ventilatory test were compared to predicted normal values. Lung function was measured by recording maximum expiratory flow-volume (MEFV) curves. Baseline data show ventilatory function impairments of the obstructive-restrictive type, as measured by the Tiffeneau index and FEV1. After one and two years of exposure, impairment in flow rates at low lung volumes became prominent. Analysis of lung function in three years of the study suggests obstructive impairments mostly in the larger airways accompanied by a restrictive component. The ventilatory flow at low lung volumes was characterized by obstruction, but not by restrictive findings. Women appear to be more sensitive than men to the irritant effects of these exposures as measured by flow rates at low lung volumes--the smaller airways (FEF50% = 82.7 +/- 23.6 in women and FEF50% = 92.1 +/- 32.1 in men; p = 0.017), while

men experienced greater changes than women to irritant effects on their ventilatory capacity--the large airways (FVC = 99.6 +/- 10.6 in men and FVC = 106.74 +/- 9.8 in women; p = 0.001). The additive effect of smoking to environmental irritation is demonstrated by the proportionately lower lung capacity in smokers. Overall, the effect of these pollutants in women is more synergistic than additive.

Hytonen, M., L. Kanerva, et al. (1997). "The Risk of Occupational Rhinitis." International Archives of Occupational and Environmental Health **69**(6): 487-490.

The occupations with an increased risk of occupational rhinitis (OR) and asthma were identified and age and gender differences were analyzed. Cases of OR and asthma reported to the Finnish Register of Occupational Diseases were assessed, and a standardized rate ratio method was used to compare the rate of OR in different occupations. The relative risk of OR was expressed as the age standardized rate ratio (SRR). During 1986 to 1991, 1,244 new cases of OR (40% men; 60% women) and 1,867 new cases of occupational asthma (49% women; 51% men) were reported. Occupations with the highest SRR included furriers, bakers, livestock breeders, food processors, veterinarians, agricultural workers, electronic assemblers, boat builders, horticulturists, textile dyers, metal workers, hairdressers, cabinet makers and tanners. The leading causes of OR included animal dander, flours, wood dust, textiles, mites, organic materials, formaldehyde (50000), natural resins, and minerals. The authors conclude that exposure to allergens should be minimized through technical improvements and protective clothing in occupations with a high risk of developing OR.

Illing, H. P. (1991). "Extrapolating from toxicity data to occupational exposure limits: some considerations." Ann Occup Hyg **35**(6): 569-580.

This paper evaluates procedures relevant to extrapolating from toxicity data in man and animals to Occupational Exposure Limits. It examines effects at or around the "No Observed Adverse Effect Level' (NOAEL) and the magnitude of safety factors which can be applied in developing occupational exposure limits for non-stochastic effects. The relationship between incidence of stochastic effect and occupational exposure limit is also discussed.

Illing, H. P. A. (1991). "Extrapolating from Toxicity Data to Occupational Exposure Limits: some considerations." The Annals of Occupational Hygiene **36**(6): 569-580.

Illing, H. P. A. and M. House (1993). Occupational exposure limits-health based values or administrative norms? Visby, Sweden, National Institute of Occupational Health**:** 41-52.

Indulski, J. A., Z. Kowalski, et al. (1988). "Theory and practice of establishing occupational exposure limits in Poland." Pol J Occup Med **1**(2): 111-126.

Innocenti, A. (2000). "[A "technically attainable" refernce value for exposure to wood dust in the light of Law 66/2000]." Med Lav **91**(6): 565-574.

The question of appropriate exposure standards for wood dust is addressed by reference to the major health effects, especially sino-nasal cancer, that have been investigated. A review of several key papers on wood dust exposure permits some associations to be made between exposure data and effects, particularly impaired/suppressed nasal mucociliary clearance, according to which it may be suggested, based on available evidence, that a standard of 1.5-2 mg/m3 of total suspended wood dust could reasonably protect against the observed effects. Moreover, data from the literature show that reducing personal wood dust exposures to below 2 mg/m3 is accomplished relatively easily, whereas reducing exposures to below 1 mg/m3 is considerably more difficult and expensive. The exposure level of 1.5-2 mg/m3 is suggested for all wood dusts; it does not seem reasonable at the present time to distinguish between hardwood and softwood because many of the important mortality studies report results based on patients with mixed exposures. The threshold exposure value of 5 mg/m3 for hardwood proposed from 1/1/2003 by Law 66/2000 is deemed to be too high as a health-based occupational exposure limit.

Iregren, A. (1986). "Subjective and objective signs of organic solvent toxicity among occupationally exposed workers. An experimental evaluation." Scand J Work Environ Health **12**(5): 469-475.

A questionnaire consisting of 55 items concerning acute and long-term symptoms associated with exposure to organic solvents, as well as questions about type and duration of exposure, was distributed to 225 male spray painters in the Stockholm region. From the 152 respondents, two extreme groups were selected on the basis of frequency of solvent-related symptoms. Subjects for the experimental study (N = 26) were chosen from these groups and matched with respect to age and number of years employed as a painter. The subjects were experimentally exposed for 4 h to 3.2 mmol/m3 (300 mg/m3) of toluene and a control condition in an exposure chamber. Effects on performance were assessed with a computerized battery of four tests. Ratings of acute symptoms were also studied, and toluene exposure was found to affect them. However, there were no indications of toluene effects on performance, nor was there any correlation between symptom frequencies and performance levels. The only difference found between the two groups was a higher frequency of symptoms of local irritation in the group which had reported high symptom frequencies on the questionnaire.

Iregren, A., M. Tesarz, et al. (1993). "Human experimental MIBK exposure: effects on heart rate, performance, and symptoms." Environ Res **63**(1): 101-108.

Heart rate, performance, and symptoms were studied in six female and six male volunteers, aged 19 to 47 years, during experimental 2-hr exposures to 10 and to 200 mg/m3 of methyl isobutyl ketone (MIBK). No effects from exposure on performance of a reaction time task or an arithmetic test could be demonstrated,

and no consistent effects on heart rate were found. Subjects reported significantly more symptoms from the central nervous system, e.g., fatigue, due to the exposure. There was also an indication of an increase in ratings of irritation to the airways. A reduction of the threshold limit value (TLV) of 205 mg/m3 for MIBK exposure presently indicated by the American Conference of Governmental Industrial Hygienists, is therefore recommended.

Jahr, J. (1974). "Dose-response basis for settling a quartz threshold limit value: a new, simple formula for calculating the "lifetime dose" of quartz." Arch Environ Health **29**(6): 338-340.

Jankovic, J. and F. Drake (1996). "A screening method for occupational reproductive health risk." Am Ind Hyg Assoc J **57**(7): 641-649.

Most currently recognized occupational exposure limits do not consider reproductive toxicological end points consistently when establishing recommended exposure limits. In many cases the information is not available, but perhaps as often, existing data is not employed. Further, many manufacturer's material safety data sheets omit reproductive hazard information. A method for identifying potential reproductive toxins and screening levels for associated health risks useful for hazard communication and exposure control is presented. To date, the Registry of Toxic Effects of Chemical Substances lists between 5000 and 6000 chemicals, drugs, and natural substances that show a positive outcome in at least 1 reproductive effects study. This reproductive health risk assessment began with these substances. Using elements of the Environmental Protection Agency's health risk assessment process, the list was reduced to 213 chemicals during the hazard identification step. Occupational reproductive guidelines (ORGs) were developed in the dose-response evaluation step. At the time of this writing, 85% of the chemicals identified in the hazard identification step have had a screening level dose-response assessment completed. Of these, 13% are greater than or equal to a threshold limit value (TLV). The remaining 87% do not have a TLV or ORGs below the TLV. The reproductive toxins list, along with the corresponding dose-response-derived ORGs that have been completed, appears at the end of the text.

Jardine, C., S. Hrudey, et al. (2003). "Risk management frameworks for human health and environmental risks." J Toxicol Environ Health B Crit Rev **6**(6): 569-720.

A comprehensive analytical review of the risk assessment, risk management, and risk communication approaches currently being undertaken by key national, provincial/state, territorial, and international agencies was conducted. The information acquired for review was used to identify the differences, commonalities, strengths, and weaknesses among the various approaches, and to identify elements that should be included in an effective, current, and comprehensive approach applicable to environmental, human health and occupational health risks. More than 80 agencies, organizations, and advisory councils, encompassing more than 100 risk documents, were examined during

the period from February 2000 until November 2002. An overview was made of the most important general frameworks for risk assessment, risk management, and risk communication for human health and ecological risk, and for occupational health risk. In addition, frameworks for specific applications were reviewed and summarized, including those for (1)contaminated sites; (2) northern contaminants; (3) priority substances; (4) standards development; (5) food safety; (6) medical devices; (7) prescription drug use; (8) emergency response; (9) transportation; (10) risk communication. Twelve frameworks were selected for more extensive review on the basis of representation of the areas of human health, ecological, and occupational health risk; relevance to Canadian risk management needs; representation of comprehensive and well-defined approaches; generalizability with their risk areas; representation of "state of the art" in Canada, the United States, and/or internationally; and extent of usage of potential usage within Canada. These 12 frameworks were: 1. Framework for Environmental Health Risk Management (US Presidential/Congressional Commission on Risk Assessment and Risk Management, 1997). 2. Health Risk Determination: The Challenge of Health Protection (Health and Welfare Canada, 1990). 3. Health Canada Decision-Making Framework for Identifying, Assessing and Managing Health Risks (Health Canada, 2000). 4. Canadian Environmental Protection Act: Human Health Risk Assessment of Priority Substances(Health Canada, 1994). 5. CSA-Q8550 Risk Management: Guidelines for Decision-Makers (Canada Standards Association, 1997). 6. Risk Assessment in the Federal Government: Managing the Process (US National Research Council, 1983). 7. Understanding Risk: Informing Decisions in a Democratic Society (US National Research Council, 1996). 8. Environmental Health Risk Assessment (enHealth Council of Australia, 2002). 9. A Framework for Ecological Risk Assessment (CCME, 1996). 10. Ecological Risk Assessments of Priority Substances Under the Canadian Environmental Protection Act (Environment Canada, 1996).11. Guidelines for Ecological Risk Assessment (US EPA, 1998b). 12. Proposed Model for Occupational Health Risk Assessment and Management (Rampal & Sadhra, 1999). Based on the extensive review of these frameworks, seven key elements that should be included in a comprehensive framework for human health, ecological, and occupational risk assessment and management were identified: 1. Problem formulation stage. 2. Stakeholder involvement. 3. Communication. 4. Quantitative risk assessment components. 5. Iteration and evaluation. 6. Informed decision making. 7. Flexibility. On the basis of this overarching approach to risk management, the following "checklist" to ensure a good risk management decision is proposed: - Make sure you're solving the right problem. - Consider the problem and the risk within the full context of the situation, using a broad perspective. - Acknowledge, incorporate, and balance the multiple dimensions of risk. - Ensure the highest degree of reliability for all components of the risk management process. - Involve interested and effected parties from the outset of the process. - Commit to honest and open communication between all parties. - Employ continuous evaluation throughout the process (formative, process, and outcome evaluation), and be prepared to

change the decision if new information becomes available. Comprehensive and sound principles are critical to providing structure and integrity to risk management frameworks. Guiding principles are intended to provide an ethical grounding for considering the many factors involved in risk management decision making. Ten principles are proposed to guide risk management decision making. The first four principles were adapted and modified from Hattis (1996) along with the addition of two more principles by Hrudey (2000). These have been supplemented by another four principles to make the 10 presented. The principles are based in fundamental ethical principles and values. These principles are intended to be aspirational rather than prescriptive--their application requires flexibility and practical judgement. Risk management is inherently a process in search of balance among competing interests and concerns. Each risk management decision will be "balancing act" of competing priorities, and trade-offs may sometimes have to be made between seemingly conflicting principles. The 10 decision-making principles, with the corresponding ethical principle in italics are: 1. Do more good than harm (beneficence, nonmalificence).- The ultimate goal of good risk management is to prevent or minimize risk, or to "do good" as much as possible. 2. Fair process of decision making (fairness, natural justice). - Risk management must be just, equitable, impartial, unbiased, dispassionate, and objective as far as possible given the circumstances of each situation. 3. Ensure an equitable distribution of risk (equity). - An equitable process of risk management would ensure fair outcomes and equal treatment of all concerned through an equal distribution of benefits and burdens (includes the concept of distributive justice, i.e., equal opportunities for all individuals). 4. Seek optimal use of limited risk management resources (utility). - Optimal risk management demands using limited resources where they will achieve the most risk reduction of overall benefit. 5. Promise no more risk management that can be delivered (honesty).- Unrealistic expectations of risk management can be avoided with honest and candid public accounting of what we know and don't know, and what we can and can't do using risk assessment and risk management. 6. Impose no more risk that you would tolerate yourself (the Golden Rule). - The Golden Rule is important in risk management because it forces decision makers to abandon complete detachment from their decisions so they may understand the perspectives of those affected. 7. Be cautious in the face of uncertainty ("better safe than sorry"). - Risk management must adopt a cautious approach when faced with a potentially serous risk, even if the evidence is uncertain. 8. Foster informed risk decision making for all stakeholders (autonomy). - Fostering autonomous decision making involves both providing people with the opportunity to participate, and full and honest disclosure of all the information required for informed decisions. 9. Risk management processes must be flexible and evolutionary to be open to new knowledge and understanding (evolution, evaluation, iterative process). - The incorporation of new evidence requires that risk management be a flexible, evolutionary, and iterative process, and that evaluation is employed at the beginning and througthout the process. 10. the complete elimination fo risk is not possible (life is not risk free).- Risk is

pervasive in our society, and cannot be totally eliminated despite an oft-expressed public desire for "zero risk". However, the level of risk that may ve tolerable by any individual is dependent on values of beliefs, as well as scientific information. Each agency must continue to employ a process that meets the needs of their specific application of risk management. A single approach cannot satisfy the diverse areas to which risk decisions are being applied. However, with increasing experience in the application of the approaches, we are evolving to a common understanding of the essential elements and principles required for successful risk assessment, risk management, and risk communication. Risk management will continue to be a balancing act of competing priorities and needs. Flexibility and good judgement are ultimately the key to successfully making appropriate risk decisions.

Jayjock, M. A. and P. G. Lewis (2002). "Implications of hormesis for industrial hygiene." Hum Exp Toxicol **21**(7): 385-389.

This paper considers hormesis as a valid and potentially valuable alternative hypothesis for low-dose response in the context of occupational health risk assessment. It outlines the current occupational risk assessment paradigm and its use of high-dose toxicological data in setting occupational exposure limits (OELs). This present effort is a call to science to investigate the potential promise of hormesis in providing prima facie experimental evidence for a low-dose threshold of toxic effect to chemical agents. The scientific effort and advancement advised in this piece could also lead to experimentally validated quantitative estimates of the toxic effect extant at occupational exposures in the region of the OEL.

Jayjock, M. A. and P. G. Lewis (2002). "Jayjock and Lewis reply." Hum Exp Toxicol **21**(7): 407-408.

The current state-of-the-science, in our opinion, is incapable of accurately predicting the human health risk at environmental exposures to chemicals. We believe that dose-response models represent an integral part of the scientific method but that all models require valid scientific data in the realm of actual exposure in order to be derived and function properly. Given this current state, the evidence to date and the promise of hormesis to provide a detectable signal at low-dose, we view it as a variable and valuable hypothesis worthy of significant scientific effort.

Jayjock, M. A., P. G. Lewis, et al. (2001). "Quantitative level of protection offered to workers by ACGIH threshold limit values occupational exposure limits." AIHAJ **62**: 4-11.

Kane, L. E., C. S. Barrow, et al. (1979). "A short-term test to predict acceptable levels of exposure to airborne sensory irritants." Am Ind Hyg Assoc J **40**(3): 207-229.

An animal model has been developed using decrease in respiratory rate in mice as an index of sensory irritation. Concentration-response relationships were developed for 11 sensory irritants. The RD50, defined as the concentration

associated with a 50% decrease in respiratory rate, has been shown to have a predictable relationship to sensory irritation in man. By extending the accepted toxicological principle that the ratio lethal/toxic/effective/ineffective/acceptable in diet is 10/1/10(-1)/10(-2)/10(-3) dosage units to air concentrations, exposure guidelines can be proposed for TLVs, STELs, etc.

Kaneko, T., P. Y. Wang, et al. (1998). "Development of occupational exposure limits in Japan." Int J Occup Med Environ Health **11**(1): 81-98.

The development of occupational exposure limits (OELs) in Japan is discussed by describing the OELs of two chemical compounds, benzene and trichloroethylene, as typical examples. As for benzene, sufficient epidemiological evidence has accumulated indicating that benzene is a human carcinogen. To establish the OEL for benzene, the OEL committee of the Japan Society for Occupational Health (JSOH) selected 9 cases of acute myeloic or monocytic leukemia out of the 14 cases of leukemia in the Pliofilm cohort, adopted the exposure estimate of Paustenbach et al. (52), and calculated the risk of benzene-induced leukemia by means of an average relative risk model. The lifetime risk of leukemia by exposure to benzene at 1 ppm for 40 years was calculated as 0.762 x 10(-3) with a 95% confidence interval between 0.621 x 10(-3) and 0.98.10(-3). The benzene level that causes one lifetime excess death from leukemia among 1,000 workers exposed to benzene for 40 years was 1.31 ppm, with a 95% confidence interval between 1.01 and 1.61 ppm. The OEL committee decided that benzene exposure should be controlled by a reference value corresponding to a lifetime risk (10(-3) or 10(-4)) of leukemia rather than by a time-weighted average (TWA) concentration. The committee has proposed that the benzene exposure level corresponding to the lifetime risk of 10(-3) is 1 ppm and that corresponding to the risk of 10(-4) is 0.1 ppm. In 1995, the International Agency for Research on Cancer (IARC) changed the carcinogenicity classification of trichloroethylene from Group 3 (not classifiable as to carcinogenicity to humans) to Group 2A (probably carcinogenic to humans). The OEL committee of the JSOH, however, reached the conclusion that since it has not been confirmed that trichloroethylene is a human carcinogen, and since carcinogenicity, if any, may be based on an epigenetic rather than genotoxic mechanism, it is not appropriate to establish the OEL of trichloroethylene presupposing that trichloroethylene is a carcinogen. The judgment of the OEL committee is that the OEL for trichloroethylene should be established on other than carcinogenicity findings, particularly on the basis of its neurological effects. In the light of accumulated evidence that a long-term exposure to trichloroethylene at 50 ppm will cause neurotoxic effects to industrial workers, the OEL committee has proposed 25 ppm (135 mg/m3) as a reference value for work environments. Finally, we propose that the general environmental air standards of benzene and trichloroethylene should be about 1/1,000 of the respective reference values for work environment.

Kasanen, J. P., A. L. Pasanen, et al. (1999). "Evaluation of sensory irritation of delta3-carene and turpentine, and acceptable levels of monoterpenes in occupational and indoor environment." J Toxicol Environ Health A **57**(2): 89-114.

The standard mouse bioassay was used for obtaining the RD50 (i.e., the concentration that causes a 50% decrease in respiratory frequency) and for estimating the irritation properties of d-delta3-carene (i.e., (+)-delta3-carene) and commercial turpentine. The chemicals studied possess mainly sensory irritation properties similar to the previously studied monoterpenes, pinenes. The irritation potency of d-delta3-carene (RD50 = 1345 ppm) was almost equal to that of d-pinenes. Thus, d-delta3-carene was about four times more potent as a sensory irritant than l-beta-pinene, whereas the difference with l-alpha-pinene was more marked; as a sensory irritant, l-alpha-pinene is almost inactive. Based on sensory irritation potency and physicochemical and structural properties of pinenes and delta3-carene, the potency of a closely related monoterpene, limonene, is discussed. For commercial turpentine, a mixture of monoterpenes (mainly d-delta3-carene, l-beta-pinene, alpha-pinenes, and limonenes), the RD50 (1173 ppm) was the same order of magnitude as those of d-pinenes and d-delta3-carene. Apparently, d-monoterpenes are responsible for the sensory irritation caused by turpentine. In the wood industry and in the indoor air of nonindustrial environments, monoterpenes are thought to be one of the causative agents for irritation symptoms. The occupational exposure limit (OEL) of turpentine (100 ppm in Finland and the United States) is also used for individual monoterpenes, excluding limonene. Using results from this and our previous study, proposed OELs and recommended indoor levels (RILs) for selected monoterpenes and turpentine were determined based on their RD50 values. According to our studies, the present OEL of turpentine (100 ppm; 560 mg/m3) in Finland and in the United States seems to be suitable only for l-pinenes. For d-monoterpenes and turpentine, an OEL about three times lower is suggested. Our results show that recommended indoor levels (RILs) for monoterpenes are high compared to the concentrations measured indoors in nonindustrial environments. Thus, it is very unlikely that monoterpenes alone can cause irritation symptoms in homes or offices under normal conditions.

Kayama, F., K. Murata, et al. (2003). "Recommendation of occupational exposure limits (2003-2004)." J Occup Health **45**(4): 254-269.

Kendal-Reed, M. (2001). "Approaches to understanding chemosensory responses: new directions and new caveats." Aihaj **62**(6): 717-722.

This article describes recent research on sensory irritants that should prove helpful to setting occupational exposure limits (OELs) for this class of chemicals. In addition, background information is provided to assist in recognizing the relevance and importance of this type of work. Research conducted by Dr. Steven Youngentob and others addresses the recovery of olfactory function following exposure to high concentrations of sensory irritants. Their research has combined several different experimental methods to gain insight on how olfactory

receptor neurons (ORNs) are replaced. Other important work relevant to setting OELs has been conducted by Professor Gerd Kobal, who has relied on human brain imaging during chemosensory stimulation. Commentary on these two approaches is followed by suggestions on how to address the relative lack of detailed normative information on human responses to odors and irritants.

Kendal-Reed, M., J. C. Walker, et al. (2001). "Investigating sources of response variability and neural mediation in human nasal irritation." Indoor Air **11**(3): 185-191.

A major component of indoor air complaints is nasal irritation (NI), yet there is an extreme paucity of quantitative concentration-response data from normosmics (individuals who report normal odor sensation). Due to an assumption that NI is mediated solely by the activation of the trigeminal (fifth cranial) nerve, much of the small amount of available information has been obtained from anosmic individuals, who lack olfactory (first cranial) nerve input to the brain and, thus, only have nasal trigeminal input remaining. In a repeated measurements design, the NI responses of 31 normosmic and four anosmic individuals were quantified in response to a range of concentrations of propionic acid generated by an automated air-dilution olfactometer. A variance analysis approach was used to apportion different nested sources of variation (within-session, within-individual, inter-individual) in NI responses. In contrast to anosmic NI and normosmic odor performance, NI response by normosmics exhibited considerable variation at all three levels. However, this variation did not obscure the observation that, in agreement with electrocortical measurements by Hummel et al. (1996), NI sensitivity in normosmics clearly exceeded that of anosmics. These observations provide support for enhanced research efforts to better understand the neural basis of NI so that its occurrence in actual environments may be effectively minimized.

Kilburn, K. H. (2000). "Chlorine-induced damage documented by neurophysiological, neuropsychological, and pulmonary testing." Arch Environ Health **55**(1): 31-37.

Chlorine causes acute pulmonary edema and damages airways, thus producing obliterative bronchiolitis. In the case series in this study, its adverse effects were extended to visual and central nervous system impairment. Twenty-two patients exposed briefly to undiluted chlorine at home or work were evaluated with a battery of neurobehavioral and visual tests. Their test scores, expressed as percentage predicted, were compared with those of unexposed subjects. Chlorine-exposed subjects had impaired balance (with eyes open and eyes closed), delayed simple and choice reaction times, impaired color discrimination, impaired visual field performance, decreased hearing, and decreased grip strength. Blink reflex latency was delayed on the right. Cognitive performance (i.e., digit symbol and vocabulary), peg placement, trail making A and B, and verbal recall were significantly below predicted levels. Well-learned memory functions were not impaired. Adverse mood states scores were elevated as were the frequencies of 28 of 35 common symptoms. Forced vital capacities were reduced. The duration of chlorine exposures was from a breath or two to several

hours, and exposures were associated with impaired neurophysiologic and neuropsychologic functions. Impairments appeared insidiously, were noted 1 to 48 mo after exposure, and persisted. Such functional losses must be prevented. Additional chlorine-exposed patients should be evaluated for neurological and pulmonary damage.

Kim, Y. C. and G. P. Carlson (1986). "The effect of an unusual workshift on chemical toxicity. I. Studies on the exposure of rats and mice to dichloromethane." Fundam Appl Toxicol **6**(1): 162-171.

The 10- or 12-hr workday has become increasingly popular in industry. Current occupational exposure limits are designed to protect workers on the standard 8-hr/day workshift and are not intended for use for longer workshifts. Experiments were conducted to compare the effects of a 12-hr exposure schedule to those of an 8-hr schedule on the carboxyhemoglobin (COHb) formation resulting from dichloromethane (DCM) inhalation. Rats and mice were exposed to 200, 500, or 1000 ppm DCM for 8 hr/day for 5 days or 12 hr/day for 4 days. The effect of the unusual exposure schedule on COHb levels was not significant. The metabolic pathway for the formation of COHb appeared to be saturated even at the lowest concentration of DCM. To examine the possible increase in the retention of inhaled DCM in the longer exposure schedule, single exposures for 8 and 12 hr were compared. The peak blood DCM level was dependent upon the DCM exposure concentration, but the half-life was independent of the duration of exposure and the concentration of DCM. The half-life of COHb in blood was prolonged by increasing the DCM concentration, but was not affected by the exposure period. Pyrazole treatment decreased COHb level and increased blood DCM level in rats exposed to DCM. These results suggest that the exposure limit for a chemical with a short biological half-life and readily reversible toxic effect may not need to be adjusted for a longer workshift which is in agreement with some of the mathematical models based upon the pharmacokinetics of a toxicant.

Kjaergaard, S., O. F. Pedersen, et al. (1992). "Sensitivity of the eyes to airborne irritant stimuli: influence of individual characteristics." Arch Environ Health **47**(1): 45-50.

The purpose of this study was to measure trigeminal sensitivity of the eyes to irritative exposures and to examine the influence of individual characteristics, e.g., gender, age, and smoking, on this sensitivity. During an experimental study, 158 of 2,025 randomly selected volunteers were examined for sensory irritation threshold in the eyes to carbon dioxide (CO2). Eyes were exposed to progressive concentrations of CO2 (10, 20, 40, 80, and 160 ml/l), until the subject claimed a distinct irritation. Each exposure level lasted 2 min. A special exposure mask system was used for eyes-only exposure. No significant dependence of gender or smoking was found, but subjects who were less than 40 y of age were more sensitive than were the elderly subjects. Subjects who reported frequent "sick building syndrome" irritation symptoms had lower thresholds (i.e., higher sensitivity). The CO2 threshold was related to skin irritation sensitivity, i.e.,

response to lactic acid smeared on the cheek, and there were indications that occupational stress was associated with low thresholds. Studies of irritation to n-decane indicate that the CO2 threshold may be an important factor in the prediction of individual sensitivity to irritation from airborne pollutants. The CO2 threshold of the eyes may be of value in the evaluation of hypersensitivity to indoor air pollution. Furthermore, the threshold may be used to assess important relationships between the different trigeminal innervated areas, e.g., skin and eyes. Finally, the method has the advantage of avoiding interference from olfactory stimulation.

Kjaergaard, S. K. and M. Hodgson (2001). "The assessment of irritation using clinical methods and questionnaires." Aihaj **62**(6): 711-716.

Sensory irritant responses to chemical exposures are measured by a variety of methods; however, studies can be influenced from biases associated with study design and subject responses. This article reviews the different methods used to quantitate irritation. These methods primarily focus on eye and nasal mucosal irritation. Although methods to evaluate mouth, throat mucosal, and dermal irritation are also relevant, they are seldom used in actual practice. Measurements for eye irritation include tear film stability, epithelial damage, foam formation, blinking frequency, tear flow, inflammation, and hyperemia. Methods for detecting nasal mucosa irritation include measuring swelling of the nasal mucosa, peak airflows through the nose, acoustic rhinometry, and rhinostereometry, which measures thickness of the anterior nasal turbinate. Questionnaires are useful for defining a set of symptoms in an attempt to characterize dose-response relationships from controlled exposure studies or field studies, to compare rates of events in field studies, or to screen for disease. However, it is important to consider carefully the study design, goal of utilization, and constraints surrounding their application. Whichever method is used in medical surveillance or to evaluate effectiveness of industrial hygiene or engineering controls in preventing irritation effects from chemical exposure, the sensitivity, specificity, and predictive value of the irritation measurements are important factors in interpreting the results. This article reviews these various issues and offers some advice.

Klimek, L., I. Hundorf, et al. (2002). "Assessment of rhinological parameters for evaluating the effects of airborne irritants to the nasal epithelium." Int Arch Occup Environ Health **75**(5): 291-297.

OBJECTIVES: The initial contact area of inhaled toxins with the human body is the nasal mucosa. Upon irritation, nasal symptoms may occur that are well known as common viral infections of the airway and thus neglected by patients and physicians. Therefore, objective methods should be used to determine even minor irritative or inflammatory changes. METHODS: Objective methods to assess changes in the nasal epithelium include endoscopy, rhinomanometry, acoustic rhinometry, anemometry, thermometry, laser Doppler flowmetry, measurements of mucociliary transport time and ciliary beat frequency, analysis

of nasal secretions, nasal cytology, and subjective (UPSIT, CCCRC, Sniffin Sticks) and objective (electro-olfactogram, olfactory event related potentials) and olfaction tests. RESULTS: Several different inhaled irritative and toxic substances, including metal dusts and steam, volatile organic substances, and inorganic gases, may harm the nasal epithelium. CONCLUSIONS: The objective evaluation of nasal functions should be used to assess effects of airborne irritants. For patients complaining of toxic effects, early diagnosis is important in the prevention of severe damage to the upper and lower airways.

Knasko, S. C. (1993). "Performance, mood, and health during exposure to intermittent odors." Arch Environ Health **48**(5): 305-308.

The effects of intermittent bursts of pleasant, unpleasant, and no experimental odor on human task performance, mood, and perceived health were tested in this study. Odors did not influence any of these measures; however, subjects who had been exposed to the malodors reported retrospectively that they thought the odors had a negative effect on all of these factors. These findings have implications for the methodological design and interpretation of air quality studies.

Kok, P. W. and C. N. Ong (1994). "Blood and urinary benzene determined by headspace gas chromatography with photoionization detection: application in biological monitoring of low-level nonoccupational exposure." Int Arch Occup Environ Health **66**(3): 195-201.

A simple and sensitive gas chromatography (GC) headspace method was developed for the determination of benzene in blood and urine. 1.0 ml of venous blood or urine sample in a headspace vial containing chlorobenzene as an internal standard was incubated at 60 degrees C for 30 min and 0.5 ml headspace gas was used for GC analysis. Unmetabolized benzene in blood or urine was detected at 2.5 min using a silicone gum capillary column and a photoionization detector. The proposed method appears to be more sensitive and reliable than other existing methods, with recovery and reproducibility generally over 90% and a detection limit of 0.64 and 0.51 nmol/l for blood and urinary benzene, respectively. The proposed method was validated with blood and urine samples collected from 25 nonsmokers and 50 smokers. The blood and urine concentrations of benzene in nonsmokers were significantly lower ($P < 0.001$) than those in smokers: the mean concentrations for blood and urinary benzene, respectively, were 1.42 and 4.21 nmol/l for nonsmokers and 1.49 and 5.19 nmol/l for smokers. A significant correlation ($r = 0.61$, $P < 0.001$) was also found between benzene in blood and benzene in urine. These findings suggest that benzene in urine as well as benzene in blood can be used for the biological monitoring of low levels of benzene exposure. Although there was a close correlation between benzene in blood and benzene in urine, no correlation was found between benzene in blood or benzene in urine and the number of cigarettes smoked.

Kramer Alkalde, T., M. do Carmo Ruaro Peralba, et al. (2004). "Quantitative analysis of benzene, toluene, and xylenes in urine by means of headspace solid-phase microextraction." J Chromatogr A **1027**(1-2): 37-40.

A simple method for benzene, toluene, and xylenes (BTX) quantitative analyses in human urine was developed, using headspace solid-phase microextraction (HS-SPME) and gas chromatography coupled to mass spectrometry detection in the single ion monitoring mode. The developed method is solventless, non-invasive, requires small volume of sample (1 ml), shows high selectivity, sensitivity, repeatability, and linearity (correlation coefficients >0.998), providing a useful alternative to assess human exposure to BTX compounds due to occupational reasons or eventual exposure to organic solvents. Detection limit varies from 0.28 to 0.5 ppb (v/v).

Krewski, D., K. Bakshi, et al. (2004). "Development of acute exposure guideline levels for airborne exposures to hazardous substances." Regul Toxicol Pharmacol **39**(2): 184-201.

Hazardous substances can be released into the atmosphere due to industrial and transportation accidents, fires, tornadoes, earthquakes, and terrorists, thereby exposing workers and the nearby public to potential adverse health effects. Various enforceable guidelines have been set by regulatory agencies for worker and ambient air quality. However, these exposure levels generally are not applicable to rare lifetime acute exposures, which possibly could occur at high concentrations. Acute exposure guideline levels (AEGLs) provide estimates of concentrations for airborne exposures for an array of short durations that possibly could cause mild (AEGL-1), severe, irreversible, potentially disabling adverse health effects (AEGL-2), or life threatening effects (AEGL-3). These levels can be useful for emergency responders and planners in reducing or eliminating potential risks to the public. Procedures and methodologies for deriving AEGLs are reviewed in this paper that have been developed in the United States, with direct input from international representatives of OECD member-countries, by the National Advisory Committee for Acute Exposure Guidelines for Hazardous Substances and reviewed by the National Research Council. Techniques are discussed for the extrapolation of effects across different exposure durations. AEGLs provide a viable approach for assisting in the prevention, planning, and response to acute airborne exposures to toxic agents.

Kristiansen, E. (1984). "Nordic Expert Group for Documentation of Occupational Exposure Limits - 51. Phenol." **171**(84).

Kristiansen, U., L. Hansen, et al. (1986). "Sensory irritation and pulmonary irritation of cumene and n-propanol: mechanisms of receptor activation and desensitization." Acta Pharmacol Toxicol (Copenh) **59**(1): 60-72.

Cumene and n-propanol, model substances for alcohols and alkylbenzenes, were investigated for sensory irritation in mice. The concentrations within the first

2 min. depressing the respiratory rate by 50% due to the effect in the upper respiratory tract were 2,058 p.p.m. and 22,080 p.p.m., respectively. Activation of the sensory irritant receptor followed the dynamics of reversible bimolecular reactions. The extrapolated maximum response and the apparent dissociation constant were 114.3% and 2,723 p.p.m. for cumene and 68.4% and 8,178 p.p.m. for propanol, respectively. Later on desensitization was observed. The effect was weak for cumene but conspicuous for propanol. For cumene desensitization had the origin in the rise of a threshold. No change in the dissociation constant or the maximum response was found. For propanol a decrease in the maximum response, which may be explained by an allosteric effect, was observed. The pulmonary irritation response was weak for cumene but was for propanol more important than sensory irritation at high concentrations. The following hypotheses are put forward: the effect of pulmonary irritation on the tidal volume is mediated via the stretch receptors while the effect on the respiratory frequency is mediated via the J-receptors.

Krystofiak, S. P. and M. M. Schaper (1996). "Prediction of an occupational exposure limit for a mixture on the basis of its components: application to metalworking fluids." Am Ind Hyg Assoc J **57**(3): 239-244.

Using a previously developed mouse bioassay, a semisynthetic metalworking fluid (MWF "B") and its major components were evaluated. In mice MWF "B" and its components produced both sensory (S) and pulmonary (P) irritation. Using respiratory frequency (f) depression, concentration-response relationships were developed for each component as well as for MWF "B." From such relationships the concentration capable of evoking a 50% decrease in mean f was determined for each component and designated as RD50S if the decrease in f was due to sensory irritation, or RD50P if the decrease in f was due to pulmonary irritation. Based on RD50P values, the results indicated that the alkanolamides, potassium soap, sodium sulfonate, and triazine components were similar in irritation potency both to one another and to MWF "B." Through an examination of potency and fractional composition it was concluded that these five components largely contributed to the irritancy of MWF "B." From the RD50P values, occupational exposure limits that would protect workers from respiratory irritation were proposed for MWF "B" and each of its components. Using the approach of the American Conference of Governmental Industrial Hygienists for mixtures, an occupational exposure limit was calculated for MWF "B" employing the component data. The two limits for MWF "B" were similar to one another, suggesting that exposure limits for MWFs may be obtained through the evaluation of the fluids themselves or through evaluation of the components.

Kumagai, S., I. Matsunaga, et al. (1992). "[Assessment of occupational exposures to industrial hazardous substances. V. A proposed method for evaluating employee's exposure averages (8-h TWAs) using a single day measurement]." Sangyo Igaku **34**(1): 30-38.

Daily exposure averages (8-h TWAs) to hazardous substances may vary considerably day to day, even though a worker is engaged in the same job. Previously we proposed a method to evaluate a long-term exposure condition with interday fluctuation using some exposure measurements. As it is assumed that 8-h TWAs are log-normally distributed, geometric standard deviation (sigma g) representing true interday fluctuation of 8-h TWAs should be estimated. If a single day's 8-h TWA of a worker is measured, sigma g of his own distribution of 8-h TWAs cannot be estimated. Therefore, to evaluate a long-term condition using a single day's 8-h TWA, representative sigma g in all industrial workplaces must be determined beforehand. To investigate sigma g observed in many industrial workplaces, two days' 8-h TWAs of each worker were measured in a week on 260 workers exposed to 19 hazardous substances. Sg2 (geometric standard deviation estimated by two samples) ranged from 1.00 to 8.22 with a median of 1.47 and a 90% upper limit of 2.47. Transforming Sg2 into sigma g, median and 90% upper limit of sigma g were 1.75 and 2.47, respectively. According to a classification scheme in the proposed method, exposure levels (I to III) were calculated using sigma g of 1.75 and 2.47. A long-term exposure condition to hazardous substances can be evaluated by comparing a single day's 8-h TWA with the exposure levels.

Kumagai, S., I. Matsunaga, et al. (1989). "[Assessment of occupational exposures to industrial hazardous substances. III. On the frequency distribution of daily exposure averages (8-h TWA)]." Sangyo Igaku **31**(4): 216-226.

A method based on interday fluctuation of contaminant concentrations for evaluating employee's exposure averages (8-h TWAs) was proposed in our previous report. The method was established on the assumption that daily exposure averages of the workers are lognormally distributed in actual workplaces. The study was conducted to elucidate whether the distribution of daily exposure averages is statistically lognormal or not and to examine the relationship between sample geometric standard deviation (sg) of worker's daily exposure averages and its estimate (sg2) calculated by measurements for two consecutive days. These are critical for our proposed method. The data on daily exposure concentrations over five to six weeks were collected from workers exposed to cobalt, acetone, n-hexane, toluene, xylene, ethylbenzene and ethylacetate. The data on organic lead, inorganic lead and mercury exposures reported by Cope et al. and Lindstedt et al. were also used for the study. The result can be summarized as follows: 1. Lognormal distribution of daily exposure averages was confirmed by plotting on normal probability paper and chi 2-test. 2. Median of sg2 on daily exposure averages obtained from individual worker was smaller than sg. 3. sg calculated by a set of measurements for two consecutive days in every worker can be corrected by the equation: (sg2) 1.48 in obtaining a better estimate of sigma g. 4. Statistical analysis on daily exposure averages of all workers showed that median of sg2 was smaller than that of sg, and 88% upper limit of sg2 was equal to that of sg. 5. Therefore, in evaluating TWA obtained by only single day's measurement using the proposed method, median

of sg representative of industrial hazardous substance exposure workplaces could be also corrected by the equation described above. However, correction of 90% upper limit of sg2 is not necessary.

Kumagai, S., I. Matsunaga, et al. (1988). "[Assessment of occupational exposures to industrial hazardous substances. II. Interday fluctuations of the daily exposure averages among workers exposed to lead]." Sangyo Igaku **30**(3): 186-195.

An assessment of the employee's exposures to industrial hazardous substances using the proposed method described earlier was conducted on 49 workers exposed to lead. As it is assumed that the daily exposure averages are lognormally distributed, geometric standard deviation (sigma g) representing true interday fluctuations of the daily exposures was estimated by personal exposure measurements of every worker for two consecutive days. The estimates (Sg) ranged from 1.00 to 5.35 with a median of 1.4 and a 90% upper limit of 2.4. According to a classification scheme in the proposed method, exposure levels (I to III) were calculated using sigma g of 1.4 and 2.4. An exposure class based on a single day measurement was evaluated and compared to that based on measurements for two consecutive days. As a result, the decision of the exposure levels and classes from only one day monitoring could be made by using both sigma g of 1.4 and 2.4, representing ordinary and high interday fluctuations, respectively. More accurate estimate of geometric standard deviation of interday fluctuations by exposure monitorings would provide a more reliable assessment of the worker's long-term exposure situation.

Kumagai, S., I. Matsunaga, et al. (1998). "[A proposed method for evaluating short-term exposure condition]." Sangyo Eiseigaku Zasshi **40**(4): 113-120.

High short-term exposure to toxic chemicals can occur during a workday, even if the daily average exposure is lower than the permissible exposure limit, because the exposure concentration varies from minute to minute. To protect workers from acute health effects due to high short-term exposure, the Japan Society for Occupational Health recommends that the maximum value for 15-min time-weighted average (15-min TWA) exposure during a workday should not exceed 1.5 times the occupational exposure limit for 8-hr TWA, and the American Conference of Governmental Industrial Hygienists issues the threshold limit value-short-term exposure limit (TLV-STEL), that is a 15-min TWA exposure which should not be exceeded at any time during a workday. A workday (8 hr) consists of thirty two 15-min periods. If the thirty-two 15-min TWAs are measured, the short-term exposure situation can be appropriately evaluated by comparing the highest measured value with the standard value (e.g. TLV-STEL), but such continuous monitoring consumes a lot of cost and time. In this paper, we propose a method for evaluating short-term exposure by using three or more measured values. This evaluation method corresponds to two different types of selection of sampling periods. One is a random selection of three or more 15-min periods among the 32 periods. If this selection is adopted, a comparison between the 98.44 percentile of the within-day distribution of 15-min TWAs and the

standard value can be made by using one-sided tolerance factors, KI, KII and KIII, and the exposure situation is classified into four exposure classes at 95% and 50% confidence levels. Another is a random selection among high exposure periods. If this selection is adopted, a comparison between the specific percentile of the distribution and the standard value can be made with modified one-sided tolerance factors, and the exposure class is determined similarly. This method can provide a precise evaluation of exposure, so that it is useful in the industrial hygiene field.

Kumar, S. (2004). "Occupational exposure associated with reproductive dysfunction." J Occup Health **46**(1): 1-19.

Evidence suggestive of harmful effects of occupational exposure on the reproductive system and related outcomes has gradually accumulated in recent decades, and is further compounded by persistent environmental endocrine disruptive chemicals. These chemicals have been found to interfere with the function of the endocrine system, which is responsible for growth, sexual development and many other essential physiological functions. A number of occupations are being reported to be associated with reproductive dysfunction in males as well as in females. Generally, occupations involving the manufacture/or application of some of the persistent chemicals that are not easily degradable as well as bio-accumulative chemicals, occupations involving intensive exposure to heat and radiation, occupations involving the use of toxic solvents as well as toxic fumes are reported to be associated with reproductive dysfunction. Occupational exposure of males to various persistent chemicals have been reported to have male mediated adverse reproductive outcomes in the form of abortion, reduction in fertility etc. with inconclusive or limited evidence. Nevertheless, there is a need for more well designed studies in order to implicate any individual chemical having such effects as in most occupations workers are exposed to raw, intermediate and finished products and there are also several confounding factors associated with lifestyles responsible for reproductive dysfunction. There is an urgent need to look at indiscriminate use of persistent chemicals especially pesticides and persistent organic pollutants (POP's) as these chemicals enter the food chain also and could be potential for exposure during the critical period of development. It is also necessary to impart information, and to educate about the safe use of these chemicals, as a very sensitive reproduction issue is involved with exposure to these chemicals. Occupational exposures often are higher than environmental exposures, so that epidemiological studies should be conducted on these chemicals, on a priority basis, which are reported to have adverse effects on reproduction in the experimental system.

Kupczewska-Dobecka, M. and S. Czerczak (2004). "[Hygienic standards of the occupational air quality established by the Experts on Chemical Agents, 2002]." Med Pr **55**(1): 7-12.

In 2002, it was necessary to harmonize Polish law on admissible limits of occupational exposure with EU requirements. To this end, the Expert Group on Chemical Agents proposed maximum admissible concentration values for 29 chemicals: acrylaldehyde (107-02-8); cresols, mix of isomers (95-48-7), 108-39-4, 106-44-5, 1319-77-3); tetraphosphorus decaoxide (1314-56-3); ethylamine (75-04-7); naphtalene (91-20-3); nitrobenzene (98-95-3); nitrogen oxide (110-54-5); nitrogen dioxide (10102-44-0); pyridine (110-86-1); butan-2-one (78-93-3); carbon oxide (630-08-0); 1,4-dichlorobenzene (106-46-7); 1,2-dichlorobenzene (95-50-1); hexane (110-54-5); aluminum hydroxide (21645-51-2); aluminum (fumes and dusts) (7429-90-5); amitrole (61-82-5); 2,2-bis(4-hydroxyphenyl)propane (bisphenol A) (80-05-7); 3a,4,7,7a-terahydro-4,7-metanoindene (dicyclopentadiene) (77-73-6); trimethoxyphosphane (121-45-9); methyl chloroacetate (96-34-4); 4-methoxyphenol (150-76-5); methyl formate (107-31-3); 2-phenoxyethanol (122-99-6); divinylbenzene (1321-74-0); Diesel exhausts (-); hexane-6-lactam (dusts and fumes) (105-60-2); 2-isopropoxyethanol (109-59-1); and methyl 2-cyanoacrylate (137-05-3).

Lanska, D. J. (1999). "Limitations of occupational air contaminant standards, as exemplified by the neurotoxin N-hexane." J Public Health Policy **20**(4): 441-458.

Available industry guidelines and federal standards have failed to fully protect workers from chemical toxicity: none exist for most chemicals, many are biased toward what can easily be achieved, and many were developed long after health consequences became evident. Limitations of occupational air contaminant standards in the United States are well illustrated by standard-setting for the neurotoxin n-hexane. In the 1940s, the American Conference of Governmental Industrial Hygienists (ACGIH) first promulgated industrial guidelines known as "threshold limit values" (TLVs), including an 8-hour time-weighted average of 500 ppm for inspired n-hexane. Despite subsequent recognition of the neurotoxicity of n-hexane with industrial outbreaks of polyneuropathy beginning in the 1960s, the TLV for n-hexane remained unchanged until 1976 when a value of 100 ppm was adopted. Because a growing number of clinical reports have identified clinical and subclinical neurotoxicity from n-hexane near, at, and below the current time-weighted average TLV of 50 ppm, even this level is too high to protect all workers. In part due to procedural and political constraints, the Occupational Safety and Health Administration (OSHA) has independently developed only a small number of exposure standards in the past 25 years, and has been incapable of providing needed revisions for existing standards. Most OSHA standards--including those for n-hexane--were adopted in 1971 from the 1968 ACGIH TLVs and have never been revised. From 1971 to 1989 the OSHA permissible exposure level (PEL) for n-hexane remained at 500 ppm, 5-10 times as great as other contemporary standards. To help correct its regulatory backlong, OSHA promulgated 375 new or revised PELs in 1989--including a new standard of 50 ppm for n-hexane--but all of these were vacated by the 11th U.S. Court of Appeals in 1992. As a result, the current OSHA PEL for n-hexane remains at the 500 ppm level adopted in 1971, which even then was too high

based upon available scientific evidence. New information over this long period, including that obtained from industrial outbreaks of disease due to chemical exposures, has not been incorporated into revised federal standards.

Lawson, C. C., T. M. Schnorr, et al. (2003). "An occupational reproductive research agenda for the third millennium." Environ Health Perspect **111**(4): 584-592.

There is a significant public health concern about the potential effects of occupational exposure to toxic substances on reproductive outcomes. Several toxicants with reported reproductive and developmental effects are still in regular commercial or therapeutic use and thus present potential exposure to workers. Examples of these include heavy metals, organic solvents, pesticides and herbicides, and sterilants, anesthetic gases, and anticancer drugs used in health care. Many other substances are suspected of producing reproductive or developmental toxicity but lack sufficient data. Progress has been limited in identifying hazards and quantifying their potencies and in separating the contribution of these hazards from other etiologic factors. Identifying the causative agents, mechanisms by which they act, and any potential target populations, present the opportunity to intervene and protect the reproductive health of workers. The pace of laboratory studies to identify hazards and to underpin the biologic plausibility of effects in humans has not matched the pace at which new chemicals are introduced into commerce. Though many research challenges exist today, recent technologic and methodologic advances have been made that allow researchers to overcome some of these obstacles. The objective of this article is to recommend future directions in occupational reproductive health research. By bridging interdisciplinary gaps, the scientific community can work together to improve health and reduce adverse outcomes.

Lee, B. L., H. Y. Ong, et al. (2005). "A sensitive liquid chromatographic method for the spectrophotometric determination of urinary trans,trans-muconic acid." J Chromatogr B Analyt Technol Biomed Life Sci **818**(2): 277-283.

Benzene is a human carcinogen and its metabolite, urinary trans,trans-muconic acid (ttMA), is a biomarker for risk assessment. However, most of the existing methods were not sensitive enough for monitoring of low level exposure. This paper describes a HPLC-UV method for ttMA determination with enhanced selectivity and sensitivity. A 30 mg OasisMAX cartridge was used to clean-up 50 microl of urine sample and gradient elution was performed on a Zorbax SB-C(18) column (30 degrees C). ttMA was detected at wavelength 263 nm using a UV diode array detector (DAD). The two mobile phases used were (A) 150 mM ortho-phosphoric acid containing of 9% (v/v) methanol; and (B) 125 mM ortho-phosphoric acid containing 30% (v/v) acetonitrile. The method was validated with 61 urine samples collected from non-occupationally benzene exposed individuals and 14 quality control specimens from an international quality assessment scheme. The urinary ttMA concentrations (mean+/-S.D.microg/g creatinine) were 90+/-34 for smokers (n=26), 49+/-39 for non-smokers (n=21) and 23+/-18 for non-smoking hospital staff (n=14). A correlation coefficient, r=0.99 was found

with 14 external quality specimens for ttMA ranged from 0.4 to 6.8 mg/l. The recovery and reproducibility were generally over 90% and the detection limit was 5 microg/l.

Lee, L. Y. and J. G. Widdicombe (2001). "Modulation of airway sensitivity to inhaled irritants: role of inflammatory mediators." Environ Health Perspect **109 Suppl 4**: 585-589.

Bronchopulmonary C-fiber endings and rapidly adapting pulmonary receptors (RARs) are primarily responsible for eliciting the defense reflexes in protecting the lungs against inhaled irritants. In anesthetized animals, inhalation of cigarette smoke, one of the common inhaled irritants, into the lungs elicits pulmonary chemoreflexes that are mediated through the stimulation of pulmonary C fibers. When the C-fiber conduction is selectively blocked in the vagus nerves, the same smoke inhalation triggered only augmented breaths, a reflex effect of activating RARs, in the same animals. Indeed, electrophysiologic study shows that inhaled smoke exerts a direct stimulatory effect on both types of afferents. Increasing evidence indicates that the excitability of these afferents and therefore their reflex actions are enhanced by airway mucosal inflammation; one such example is the airway hyperresponsiveness induced by acute exposure to ozone. Although the mechanism underlying the inflammation-induced hypersensitivity of C-fiber endings is not fully understood, the possible involvement of local release of certain inflammatory mediators, such as histamine and prostaglandin E(2) (PGE(2), should be considered. It is believed that changes in the membrane properties mediated by the activation of certain specific receptor proteins located on the membrane of these nerve terminals are involved, as the sensitizing effects of PGE(2) can be also demonstrated in cultured pulmonary C neurons.

Lehnert, G. (1989). "[Occupational medicine limit values for hazardous materials in the Federal Republic of Germany]." Z Gesamte Hyg **35**(8): 477-480.

In all industrial countries ambient air quality guides for working materials are introduced serving the objective of protecting health in groups of workers, if exposure takes place solely or predominantly by way of inhaling noxious substances. Individually there may be, however, a lot of marginal conditions modifying atmospheric dose-response relationships. Therefore today in many countries biological monitoring became an additional approach in the prevention of occupational health risks. In this connection in the Federal Republic of Germany a second safety-barrier Biological Tolerance Values for Working Materials (BAT-values) were established. For carcinogenic substances, however, scientifically well founded health protection criteria cannot be established. But, from practical point of view, certain biological quality guides should be useful for carcinogenic substances too, especially for skin penetrating compounds. This was the background to establish Equivalents of Exposure for Carcinogenic Compounds, standing for correlations between the concentration of a carcinogen in the air of the workplace and the concentration of the agent or its metabolites in biological material, resulting from mere inhalation. Substance concentrations in

biological materials being higher than predicted from concentration in the air of the workplace are suspicious of an additional skin absorption. For risk assessment, from industrial-hygienic point of view, it is a good approach to quantify the exposure by air monitoring. From clinical point of view it is a better one to exclude adverse effects by biological monitoring. For prevention of health risks it is the best way to do both.

Lehnert, G. and K. H. Schaller (1995). "Strategy of biological monitoring and setting of biological threshold limits (BAT values) in Germany." Isr J Med Sci **31**(9): 549-557.

Biological monitoring is of fundamental importance in Germany. The successful strategy of biological monitoring is based on four factors. Recommendations for the pre-analytical phase have been issued by official societies. For the analyses in blood and urine specimens around 100 methods have been recommended and standardized. All measurements must be carried out under a quality control scheme issued by the German Ministry of Labor and organized by the German Society of Occupational and Environmental Medicine. The occupational medical judgement of the biological monitoring results take place by "Biological Tolerance Values for Working Materials" (BAT values) and "Exposure Equivalents for Carcinogenic Working Materials" (EKA values). A BAT value is, by definition, the maximum allowable concentration for an individual which should be exceeded; 53 BAT values for 37 agents or groups of agents and 18 EKA values for 10 compounds have been defined. These values have been published since 1982 in an annual list of occupational standards. Every BAT or EKA value is based on extensive scientific documentation.

Leung, H. W. (1992). "Use of physiologically based pharmacokinetic models to establish biological exposure indexes." Am Ind Hyg Assoc J **53**(6): 369-374.

This paper presents a simulation modeling approach to establish biological exposure indexes (BEIs) from ambient occupational exposure limits (OELs). A physiologically based pharmacokinetic (PB-PK) model was used to describe the disposition of volatile organic chemicals in the human. The model was used to simulate an exposure regimen similar to a typical work schedule. Exposure concentrations were set to equal the ambient OELs of the corresponding chemicals. Chemical concentrations in the expired air and blood and concentrations of metabolites in the urine were estimated with the PB-PK model for this exposure condition. Because the OELs establish the criteria for ambient exposure to chemicals, the concentrations of chemicals or their metabolites in biological media resulting from exposure to the OELs would likewise define acceptable exposure standards. On the basis of this rationale and method, BEIs were developed for 13 common industrial organic chemicals.

Leung, H. W., F. J. Murray, et al. (1988). "A proposed occupational exposure limit for 2,3,7,8-tetrachlorodibenzo-p-dioxin." Am Ind Hyg Assoc J **49**(9): 466-474.

One contaminant produced unintentionally during the manufacture of chlorophenols and phenoxy herbicides is 2,3,7,8-tetrachlorodibenzo-p-dioxin

(TCDD). The resulting TCDD-containing wastes have been detected at many hazardous waste sites which in recent years have been in the process of remediation. Concerns about worker exposure to TCDD-contaminated soil (dust) during remediation of hazardous waste sites have produced a need for an occupational exposure limit (OEL) for TCDD. The animal toxicology data and human experience with TCDD are reviewed, and an occupational exposure limit for TCDD is proposed. The animal data support risk estimations which are based on TCDD as a nongenotoxic carcinogen. Studies on human populations have failed to demonstrate clearly any significant long-term health effects at levels to which humans have been exposed. The data indicate that an 8-hr time-weighted average limit of 2 ng/m3 is appropriate, and the associated risk would be consistent with other carcinogens at their corresponding OELs. A preliminary OEL of 0.2 ng/m3 (200 pg/m3) is recommended, however, in light of other sources of exposure because of TCDD's ubiquitousness in the environment, its unclear mechanism of action, and its rather long biological half-life in humans. This limit provides an ample margin of safety to prevent chloracne following repeated, acute exposure, and it addresses those chronic effects of TCDD observed in animal studies as well as those observed after accidental human exposure. The resulting body burden caused by chronic exposure to TCDD at the proposed OEL is examined. Its toxicological significance is compared with human tissue data and with other similarly persistent chemicals.(ABSTRACT TRUNCATED AT 250 WORDS)

Leung, H. W. and D. J. Paustenbach (1988). "Application of pharmacokinetics to derive biological exposure indexes from threshold limit values." Am Ind Hyg Assoc J **49**(9): 445-450.

The importance of incorporating the fundamental concepts of pharmacokinetics into biological monitoring program that involve the collection of various body fluid and tissue specimens is discussed. The application of these principles to establish biological exposures indexes bioequivalent to airborne exposure limits is described. Specific illustrative examples involving acetone, aniline, benzene, carbon tetrachloride, dieldrin, ethylbenzene, hexane, lead, methylene chloride, pentachlorophenol, phenol, styrene, toluene and xylene are presented.

Leung, H. W. and D. J. Paustenbach (1990). "Organic acids and bases: review of toxicological studies." Am J Ind Med **18**(6): 717-735.

Organic acids and bases are among the most frequently used chemicals in the manufacturing industries. However, the toxicology of only a number of them has been fully characterized, and for fewer still have occupational exposure limits been established. This paper reviews the acute and chronic toxicity data of the organic acids and bases, and considers the mechanism by which these chemicals produce their effects. A methodology for establishing preliminary occupational exposure limits based on the physicochemical properties of these chemicals is presented. Workplace exposure limits for 20 organic acids and bases which currently have no exposure guidelines are suggested. Advice

regarding appropriate medical treatment of exposure to these materials is discussed.

Leung, H. W. and D. J. Paustenbach (1995). "Physiologically based pharmacokinetic and pharmacodynamic modeling in health risk assessment and characterization of hazardous substances." Toxicol Lett **79**(1-3): 55-65.

Recent advances in physiologically based pharmacokinetic and pharmacodynamic (PBPK/PD) modeling have introduced novel approaches for evaluating toxicological problems. Because PBPK models are amenable to extrapolation of tissue dosimetry, they are increasingly being applied to chemical risk assessment. A comprehensive listing of PBPK/PD models for environmental chemicals developed to date is referenced. Salient applications of PBPK/PD modeling to health risk assessments and characterization of hazardous substances are illustrated with examples.

Liang, Y. X., B. Q. Gang, et al. (1995). "The development of occupational exposure limits for chemical substances in China." Regul Toxicol Pharmacol **22**(2): 162-171.

This paper presents a comprehensive review of the occupational exposure limits (OELs) of chemical substances in China. It provides historical background on the development of OELs in this country, with a complete list of traditionally adopted and newly developed OELs for chemicals in workplaces. The philosophical thoughts, the administrative system, the scientific protocols for setting and amending health standards, with emphasis on making health a basic criterion for setting health standards, strengthening epidemiological studies of the human population, integrating epidemiological and toxicological studies, considering technological and economical feasibilities, and making full use of literature information sources are discussed. Further perspectives with respect to practical issues of maximum allowable concentration and time-weighted average, selection of safety factors, and establishment of biological exposure limits are also considered, with the authors' contributions to a discussion on these topics.

Liang, Y. X. and X. Q. Gu (1991). "The current status of hygiene standard setting for chemical substances in workplaces in China." Sci Total Environ **101**(1-2): 65-78.

The hygiene standard setting for occupational hazards was started in the mid 1950s in China. Three documents on exposure limits for chemical substances in the work environment and some other documents related to exposure limits for physical agents have been published since then. The latest documentation on "Hygiene Standards for the Design of Industrial Premises" (Standard TJ 36-79) was promulgated in 1979. It contains a MAC list of 134 toxin agents and dusts which are most frequently used and encountered in China. However, a more sophisticated system of scientific research on hygiene standard setting has been created since the establishment of the National Scientific Commission of Hygiene Standard Setting in 1980. This system emphasizes health as a basic criterion, it strengthens epidemiological study of the human population, it integrates domestic and international information sources and it periodically reappraises the

recommended standards. Based on these principles, more than forty new standards have been set for both chemicals and dusts since the founding of the committee. These new MACs are now in the process of being promulgated and are expected to take effect as the additional part of the MAC list published in 1979. In addition, further considerations of hygiene standard setting related to the conceptual renewal, selection of safety factor, legislation and enforcement of the hygiene standard, recommendations of exposure limits for occupational carcinogens, and speeding up the pace of hygiene standard setting are proposed in this paper.

Liang, Y. X., Z. Su, et al. (2003). "New trends in the development of occupational exposure limits for airborne chemicals in China." Regul Toxicol Pharmacol **38**(2): 112-123.

Occupational exposure limits (OELs) are well established in many countries, which serve occupational professionals as benchmarks of industrial hygiene practice at workplaces worldwide. Starting in the mid-1950s, the central government of China began promulgating OELs for hazardous substances at workplaces. This paper discusses the historical basis, philosophical principles and schematic protocols of developing and setting OELs in China. The underlying principles include: (1) protection of human health being the first and the most important criterion; (2) the use of quantitative epidemiological studies in humans being given top priority; (3) integration and full use of all information sources, including animal experimental data for new chemicals or chemicals with new toxicity concerns; (4) considerations of socioeconomic and technological feasibilities in the country; and (5) amending existing standards based on new evidence. The strategy of the World Health Organization's "Two-step Procedure" is applied to convert health-based recommendations to law-based operational OELs, with considerations for national technological and socioeconomic conditions and priorities. As a result of the recent passage of the new law Occupational Diseases Prevention and Control Act of the People's Republic of China (ODPCAct), an official document Occupational Exposure Limits for Hazardous Agents in the Workplace containing a comprehensive list of new and amended OELs has been issued, which has now become one of the most essential regulations affiliated with the ODPCAct. This paper provides a brief summary of the salient features of the new law ODPCAct and the principles and processes of developing or amending OELs. This paper also discusses the challenges that lie ahead in enforcing the new regulations in China.

Lippmann, M. (1987). "Criteria and standards for occupational exposures to airborne chemicals." Clin Podiatr Med Surg **4**(3): 619-628.

Prevention of occupational exposures to chemicals at levels that can cause illness or disease depends upon having exposure limits, methods for measuring exposures, and means for limiting exposures to levels within the established limits. The development and applications of exposure standards (that is, legal limits, and other guidelines used as professional practice criteria in the U.S. and

Europe) are reviewed and discussed. Biological exposure indices, which can be used to supplement direct measurements of exposures, are also discussed.

Livermore, A. and T. Hummel (2004). "The influence of training on chemosensory event-related potentials and interactions between the olfactory and trigeminal systems." Chem Senses **29**(1): 41-51.

It is not possible to accurately predict the perceptual response to odorants and odorant mixtures without understanding patterns of suppression and facilitation that result from interactions between the olfactory and trigeminal systems. The current study extends previous findings by exploring the effect of intensive training on the interaction between these systems and also by using a different mixed chemosensory stimulus to examine whether the principles established in earlier studies generalize to different odorants. Stimuli were chosen so as to selectively activate the olfactory (H2S) and trigeminal (CO2) nerves. In addition, linalool was included as a stimulus that activated both systems. Thirty-five participants (19 men, 16 women) rated the intensity of each stimulus when presented both alone and in binary mixtures (linalool + H2S, and linalool + CO2). Chemosensory event-related potentials were obtained from three recording positions. Analysis of intensity ratings showed that linalool was significantly less intense than the other stimuli when presented alone. In binary mixtures, H2S was strongly suppressed by linalool. One week of intensive odor training produced significant and specific reductions in the intensity of linalool and H2S, both alone and in their mixture. Training with a different odor (champignol) had no effect. Chemosensory event-related potential data confirmed previous findings showing changes in topographical distribution that reflected the degree of trigeminal activity. Binary mixtures generally produced larger amplitudes than single stimuli. Latencies clearly differentiated between the three single stimuli and the binary mixtures. Changes were observed in event-related potentials that reflected those obtained for intensity ratings in that they were observed for linalool and H2S in the linalool trained group only. The amplitude of the late 'endogenous' component (P3) was significantly decreased for these odors at frontal recording sites. In summary, strong and specific training effects were observed in intensity ratings for participants trained with the test odor (linalool), but not for those trained with a different odor. This was supported by a significant decrease of amplitudes of the event-related potentials at frontal recording sites following training with the test odor only

Ljungkvist, G., M. Larstad, et al. (1999). "Specific determination of benzene in urine using dynamic headspace and mass-selective detection." J Chromatogr B Biomed Sci Appl **721**(1): 39-46.

A method for the determination of benzene in urine was developed, based on dynamic headspace and preconcentration of the analyte on a solid sorbent. The subsequent analysis by thermal desorption of the sorbent, capillary gas chromatography and mass-selective detection ascertained a low limit of detection (6.5 ng/l) and a highly specific determination. The limit of detection is an order of

magnitude lower than that reported earlier and allows reliable quantitation of occupational exposure and of most environmental exposures. Samples could be stored frozen for at least a month without significant loss.

Ljungkvist, G., M. Larstad, et al. (2001). "Determination of low concentrations of benzene in urine using multi-dimensional gas chromatography." Analyst **126**(1): 41-45.

A method for the determination of benzene in urine of occupationally or environmentally exposed persons was developed. The method was based on dynamic headspace, preconcentration on a solid sorbent, followed by thermal desorption and gas chromatographic determination. To achieve sufficient selectivity, we used multi-dimensional gas chromatography in combination with the inexpensive and robust flame ionisation detector. The limit of detection was 7 ng l-1 and the limit of quantification was 23 ng l-1. The linearity was good (correlation coefficient 0.999) in the range examined (20-4000 ng l-1) and the repeatability was 9%. The average recovery at low concentrations (20-400 ng l-1) was 86%. Analysis of a certified reference material of benzene in water, traceable to NIST, did not differ significantly from the certified value. Samples, frozen (-20 degrees C) in glass bottles sealed with Teflon-silicon septa, were stable for 1 year and refrigerated samples (4 degrees C) for at least 1 week. Loss of benzene during the collection and transfer of urine was investigated and found to be acceptable. The method is a cost effective and robust alternative to GC-MS and permits reliable quantification of occupational exposure and, in most cases, also of urine concentrations that can be expected from environmental exposure.

Locke, J. (1986). "Fixing exposure limits for toxic chemicals in the UK--some case studies." Sci Total Environ **51**: 237-260.

The former Director of the Health and Safety Executive in Britain describes the process by which limits are fixed for exposure of workers to toxic chemicals. Four examples of the process are analysed in detail, examining the controls introduced since 1975 for asbestos, man-made mineral fibres, styrene, and MbOCA. The toxicity assessments available to the decision makers are summarised, as are also the estimates of the additional costs to industry of stricter limits, and the possible economic effects on production and jobs. The author then draws some general conclusions based on British experience since 1975. These include: that decision taking was possible on the basis of uncertainty about the precise effects on humans of particular levels of exposure; that the decisions could be seen to be sensibly related to the toxicity assessments; and that the precise limit fixed was dependent as much on the costs and practicability of tighter limits as on the nature of the health effects.

Loi, A. M., F. Mariotti, et al. (1997). "Oncogenic risk in a chemical plant: a methological approach and preliminary results." J Environ Pathol Toxicol Oncol **16**(2-3): 125-132.

One of the major problems that occupational medicine has to deal with is cancer risk assessment. Recent Italian legislation requires the evaluation of occupational exposure to carcinogens in all workplaces, but a standardized method to be used

in the environmental and biological criteria is generally lacking. The objective of this report is to identify a multidisciplinary approach to the research on this topic. The study is based on a chemical plant that produces pitch. The multidisciplinary approach is based on risk- and health-damage assessments. Ethical aspects are also taken into account, and the research design incorporates an informed consent for all employees. Some preliminary results are available. From the environmental point of view, all parameters provide an airborne concentration value below threshold limit values (TLVs), but biological monitoring demonstrates an increased urinary excretion of 1-OH-pyrene in all tested subjects. In conclusion, the first objective of our study is to demonstrate the carcinogenic risk of employees, searching for an agreement between environmental analysis, biological monitoring, and health effect data. A close collaboration between different professions is necessary.

Lundberg, P. (1991). "The Nordic Expert Group, an inter-Nordic project for assessment of occupational risks." Sci Total Environ **101**(1-2): 17-24.

Risk management and risk control within the occupational environment are individual national issues in the Nordic countries. Within the area of occupational exposure limit setting there is, however, some collaboration. As an internordic project the Nordic Expert Group for Documentation of Occupational Exposure Limits was started in 1977, in order to develop scientific criteria documents. The documents are used by the five national regulatory authorities as a common scientific basis for setting national occupational exposure limits. In risk management in the Nordic countries the Nordic Expert Group deals with the scientific issues and the regulatory authorities deal with the transscientific issues, taking economical aspects and technological feasibility into account. The setting of occupational exposure limits is thus an administrative (or political) concern and the limit values are norms rather than limits between hazardous and nonhazardous concentrations. The work by the Nordic Expert Group exemplifies the fact that the scientific part of risk management can be preferentially performed on an international basis.

Lushniak, B. D. (2004). "Occupational contact dermatitis." Dermatol Ther **17**(3): 272-277.

The dermatologist should be aware of the many facets of occupational skin diseases, which can be caused by physical, chemical, and biological insults. The most common manifestation of occupational skin diseases is contact dermatitis (both irritant and allergic). Three factors point out the importance of occupational skin diseases as diseases that have a public health impact: 1) occupational skin diseases are common; 2) they often have a poor prognosis; and 3) they result in a noteworthy economic impact for society and for an individual. They are also diseases amenable to public health interventions. Specific industries and exposures may put a worker at risk of occupational contact dermatitis. The accuracy of the diagnosis of occupational contact dermatitis is related to the skill level, experience, and knowledge of the medical professional who makes the

diagnosis and confirms the relationship with a workplace exposure. Prevention of occupational contact dermatitis is important, and a variety of prevention strategies are available.

Luxon, S. G. (1973). "Threshold limit values for environmental monitoring in hazard assessment and control." Ann Occup Hyg **16**(4): 345-348.

Lyles, R. H. and L. L. Kupper (1996). "On strategies for comparing occupational exposure data to limits." Am Ind Hyg Assoc J **57**(1): 6-15.
Parametric statistical approaches to assessing workplace exposure levels have typically focused either on the probability that a single measurement exceeds a limit or on whether the mean exposure for a population of workers exceeds a limit. This article reviews and clarifies some methods that have been proposed for each of these two approaches, on the assumption that the exposure data represent a random sample from a lognormal distribution. For tests concerning the mean exposure level, the authors developed a potentially useful new procedure based on a bound for noncentral t critical values. Appropriate sample size calculations are emphasized, and computer simulation is used to compare competing methods for assessing mean exposure. The authors conclude that the new proposed method offers an appealing alternative to existing methods in many cases. The importance of employing an exposure assessment strategy that is in concert with underlying etiologic considerations is stressed.

Maestri, L., S. Ghittori, et al. (1993). "[The measurement of a benzene metabolite, urinary S-phenylmercapturic acid (S-PMA), in man by HPLC]." Med Lav **84**(1): 55-65.
Benzene is a widely used solvent, currently present in the industrial environment at concentrations in the order of ppm. A valid method of biological monitoring that is easy to perform is needed for assessing occupational exposures. Benzene is metabolized in the body by microsomal cytochrome P-450 mono-oxygenase system into benzene epoxide. Benzene epoxide is metabolized along three different pathways which end in the excretion of trans, trans muconic acid, S-phenyl-mercapturic (S-PMA) and different phenols. A new method has been developed to evaluate urinary S-PMA of subjects exposed to benzene. Human urine is acidified with HCl to PH 1 and passed through a Sep-Pak C18 cartridge. The cartridges are washed with diluted HCl and a mixture of water/methanol/acetic acid and then eluted with acidified chloroform. The eluate is dried and reconstituted with a buffer phosphate, then passed through an anionic exchange cartridge (SAX) which is washed with diluted buffer and diluted HCl. S-PMA is recovered by eluting with concentrated buffer and is transformed into S-phenyl-cysteine. Finally, S-phenyl-cysteine is detected by HPLC connected with a fluorescence detector (wavelengths: excitation 330 nm, emission 440 nm) after derivatization with o-phthalaldehyde (OPA) and 2-mercapto-ethanol (MCE). The detection limit of the method is about 0.5 micrograms/l, the recovery of S-PMA is 90.0% and the variation coefficient is 3.8%. The method was checked on urine samples of 8 male non-smokers and 10

smokers: median values of 1.3 and 9.2 micrograms/g creatinine respectively of S-PMA were obtained. A further analysis on urine samples of 66 occupationally exposed workers (smokers and non-smokers) revealed a median value of S-PMA of 46.6 micrograms/g creatinine, compared with a median environmental benzene exposure of 1.99 mg/m3. These results suggest that S-PMA can be regarded in the future as a useful indicator for monitoring individual and collective low-level benzene exposure.

Maestri, L., S. Negri, et al. (2005). "Determination of urinary S-phenylmercapturic acid, a specific metabolite of benzene, by liquid chromatography/single quadrupole mass spectrometry." Rapid Commun Mass Spectrom **19**(9): 1139-1144.

A high-performance liquid chromatography/single quadrupole mass spectrometry (LC/MS) method is described for the determination of urinary S-phenylmercapturic acid (S-PMA), a specific metabolite of benzene. Urine samples were spiked with [13C6]S-PMA (used as the internal standard) and acidified; then they were purified by solid-phase extraction (SPE) on C18 cartridges. Analyses were conducted on a reversed-phase column by gradient runs with 1% aqueous acetic acid/methanol mixtures at different proportions as the mobile phase. The detector was used in electrospray negative ion mode (ESI-), the ions m/z 238 for S-PMA and 244 for [13C6]S-PMA being recorded simultaneously. The detection limit (for a signal-to-noise ratio = 3) was 0.2 microg/L, thus allowing for the measurement of background excretion of S-PMA in the general population. The use of the internal standard allowed us to obtain good precision (CV% values < 3%) and a linear calibration curve within the range of interest for monitoring occupational exposure to benzene (up to 500 microg/L). The method was applied to assay the metabolite concentration in a group of 299 workers (68 smokers and 231 non-smokers) occupationally exposed to relatively low levels of benzene (environmental concentration = 0.4-220 microg/m3, mean 11.4 microg/m3 and 236 non-exposed subjects (134 smokers and 102 non-smokers). The results clearly showed that smoking must be taken into account for the correct interpretation of the results of S-PMA measurements for the assessment of work-related benzene exposure. When only non-smokers were selected, the mean excretion of S-PMA was significantly higher in workers exposed to benzene (1.2 +/- 0.9 microg/g creatinine) than in the control group (0.7 +/- 0.6 microg/g creatinine) ($p < 0.001$), thus confirming the role of S-PMA as a biomarker of benzene on a group basis, even for relatively low exposure degrees.

Maidment, S. C. (1998). "Occupational hygiene considerations in the development of a structured approach to select chemical control strategies." Ann Occup Hyg **42**(6): 391-400.

This paper explains the occupational hygiene basis of a new scheme to help small firms control the health risks from supplied chemicals. The scheme groups hazard information and the potential for a material to become airborne into bands and, from this information, predicts the control strategy necessary to ensure that

the hazardous substance is used safely. To do this a simple model based upon an empirical approach to risk assessment and risk management has been developed. This work was undertaken in a working group established by the Health and Safety Commission's Advisory Committee on Toxic Substances.

Maina, G., F. Larese, et al. (2002). "[RISKOFDERM: European research project for assessment of occupational skin exposure to chemicals]." Med Lav **93**(2): 73-79.

OBJECTIVES: RISKOFDERM is a research project whose aim is to develop instruments to assess and manage occupational dermal exposure to chemical substances. METHODS: The research, funded by the European Commission, involves 15 Institutes from 10 member countries; it is a continuation of the Dermal Exposure Network experience and consists of four interrelated parts. The first phase (Qualitative survey) assumed that dermal exposure can be extrapolated from one compound to another when it is task-based: therefore six Dermal Exposure Operation units (DEOu) were defined that lead back to the variety of occupational dermal exposure conditions and an extensive Questionnaire was developed for on-site surveys to perform standard observations in selected working situations (scenarios). RESULTS: The Italian group, participating in the research, obtained a set of observations relating to two "scenarios" in different working sectors: asphalt, ceramic and pottery workers, spectacle decorators and paint production: the aim was to verify the validity of the methodology in assessing the risk of percutaneous absorption, time, frequency and extension of skin exposure. CONCLUSIONS: From the observations made it was shown that the perception of risk was poor; it is necessary to rationalise work organization, and train and inform the employees on the correct use of personal protection devices.

Makinen, M., M. Hamalainen, et al. (2002). "Chemical exposure and risk assessment at workplaces--modeling approach." Appl Occup Environ Hyg **17**(11): 744-749.

Markowitz, G. and D. Rosner (1995). "The limits of thresholds: silica and the politics of science, 1935 to 1990." Am J Public Health **85**(2): 253-262.

Since the 1930s threshold limit values have been presented as an objectively established measure of US industrial safety. However, there have been important questions raised regarding the adequacy of these thresholds for protecting workers from silicosis. This paper explores the historical debates over silica threshold limit values and the intense political negotiation that accompanied their establishment. In the 1930s and early 1940s, a coalition of business, public health, insurance, and political interests formed in response to a widely perceived "silicosis crisis." Part of the resulting program aimed at containing the crisis was the establishment of threshold limit values. Yet silicosis cases continued to be documented. By the 1960s these cases had become the basis for a number of revisions to the thresholds. In the 1970s, following a National Institute for Occupational Safety and Health recommendation to lower the threshold limit value for silica and to eliminate sand as an abrasive in blasting, industry fought

attempts to make the existing values more stringent. This paper traces the process by which threshold limit values became part of a compromise between the health of workers and the economic interests of industry.

Maroni, M., M. Tiramani, et al. (2003). "[Definition of acceptable operator exposure levels (AOELs) to pesticides]." G Ital Med Lav Ergon **25**(3): 355-356.

A guidance document entitled "Recommended method for the establishment of Acceptable Operator Exposure Levels" has been prepared within the EU 5th Framework program. The paper describes the main outcomes of the project and the issues that apply particularly to agricultural workers and bystanders and the difficulties in developing an agreed uniform approach. The scientific basis of the process is discussed, to be used by the European Commission and Member States when making decision about the inclusion of an active substance in Annex 1 of Directive 91/414/EEC.

Matsunaga, I., S. Kumagai, et al. (1988). "[Assessment of occupational exposures to industrial hazardous substances. I. A proposed method based on interday fluctuation of contaminant concentrations for evaluating employee's exposure averages (TWAs)]." Sangyo Igaku **30**(3): 179-185.

Occupational exposures to potentially hazardous substances may vary considerably because of factors such as sampling and analytical errors, and intraday and interday environmental fluctuations in contaminant concentration. Of these factors, day-to-day environmental fluctuations most likely affect daily exposure averages over days, weeks, months or years. A new method based on day-to-day fluctuations of daily exposure averages (geometric standard deviation) was developed for making reliable assessment of the employee's exposure situation. It is assumed that daily exposure averages of a worker are lognormally and independently distributed statistically. Finally, a classification scheme on the basis of n days measurements is presented. 95% upper limit or arithmetic mean of individual exposure averages (8-h TWAs) can be evaluated in comparison with an established standard. The method may provide an approximate estimate because of statistical premise, but it can be utilized for practical purposes, particularly, in case where only one or two days are being monitored. An action level concept based on random sampling and analytical errors and interday variations developed by OSHA/NIOSH, and a sampling and decision scheme based on one-sided tolerance limits proposed by Tuggle (1982) are also discussed.

Matsunaga, I., S. Kumagai, et al. (1989). "[Assessment of occupational exposures to industrial hazardous substances. IV. A proposed method based on one-sided tolerance limits]." Sangyo Igaku **31**(4): 227-234.

Occupational exposures to potentially hazardous substances may vary considerably because of interday environmental behavioral fluctuations in the contaminant concentration. Such occupational exposures including those of non-monitored days can be theoretically evaluated by the following three ways: 1)

assessment of geometric mean and geometric standard deviation, 2) assessment of arithmetic mean, and 3) assessment of upper limits of daily exposure distribution. In our previous report, an evaluation method on 95% upper limit or arithmetic mean of exposures was proposed. The method is useful, particularly, in case where only one or two days are being monitored, but may provide an approximate estimate because of statistical assumption. A sampling and decision scheme using one-sided tolerance limits (OTL) proposed by Tuggle (1982) can precisely evaluate the upper limits of exposures. However, many cases would be evaluated as "no decision," unless the sample size is extremely large in number. We developed a revised method based on OTL for assessment of occupational exposures. The characteristic features of this method can be summarized as follows: 1. Upper limits of lognormally distributed 8-h exposure concentrations can be evaluated in comparison with an established standard. 2. A third OTL factor was introduced into Tuggle's scheme in which two OTL factors were used. A comparison between the upper limits of exposures and the standard can be made at 50% confidence level with the factor. The factor was calculated using non-central t-distribution. 3. The usefulness of the third OTL factor in the assessment of occupational exposures was confirmed by examining the performance characteristics of the method.(ABSTRACT TRUNCATED AT 250 WORDS)

McDougal, J. N. and M. F. Boeniger (2002). "Methods for assessing risks of dermal exposures in the workplace." Crit Rev Toxicol **32**(4): 291-327.

The skin as a route of entry for toxic chemicals has caused increasing concern over the last decade. The assessment of systemic hazards from dermal exposures has evolved over time, often limited by the amount of experimental data available. The result is that there are many methods being used to assess safety of chemicals in the workplace. The process of assessing hazards of skin contact includes estimating the amount of substance that may end up on the skin and estimating the amount that might reach internal organs. Most times, toxicology studies by the dermal route are not available and extrapolations from other exposure routes are necessary. The hazards of particular chemicals can be expressed as "skin notations", actual exposure levels, or safe exposure times. Characterizing the risk of a specific procedure in the workplace involves determining the ratio of exposure standards to an expected exposure. The purpose of this review is to address each of the steps in the process and describe the assumptions that are part of the process. Methods are compared by describing their strengths and weaknesses. Recommendations for research in this area are also included.

McHattie, G. V., M. Rackham, et al. (1988). "The derivation of occupational exposure limits in the pharmaceutical industry." J Soc Occup Med **38**(4): 105-108.

McLaughlin, J. K., L. Lipworth, et al. (2001). "A critical evaluation of the scientific basis of the MAK commission's new general threshold limit values for dust." Int Arch Occup Environ Health **74**: 303-314.

Meldrum, M. (2001). "Setting occupational exposure limits for sensory irritants: the approach in the European Union." Aihaj **62**(6): 730-732.

Beginning in 1990, the European Commission initiated a program to establish European Union (EU)-wide occupational exposure limits (OELs). As in the United States and other countries, a panel of experts known as the Scientific Committee on Occupational Exposure Limits (SCOEL) was identified and brought together to identify the proper values. This article describes the approach used by SCOEL to identify appropriate values for sensory irritants. The EU panel believes that irritant effects in the eyes and respiratory tract can produce symptoms that range from trivial to serious, and that responses to irritants may be viewed as belonging to a continuum. One of the interesting differences between the approach used by the ACGIH TLV committee and the SCOEL is the use of five grades of irritation to evaluate this class of chemicals. For purposes of setting an OEL, the SCOEL makes no distinction between irritation or nuisance and related somatic effects such as headache. How the committee established an OEL for ethyl acetate is offered as an illustrative example.

Midzenski, M. A., M. A. McDiarmid, et al. (1992). "Acute high dose exposure to benzene in shipyard workers." Am J Ind Med **22**(4): 553-565.

Fifteen degassers were acutely exposed over several days to high concentrations (> 60 ppm) of benzene during removal of residual fuel (degassing) from shipboard fuel tanks. Medical surveillance evaluation mandated by the Occupational Safety and Health Administration's (OSHA) Benzene Standard initially revealed 11 workers (73%) reporting neurotoxic symptoms while degassing. Workers with more than 2 days (16 hours) of acute exposure were significantly more likely to report dizziness and nausea than those with 2 or fewer days of acute exposure. Repeated laboratory analyses performed over a 4-month period after the acute exposure revealed at least one hematologic abnormality consistent with benzene exposure in 9 (60%) of these degassers. One year later, 6 workers (40%) had persistent abnormalities; an additional worker with normal hematologic parameters at the time of our initial evaluation subsequently developed an abnormality consistent with benzene exposure. Numerous large granular lymphocytes were observed on 6 (40%) of the peripheral blood smears. Despite these laboratory findings, there were no significant associations between the presence of hematologic abnormalities and either the number of hours of acute benzene exposure or the duration of employment as a degasser. Volatilization of benzene from the residual fuel was the suspected source of benzene in the headspace of tanks. Confined space exposure to petroleum products may be exposing workers to benzene at levels above the OSHA Short-Term Exposure Limit (STEL). This situation warrants further study.

Mikheev, M. I. (1995). "Toward WHO-recommended occupational exposure limits." Toxicol Lett **77**(1-3): 183-187.

The WHO Project on Recommended Health-based Limits in Occupational Exposure resulted in the development of occupational exposure limit (OEL) values for a few groups of widely used industrial chemicals. A comparative analysis of the WHO-recommended OEL and existing OEL in selected countries has been made. It was shown that in the OEL's development, there is need for harmonization of methodology, approaches and definitions. Therefore, a new WHO project on guiding principles and guidance values for health-based occupational exposure limits has been established.

Molak, V. (1991). NIOH and NIOSH basis for an occupational health standard. Acrylamide: A review of the literature.

Money, C. D. (2003). "European experiences in the development of approaches for the successful control of workplace health risks." Ann Occup Hyg **47**(7): 533-540.

In recent years, several approaches have been proposed for the application of control banding concepts to the assessment and management of various workplace health and safety risks. Whilst many of the earlier approaches have originated in the UK, several of the most recent examples have been developed in Europe. The European schemes have attempted to build upon the lessons learned from the earlier control banding schemes and to apply them to new areas of health and safety. This paper analyses the evolution of the earlier approaches and reviews the more recent European developments in the context of continuing regulatory and societal demands for the improved assessment and regulation of workplace chemical risks.

Monster, A. C. and R. L. Zielhuis (1991). "Biological exposure and/or effect limits, facts, fallacies and uncertainties: general principles." J Soc Occup Med **41**(2): 55-59.

When looking for facts, fallacies and uncertainties of the use of biological exposure limits one has at first to discuss the general principles of biological monitoring (BM) and biological effect monitoring (BEM) because they determine the validity of the data that underpin the biological exposure limits. A difference between countries in preferred BM-methods can be observed. The terminology is still confusing: in addition to BM and BEM, biomonitoring and biological markers also are used. There are a number of problems in respect of the inter- and intra-individual variability in internal exposure and effect at similar exposure levels due to differences in for example, physical workload, body composition and genetics. Toxicokinetic models based on data from individual workers should be developed in order to get information on the variability and the cause of this. Both kinetics and dynamics may be sex-dependent. To date, BM methods have been tentatively suggested for only about 10 per cent of the regulated industrial chemicals. BM and BEM programmes yield important extra information on exposure and health risk, not to be gained by environmental monitoring alone.

Monster, A. C. and R. L. Zielhuis (1991). "Biological exposure and/or effect limits, facts, fallacies, and uncertainties: practical aspects." J Soc Occup Med **41**(2): 60-63.

In the preceding article general principles in setting biological occupational exposure limits (BOEL) and effect limits (BOEEL) were discussed. Here monitoring in every day occupational health practice is discussed. The specific objectives of biological monitoring (BM) and biological effect monitoring (BEM) determine to a large extent the choice of the parameters to be measured. According to the objective, the assessment may be either simple or sophisticated. The choice of an appropriate reference is essential for a valid evaluation of internal exposure, health risk and state of health. The measurement strategy depends on the working mechanism and the kinetics of the chemical. Protocols for BM and BEM-programmes should be regularly updated. Different compounds of the same metal may carry widely different health risks. In general it is necessary to correct the excretion of chemicals for dilution of the urine.

Moore, J. A. (1997). "An assessment of boric acid and borax using the IEHR Evaluative Process for Assessing Human Developmental and Reproductive Toxicity of Agents. Expert Scientific Committee." Reprod Toxicol **11**(1): 123-160.

BACKGROUND: Boron is a ubiquitous element widely distributed in nature in the form of borates at low concentrations in soils and rocks. Boron is released from these minerals by the natural weathering processes in the form of boric acid, which is water soluble and biologically available. High levels of boric acid are naturally found in sea water. Boric acid and borax are used in the greatest quantities and represent the major boron chemical exposures to humans and the environment. The principal use of boric acid and borax is in the manufacture of various types of glass products that do not result in exposure to the consumer. Boric acid and borax are also found in an array of consumer goods including fireproofing for fabrics and wood, insecticides, and in many cosmetics and personal care products as well. Boron may be an essential element for higher animals including humans. HUMAN EXPOSURE: Boric acid and borax are considered to be completely absorbed by the oral route of exposure. Absorption through intact skin is considered negligible, although absorption can occur through denuded or irritated skin. Boron levels in the body do not persist upon cessation of exposure. People may be exposed to boron through three primary sources: 1) consumption of private, municipal, or commercial (bottled) sources of drinking water; 2) dietary consumption of crops and other foodstuffs (including dietary supplements for body building); and 3) inhalation of boron compounds during their mining, manufacturing, and other industrial processing. While boron has been detected in 81.8% of the municipal water systems, it is a minor source of boron in most parts of the U.S. The mean boron concentration is reported as 0.2 mg B/L. However, residents of California and other western states with boron-rich geologic deposits may be regularly exposed to higher levels in drinking water. Individuals who drink bottled mineral water may also increase their exposure to boron. An EPA health advisory, recommends boron

concentrations in drinking water not exceed 0.6 mg B/L [0.06 mM B] over a lifetime of exposure. Dietary exposure to boron for an adult typically ranges from ranges from 0.25 to 3.1 mg B/d with an average of 1.5 mg B/d. The high end of the exposure range, 3.1 mg B/d, was selected by the Expert Committee as best estimate of exposure. It should be noted that a diet high in fruits, vegetables, grains, legumes, and other food stuffs with high boron contents may lead to daily exposures as high as 10 mg B/d from diet alone. Some body building supplements contain boron at levels ranging from 1.5 to 10 mg B, with a median of 4 mg B. Use of the supplements containing the median concentration of boron could equal the daily intake an individual receives from diet and drinking water combined. Adults in the U.S. at the high end of the food exposure range may typically ingest up to 3.5 mg B/d, or a daily dose of 0.005 mmol B/kg b.wt., through exposure from diet (3.1 mg B/d) and drinking water (0.4 mg B/d). Individuals who also use body-building supplements may have a total daily boron intake of 7.5 mg B resulting in a daily dose of 0.01 mmol B/kg b.wt./d. Occupational exposure to boron is mainly through inhalation of borate containing dust during mining and manufacturing processes. Current occupational exposures to boron are reported to result in a daily dose of < 0.0001 to 0.2 mmol B/kg b.wt./d. Current U.S. OSHA permissible exposure limit (PEL) for sodium tetraborates is 10 mg/m3, and the California Occupational Safety and Health Administration PEL is 5 mg/m3. An exposure of 5 mg B/m3 translates to approximately 0.01 mmol B/kg b.wt./d that, coincidentally, is the same as exposure levels associated with combined municipal drinking water, diet, and body building supplement consumption. Infants may receive exposures to boric acid when it is used as a household insecticide for cockroach control. Exposure from boric acid-containing cosmetic and personal care products applie

Moorman, W. J., H. W. Ahlers, et al. (2000). "Prioritization of NTP reproductive toxicants for field studies." Reprod Toxicol **14**(4): 293-301.

Population studies that evaluate human reproductive impairment are time consuming, expensive, logistically difficult, and with limited resources must be prioritized to effectively prevent the adverse health effects in humans. Interactions among health scientists, unions, and industry can serve to identify populations exposed to potential hazards and develop strategies to evaluate and apply appropriate controls. This report describes a systematic method for prioritizing chemicals that may need human reproductive health field studies. Rodent reproductive toxicants identified from the National Toxicology Program (NTP) Reproductive Assessment by Continuous Breeding (RACB) protocol were prioritized on the basis of potency of toxic effect and population at risk. This model for prioritization links NTP findings with data from the National Occupational Exposure Survey (NOES) and the Hazardous Substance Data Base (HSDB) or the High Production Volume Chemical Database (HPVC) to prioritize chemicals for their potential impact on worker populations. The chemicals with the highest priority for field study were: dibutyl phthalate, boric acid, tricresyl phosphate, and N, N-dimethylformamide.

Morgan, M. S. (1997). "The biological exposure indices: a key component in protecting workers from toxic chemicals." Environ Health Perspect **105 Suppl 1**: 105-115.

Biological monitoring of exposure to chemicals in the workplace is an important component of exposure assessment and prevention of adverse health effects. It should be employed in conjunction with ambient air monitoring to provide information on the absorbed dose of a chemical agent and the effect of all routes of exposure. Judgments regarding the acceptable level of a chemical or its metabolite in biological samples are facilitated by comparison to a reference value. The American Conference of Governmental Industrial Hygienists has established a series of recommended reference values called the Biological Exposure Indices (BEI). The history and characteristics of the BEI are reviewed, and their suitability for use by occupational health specialists is examined. A number of challenges and stimuli to the continued development and improvement of these reference values are described, and the impact of recent advances in macromolecular biology is assessed.

Morgan, M. S. and K. H. Schaller (1999). "An analysis of criteria for biological limit values developed in Germany and in the United States." Int Arch Occup Environ Health **72**(4): 195-204.

The biological tolerance values established by the German Research Foundation and the biological exposure indices developed by the American Conference of Governmental Hygienists represent two extensive lists of occupational exposure guidelines for use in biological monitoring. Although there is substantial agreement between the two organizations on most points, there are several important differences in the approaches taken in setting of the guideline values. Analysis of these distinctions serves to focus attention on the current issues impeding international agreement over occupational exposure guidelines. Among these issues are (1) the specification of the biological monitoring guidelines as ceiling or average values; (2) whether carcinogenic substances should be treated differently from agents with other toxic outcomes; (3) the method of accounting for variability among individual workers; and (4) the extent to which these guidelines should be extended to include genetic markers, indicators of susceptibility, or indicators of early biological response.

Morton, W. E. (1988). "The nature and significance of the corporate influence on threshold limit values." Am J Ind Med **14**(6): 721-723.

Muir, D. C. (1988). "TLVs--what now?" Am J Ind Med **13**(5): 605-606.

Muller, W. J. and V. H. Schaeffer (1996). "A strategy for the evaluation of sensory and pulmonary irritation due to chemical emissions from indoor sources." J Air Waste Manag Assoc **46**(9): 808-812.

Sensory and pulmonary irritation are physiological responses to chemical exposure which result in characteristic, measurable changes in respiratory

activity in mice. A standard method has been applied to the estimation of sensory irritation associated with a specific chemical exposure. This method has been correlated with human responses to these chemicals. Symptoms associated with chemical irritants are consistent with complaints due to problems with indoor air quality, which may include eye and upper respiratory tract irritation, headaches, and nausea. A stepwise strategy for assessing the contribution of indoor products to sensory and pulmonary irritation is discussed in the current paper. The strategy includes product emissions testing using dynamic environmental chambers, the selection of suspected irritants for respiratory irritation testing, respiratory irritation testing of individual compounds are representative mixtures using synthesized atmospheres, and the evaluation of test data to determine those compounds which may contribute to sensory and pulmonary irritation in humans. The current strategy is being applied to evaluate carpet system materials and their constituent chemicals.

Mustajbegovic, J., E. Zuskin, et al. (2000). "Respiratory findings in chemical workers exposed to low concentrations of organic and inorganic air pollutants." Am J Ind Med **38**(4): 431-440.

BACKGROUND: Occupational exposure to respiratory irritants may effect respiratory function in workers exposed to ambient air pollutants in the workplace. METHODS: We studied 567 male and 135 female workers employed in two chemical plants in Zagreb, Croatia. Measurements of the ambient concentrations of air pollutants were performed. The mean age of the men was 37 years and mean duration of employment was 12 years; a majority of these workers were smokers. The mean age of the women was 37 years with a mean duration of employment of 14 years; only one-third of the women smoked. An unexposed group of 340 male and 110 female unexposed workers was also studied. Acute and chronic work related symptoms were recorded for all workers. Ventilatory capacity was measured by recording maximum expiratory flow-volume (MEFV) curves. RESULTS: There were higher prevalences for all chronic respiratory symptoms in exposed than in unexposed workers particularly among women, a majority of which were nonsmokers. Occupational asthma was recorded in three (0. 5%) of the men and in two (1.5%) of the women workers. Logistic regression analysis indicated that the presence of chronic respiratory symptoms among exposed workers was primarily associated with the amount of smoking. Additionally, there were high prevalences of acute symptoms during the work shift. Among the chemical workers these were greatest for eye irritation (male: 43. 9%; female: 51.9%), dryness of the throat (male: 43.4%; female: 57. 0%) and irritation of the throat (male: 37.4%; female: 56.6%). Ventilatory capacity data among the chemical workers demonstrated that most of the measured tests, particularly the FVC and FEV1 were significantly decreased compared to predicted ($P < 0.01$ or $P < 0. 05$)). In particular nonsmoking women exhibited abnormal lung function. The effect of smoking among exposed workers was demonstrated on all ventilatory capacity tests by regression analysis for all measured respiratory parameters. Both length of exposure and age were

correlated with lung function loss for FVC. Measured pollutant levels were for the most part within acceptable standard limits. CONCLUSIONS: Our data suggest that in this population of chemical workers exposed to low levels of pollutants respiratory symptoms were primarily associated with smoking. Environmental effects, possibly due to an interaction of pollutants were also suggested.

Nano, G. (1990). "[Strategies for controlling chemical risk factors in work environments]." G Ital Med Lav **12**(5-6): 191-193.

The strategy involves an initial phase during which environment characteristics, substances used, apparatus involved and working procedures are investigated. Such information is used to define areas to be monitored, periods of sampling and number of measurements to be performed. The adopted procedure takes into account the results obtained on an interaction basis. The scheme makes use of a decisional criterion based on the one sided tolerance limit (OTL) test in order to estimate risk evaluation trends. Each decision is based on a simultaneous control action on ambient and on men. The procedure minimizes the number of measurements, makes effective use of technical and human resources, reduces decisional errors in establishing engineering techniques and can be readily applied to different situations.

Nauman, B. D., P. A. Weideman, et al. (1997). "Use of toxicokinetic and toxicoldynamic data to reduce uncertainties when setting occupational exposure limits for pharmaceuticals." Hum. Ecol. Risk Assess. **3**(4): 555-565.

Naumann, B. D. and E. V. Sargent (1997). "Setting occupational exposure limits for pharmaceuticals." Occup. Med. **12**(1): 67-80.

Naumann, B. D., E. V. Sargent, et al. (1996). "Performance-based exposure control limits for pharmaceutical active ingredients." Am Ind Hyg Ass J **57**: 33-42.

Naumann, B. D. and P. A. Weideman (1995). "Scientific basis for uncertainty factors used to establish occupational exposure limits for pharmaceutical active ingredients." HERA **1**(5): 590-613.

Naumann, B. D., P. A. Weideman, et al. (1997). "Use of toxicokinetic an toxicodynamic data to reduce uncertainties when setting occupational exposure limits for pharmaceuticals." Hum. Ecol. Risk Assess. **3**(4): 555-565.

Naus, A. (1985). "The occupational meaning of smell." J Hyg Epidemiol Microbiol Immunol **29**(1): 29-36.

The sense of smell has its meaning for a successful performance of certain occupations. It has further a protective meaning. The acuity of smell often changes for different reasons. The prolonged or repeated smelling is combined with the process of smell adaptation, fatigue and habituation. They diminish the flavour sensations and increase the risk of work accidents. Some chemical

compounds are characterized by a quick and high adaptation. The occupational changes of smell can be peripheral or central. The qualitative changes of the smell perception are numerous, but they have little sense in industrial hygiene. The hypersensibilisation can be temporal or lasting, where a change of profession is sometimes inevitable. The values of smell thresholds (detection, recognition, distinction) of 25 substances are given. The sensitivity of smell is greater at the smell threshold concentrations. The smell thresholds are put among the main basic properties of chemical compounds which decide about the values of MAC and about the possibilities of their passing over. 68 substances ranged according to their basic characteristics in three groups were studied. There was statistical dependence between the molecular weight, the boiling point, smell thresholds of detection and recognition. In two groups of matters there was a dependence between the threshold of irritation and the smell threshold of recognition and distinction. The regression was linear with the majority of dependencies.

Nelson, D. I. "Risk assessment in the workplace."

Nethercott, J. R., B. Finley, et al. (1994). "Safe concentrations for dermal allergens in the environment." N J Med **91**(10): 694-697.

Recent work studies have examined the relationship between allergen dose per unit of skin surface exposed and the elicitation of response for chromium. The use of such data to arrive at levels in environmental contactants is discussed with reference to soil contaminated with chromium.

Neumann, H. G., H. W. Thielmann, et al. (1997). "Proposed changes in the classification of carcinogenic chemicals in the work area." Regul Toxicol Pharmacol **26**(3): 288-295.

Carcinogenic chemicals in the work area are currently classified into three categories in Section III of the German List of MAK and BAT Values. This classification is based on qualitative criteria and reflects essentially the weight of evidence available for judging the carcinogenic potential of the chemicals. It is proposed that these Categories--IIIA1, IIIA2, and IIIB--be retained as Categories 1, 2, and 3, to conform with EU regulations. On the basis of our advancing knowledge of reaction mechanisms and the potency of carcinogens, it is now proposed that these three categories be supplemented with two additional categories. The essential feature of substances classified in the new categories is that exposure to these chemicals does not convey a significant risk of cancer to man, provided that an appropriate exposure limit (MAK value) is observed. It is proposed that chemicals known to act typically by nongenotoxic mechanisms and for which information is available that allows evaluation of the effects of low-dose exposures be classified in Category 4. Genotoxic chemicals for which low carcinogenic potency can be expected on the basis of dose-response relationships and toxicokinetics and for which risk at low doses can be assessed will be classified in Category 5. The basis for a better differentiation of

carcinogens is discussed, the new categories are defined, and possible criteria for classification are described. Examples for Category 4 (1,4-dioxane) and Category 5 (styrene) are presented. The proposed changes in classifying carcinogenic chemicals in the work area are presented for further discussion.

Neumann, H.-G., S. Vamvakas, et al. (1998). "Changes in the classification of carcinogenic chemicals in the work area." Int Arch Occup Environ Health **71**: 566-574.

Nielsen, G. D. and Y. Alarie (1982). "Sensory irritation, pulmonary irritation, and respiratory stimulation by airborne benzene and alkylbenzenes: prediction of safe industrial exposure levels and correlation with their thermodynamic properties." Toxicol Appl Pharmacol **65**(3): 459-477.

Nielsen, G. D. and J. C. Bakbo (1985). "Sensory irritating effects of allyl halides and a role for hydrogen bonding as a likely feature at the receptor site." Acta Pharmacol Toxicol (Copenh) **57**(2): 106-116.

Allyl chloride, bromide and iodide were investigated for their properties as sensory irritants in mice. The concentrations of the chemicals necessary to depress the respiratory rate by 50% (RD50) within the first 10 min. of exposure due to irritation of the upper respiratory tract were 2330, 257 and 79.8 p.p.m., respectively. No pulmonary irritation was observed. In the period 20 to 30 min., however, pulmonary irritation was observed for allyl bromide and iodide. The effect was not prominent in non-cannulated mice probably due to the scrubbing effect of the nose. According to RD50 values, thermodynamic activity as well as apparent association rate with the receptor the sensory irritating potencies of the halides were low compared to those of allyl alcohol, acetate, and ether. A mechanistic explantation could not be ascribed to metabolites, lipophilicity or chemical reactivity. Only a hydrogen bond donor ability of the receptor offered an explanation. As many industrial chemicals e.g. alcohols, ketones and esters can function as hydrogen bond acceptors this receptor-feature cannot be overemphasized.

Nielsen, G. D. and L. F. Hansen (1993). "Sensory irritation of the upper respiratory tract." Pharmacol Toxicol **72 Suppl 3**: 32-35.

Nielsen, G. D., U. Kristiansen, et al. (1988). "Irritation of the upper airways from mixtures of cumene and n-propanol. Mechanisms and their consequences for setting industrial exposure limits." Arch Toxicol **62**(2-3): 209-215.

The immediate irritation response induced by mixtures of vapours of cumene (isopropyl benzene) and n-propanol was evaluated in mice according to the standard method (Designation: E 981-84) from The American Society for Testing and Materials. The animal model allows prediction of the irritation response in humans. Analyses of the results from the initial periods of the experiments leads to the hypothesis that competitive agonism exists between the two substances. Extrapolation of the results to TLV concentration levels taking into account the

apparent dissociation constants leads further to expectation of additivity of the effects of mixtures of vapours. Following the initial response there is a fading or a desensitization stage. After desensitization, the responses were close to those of cumene alone. This may suggest that the receptor contains different binding sites which desensitize to a different extent.

Nielsen, G. D. and A. M. Vinggaard (1988). "Sensory irritation and pulmonary irritation of C3-C7 n-alkylamines: mechanisms of receptor activation." Pharmacol Toxicol **63**(4): 293-304.

Sensory irritation due to inhalation of a series of alkylamines was estimated from the decrease in respiratory rate in normal (non-cannulated) mice (American standard method E 981-84, 1984). The irritation effects rapidly reached stable levels. The concentration-response relationships followed Michaelis-Menten equations. The maximum response decreased with increasing chain length. The concentrations depressing the respiratory rate by 50% (RD-50) were 184, 121, 97, 51, and 27 p.p.m. for n-propylamine, n-butylamine, n-pentylamine, n-hexylamine, and n-heptylamine, respectively. It is suggested that the receptor is activated partly by the amines and partly by hydroxide ions. The nose has a scrubbing effect, which partly protects the lungs against water soluble irritants. Pulmonary irritation was estimated from the decrease in respiratory rate in tracheally cannulated mice. The plateau-level of the response was reached slowly. The respective concentrations depressing the respiratory rate by 50% (tRD-50) were 416, 300, 128, 66, and 36 p.p.m. for the C3-C7 n-amines. It is suggested that the pulmonary receptor environment is lipophilic and the receptor, probably the J-receptor, is activated chemically by the amines. The sensory and pulmonary irritation data were used to estimate workplace exposure limits (TLV's) which protect against these effects.

Nielsen, G. D. and M. Yamagiwa (1989). "Structure-activity relationships of airway irritating aliphatic amines. Receptor activation mechanisms and predicted industrial exposure limits." Chem Biol Interact **71**(2-3): 223-244.

Sensory irritation due to inhalation of diethyl-, triethyl-, dibutyl-, tributyl- and cyclohexylamine was estimated from the decrease in respiratory rate in normal mice (American Standard Method E981-84). The concentration-effect relations followed Michaelis-Menten equations, except for diethylamine, for which a threshold was found. The concentrations depressing the respiratory rate by 50% (RD50) for diethyl-, triethyl-, dibutyl- and cyclohexylamine were 184, 186, 81 and 27 ppm, respectively. For tributylamine the maximum response was too low to achieve a RD50 value. Pulmonary irritation was estimated from the decrease in respiratory rate in tracheal-cannulated mice. The respective concentrations depressing the respiratory rate by 50% (tRD50) were 549, 691, 101, 96 and 78 ppm for diethyl-, triethyl-, dibutyl-, tributyl- and cyclohexylamine. Only minor or no effects on the tidal volumes were found at the lower exposure concentrations. The trigeminal and pulmonary receptors are believed to be activated directly by the amines, and the receptor environments are believed to be lipophilic.

Structure-activity analysis was made by comparing the effects of the amines with the effects of previously investigated primary n-alkylamines. Occupational exposure limits (TLV) were estimated for both effects. Finally, the sensory irritation effect was found to be an important part of the odour sensation, also below the TLVs.

Nielsen, J. B. and P. Grandjean (2004). "Criteria for skin notation in different countries." Am J Ind Med **45**(3): 275-280.

BACKGROUND: Skin notation criteria was introduced almost 50 years ago as a qualitative indicator of a hazard related to dermal absorption at work. However, risk is not a qualitative term, but needs a quantitative measure to be useful for prevention. For this reason, some countries have developed alternative criteria for assigning skin notations to industrial chemicals. METHODS: The present analysis compares the current use of skin notations on lists of exposure limits for industrial chemicals in six countries. RESULTS: Up to one-third of industrial chemicals listed now have a skin notation. The criteria for assigning skin notation differ but cannot explain the substantial discrepancies between countries that otherwise have very comparable occupational exposure limits (OELs). CONCLUSIONS: The increasing number of chemicals with a skin notation requires a new approach to differentiating between degrees of risk. The first step will be to address the problems related to criteria for assigning skin notations, and the effect of penetration enhancers and mixtures.

NiPERA (1996). Occupational exposure limits: Criteria document for nickel and nickel compounds, Nickel Producers Environmental Research Association**:** 12-13 thru 12-20.

NIPERA (1996). Occupational exposure limits: Criteria document for nickel and nickel compounds. Volume 1: Summary, conclusions, and recommendations. Washington, DC, Nickel Producers Environmental Research Association**:** 1-72 plus appendix.

NIPERA (1996). Occupational exposure limits: Criteria document for nickel and nickel compounds. Volume 2: Assessment of occupational exposures. Washington, DC, Nickel Producers Environmental Research Association**:** 1-1 thru 7-8 plus appendices.

NiPERA (1996). Occupational exposure limits: Criteria document for nickel and nickel compounds. Voulme III: Health assessment of various species of nickel. Washington, DC, Nickel Producers Environmental Research Association**:** 1-1 thru 16-10.

Norback, D. and G. Wieslander (2002). "Biomarkers and chemosensory irritations." Int Arch Occup Environ Health **75**(5): 298-304.

OBJECTIVES: A literature review on studies in humans, applying physiological methods to monitor environmentally induced reactions in eyes and upper respiratory tract. The focus was on chemical exposures, but other occupational factors and indoor exposures were included. METHODS: Original articles were gathered from Medline until November 2000, combined with peer-reviewed

publications from other sources. RESULTS: Ocular methods included measurement of tear film break-up time (BUT), blink frequency, detection of corneal damage, by vital staining, and cells or inflammatory markers in tear fluid. Nasal methods included acoustic rhinometry, rhinostereometry, and nasal peak expiratory flow. In addition, nasal lavage with isotonic sodium chloride solution was applied to measure concentrations of leucocytes, or biomarkers of secretion or inflammation in nasal lavage fluid (NAL). Most occupational studies were on nasal effects of organic or inorganic dust. There were few studies on occupational exposure to organic solvents or chemical irritants. Some studies demonstrated associations between ocular and nasal physiological response and the indoor environment. Finally, there were some exposure-chamber studies on effects of specific volatile organic compounds (VOCs). Little is known about adaptation at repeated ocular or nasal exposure to irritants. CONCLUSION: Physiological measurements can be valuable complements to symptom registration, but there is a need for standardised investigations. There is a lack of studies on ocular and nasal physiological responses in relation to specific chemical compounds. Experimental studies, with repeated exposure and longer follow-up time on biomarkers, are needed. Finally, there is a need for longitudinal epidemiological studies to elucidate if observed effects should be interpreted as variation within normal physiology, or as early signs of impaired ocular and respiratory health.

Nordberg, G. F., H. Frostling, et al. (1988). "Swedish occupational exposure limits: developments in scientific evaluation and documentation." Am J Ind Med **14**(2): 217-221.

Norseth, T. (1972). "[Occupational hygiene, threshold limit values and environmental hygiene]." Tidsskr Nor Laegeforen **92**(31): 2081-2084.

Norwood, S. K. (1985). Occupational exposure assessment. Risk Analysis in the Chemical Industry. C. M. Association. Washington, DC, CMA**:** 61-73.

Notten, W. R., W. F. Passchier, et al. (1997). "Summary of the report "toxicology-based recommended exposure limits"." Regul Toxicol Pharmacol **25**(3): 289-291.

Novikov, S. M., A. B. Nurgabylova, et al. (1995). "[The forecasting of hygienic regulations for industrial substances possessing irritant action]." Gig Sanit(6): 16-20.
Computer analysis of hygienic standards in Russia and the USA and of the toxicometric parameters of chemicals characterized by predominantly irritating effects helped create a prognostic model for the calculation of maximum allowable concentrations of chemicals in the air of working zones.

Nowak, D. (2002). "Chemosensory irritation and the lung." Int Arch Occup Environ Health **75**(5): 326-331.

Airway irritation involves a variety of reflex mechanisms. Tracheal and bronchial C fibres and rapidly adapting fibres mediate cough, bronchoconstriction, and mucosal vasodilation. Workplace respiratory irritants can have a variety of effects in relation to asthma. Very high exposures can cause new-onset asthma, clinically presenting as reactive airways dysfunction syndrome or irritant-induced asthma. Symptoms after exposure to irritants depend on aggregate characteristics, water solubility and dose. Measurement of pulmonary function in response to irritants includes baseline spirometry, monitoring of across-shift changes and changes in non-specific bronchial responsiveness as well as bronchial responsiveness to inhaled allergens. Following irritant exposure, inflammatory changes within the airways are monitored by bronchoalveolar lavage or - less invasively - by sputum markers. A completely non-invasive approach not limited in repeatability is the investigation of inflammatory markers in exhaled air. However, the diagnostic and prognostic values of these novel markers have still to be demonstrated.

Oberdorster, G. (1995). "Lung particle overload: implications for occupational exposures to particles." Regul Toxicol Pharmacol **21**(1): 123-135.

Chronic pulmonary inflammation, pulmonary fibrosis, and even lung tumors developed in a number of chronic inhalation studies in rats with highly insoluble nonfibrous particles of low cytotoxicity. Concerns were expressed that these responses are due to excessive particulate lung burdens, and the term "particle overload" was coined to characterize these conditions. The hallmark of the particle-overloaded lung is an impairment of alveolar macrophage (AM)-mediated lung clearance which has been demonstrated in all species tested so far and which eventually leads to accumulation of excessive lung burdens. Experimental evidence suggests that the volume of the particles phagocytized by AM is most critical for causing their impaired clearance function, and that the condition of lung overload is reached once the retained lung particle burden reaches a level equivalent to a volume of approximately 1 microliter/g of lung. Cytotoxic particles also cause impaired AM clearance function, yet at a much lower lung burden which does not qualify as particle overload. Significant species differences exist with respect to the induction of adverse chronic effects in response to lung overload; i.e., mice and hamsters are less prone to developing chronic inflammation and pulmonary fibrosis, and lung tumors have been observed only in rat studies. Lung tumors or fibrosis in the rats were seen only at lung burdens having caused impaired particle clearance, and a threshold dose for the adverse chronic effects can be postulated which is defined by a lung particle burden not causing impairment of clearance. Thus, the lung tumors observed in chronic rat studies at very high particulate exposure concentrations may not be relevant for human extrapolation to low-exposure concentrations. Evidence in humans suggests that particle-overloaded lungs, e.g., in coal workers, respond with fibrosis, but no increased incidence of lung tumors has been found in this group. However, it cannot be excluded that other types of chronically inhaled particles may have a carcinogenic potential in the human lung if accumulating to very high

lung burdens. More research is needed for a detailed understanding of the basic mechanism leading to nonfibrous particle-induced tumorigenesis in the lungs of different species. Altered particle accumulation and retention kinetics and chronic inflammation in the overloaded lung indicate that the maximum tolerated dose (MTD) has been exceeded. No specific guidelines for inhalation studies defining the MTD have been established; general guidelines are not necessarily applicable for chronic inhalation studies.(ABSTRACT TRUNCATED AT 400 WORDS)

Ogden, T. L. (2002). "Occupational exposure limits--Britain tries again." Ann Occup Hyg **46**(5): 435-437.

Olson, M. J., S. P. Binks, et al. (1997). "Establishing guidance for the handling and containment of new chemical entities and chemical intermediates in the pharmaceutical industry." Occup Med **12**(1): 49-65.
This information is intended to guide scientists and technicians working with pharmaceutical substances early in development, before occupational exposure levels (OELs) can be set. The focus is on determining hazard categories, or occupational exposure bands, which may be applied temporarily until full health-based OEL's are in place.

Omae, K., T. Takebayashi, et al. (1999). "Occupational exposure limits based on biological monitoring: the Japan Society for Occupational Health." Int Arch Occup Environ Health **72**(4): 271-273.
The Japan Society for Occupational Health started to recommend an occupational exposure limit based on biological monitoring (OEL-B) in 1993. Up to 1998, OEL-Bs for mercury, lead, hexane and 3,3'-dichloro-4,4'-diaminodiphenylmethane had been adopted and those for 17 chemical substances (arsenic, cadmium, chromium, nickel, acetone, methanol, benzene, toluene, xylene, styrene, tetrachloroethylene, trichloroethylene, N,N-dimethylacetoamide, N,N-dimethylformamide, carbon disulfide, carbon monoxide, and organophospate insecticides) are in preparation.

Ong, C. N., P. W. Kok, et al. (1996). "Biomarkers of exposure to low concentrations of benzene: a field assessment." Occup Environ Med **53**(5): 328-333.
OBJECTIVE: To carry out a comprehensive field investigation to evaluate various conventional and recently developed biomarkers for exposure to low concentrations of benzene. METHODS: Analyses were carried out on environmental air, unmetabolised benzene in blood and urine, urinary trans, transmuconic acid, and three major phenolic metabolites of benzene: phenol, catechol, and hydroquinone. Validations of these biomarkers were performed on 131 never smokers occupationally exposed to the time weighed average benzene concentration of 0.25 ppm (range, 0.01 to 3.5 ppm). RESULTS: Among the six biomarkers studied, unmetabolised benzene in urine correlated best with environmental benzene concentration (correlation coefficient, r = 0.76), followed

by benzene in blood (r = 0.64). When urinary metabolites were compared with environmental benzene, trans, trans-muconic acid showed a close correlation (r = 0.53) followed by hydroquinone (r = 0.44), and to a lesser extent with urinary phenol (r = 0.38). No correlation was found between catechol and environmental benzene concentrations. Although unmetabolised benzene in urine correlates best with benzene exposure, owing to serious technical drawbacks, its use is limited. Among the metabolites, trans, trans-muconic acid seems to be more reliable than other phenolic compounds. Nevertheless, detailed analyses failed to show that it is specific for monitoring benzene exposures below 0.25 ppm. CONCLUSION: The overall results suggest that most of the currently available biomarkers are unable to provide sufficient specificity for monitoring of low concentrations of benzene exposure. If a lower occupational exposure limit for benzene is to be considered, the reliability of the biomarker and the technical limitations of measurements have to be carefully validated.

Opiekun, R. E., M. Smeets, et al. (2003). "Assessment of ocular and nasal irritation in asthmatics resulting from fragrance exposure." Clin Exp Allergy **33**(9): 1256-1265.

BACKGROUND: Many asthmatics report worsening of symptoms following exposure to odours and sensory irritants commonly found in household and cosmetic products. Despite this, little evidence exists to confirm the degree to which such subjective reports are correlated with localized, objective changes in the upper or lower airways following a fragranced product exposure. OBJECTIVE: Subjective symptom reports were compared to objective measures in mild asthmatics, moderate asthmatics and non-asthmatics following exposure to one of two fragranced household aerosol mixtures and a clean air control condition to determine if asthmatics reported greater subjective symptoms of nasal congestion or exhibited objective measures of elevated ocular irritation and nasal congestion following exposure than did healthy controls. METHODS: Measures of nasal mucosal swelling, using acoustic rhinometry, and photographic assessments of ocular hyperemia, using macro-photography, were taken before exposure, immediately after an initial 5-min exposure and again following a 30-min exposure to either of two, fragranced aerosol products and a clean air control. Self-reports of nasal patency at each time-point were also obtained. RESULTS: Although moderate asthmatics tended to report more nasal congestion following fragranced product exposure than did non-asthmatics, no exposure-related changes in ocular redness or nasal mucosal swelling were observed among the three groups. Spirometry readings also failed to show evidence of any exposure-related changes in pulmonary function. CONCLUSION: Despite claims that exposure to fragranced products may trigger ocular and respiratory symptoms among asthmatics, we found no evidence that 30 min of exposure to one of two fragranced aerosols elicited objective adverse effects in the ocular or nasal mucosa of mild and moderate asthmatics. While physiological mechanisms of fragrance impact may yet be responsible for some of the adverse reports among asthmatics following fragrance exposure, such

reports may also reflect a non-physiological locus of symptom perception triggered by other sensory cues.

OSHA (1987). "Final Ruling on Benzene." Fed. Reg. **29**: 34460-34578.

OSHA (1989). "Air Contaminants." Fed. Reg. **54**: 2332-2983.

OSHA (1997). "Updating Permissible Exposure Limits (PELS) for Air Contaminants; Meeting." Fed. Reg. **61**: 1947-1950.

Osterberg, K., R. Persson, et al. (2004). "Annoyance and performance of three environmentally intolerant groups during experimental challenge with chemical odors." Scand J Work Environ Health **30**(6): 486-496.

OBJECTIVES: This study investigated exposure- and subject-related determinants of annoyance and performance during the chemical odor provocation of healthy persons with self-reported environmental annoyance. METHODS: Persons with self-reported annoyance attributed to (i) chemicals or smells (smell-annoyed, SA, N=29), (ii) electrical equipment (electrically annoyed, EA, N= 16), and (iii) both smells and electricity (generally annoyed, GA, N=39) were, together with referents (N=54), challenged with n-butyl acetate in an exposure chamber at levels far below the threshold values for neurotoxic effects and trigeminal irritation. A sequence of three air concentrations, 0.37, 1.5, and 6 ppm (1.8, 7.1, and 28 mg/m3) was used, counterbalanced within groups, together with intermittent periods of room air between each exposure level. The response measures comprised ratings of annoyance and smell intensity and reaction-time tests. RESULTS: Only the GA group showed clearly elevated ratings of smell annoyance, mucous membrane irritation, and fatigue, as well as longer reaction times, compared with the referents, in response to the challenge. No group difference was found for the smell-intensity ratings. During intermittent periods without exposure, only the GA group maintained higher ratings for mucous membrane irritation and fatigue. Reaction time and all the rating dimensions showed a positive relationship with momentary n-butyl acetate concentration, while cumulative exposure had a more limited impact on the ratings and reaction time. A suggestion effect by the chamber environment before exposure could not be demonstrated. CONCLUSIONS: The results suggest that self-reported annoyance generalized to both electrical equipment and smells is a better predictor of chemical intolerance than self-reported annoyance to smells only.

Otto, D., L. Molhave, et al. (1990). "Neurobehavioral and sensory irritant effects of controlled exposure to a complex mixture of volatile organic compounds." Neurotoxicol Teratol **12**(6): 649-652.

Subjective reactions of discomfort, impaired air quality, irritation of mucosal membranes, and impaired memory have been reported in chemically sensitive subjects during exposure to volatile organic compounds (VOCs) found in new

buildings. Sixty-six normal healthy male subjects aged 18-39 were exposed for 2.75 hr to a complex VOC mixture at 0 and 25 mg/m3. Each subject completed control and exposure sessions at one-week intervals in counterbalanced order. Measurements included comfort ratings of eye, nose and throat irritation, symptom questionnaire and computerized behavioral tests. Subjects found the odor of VOCs unpleasantly strong and reported that VOC exposure degraded air quality, increased headache and produced general discomfort. VOC exposure did not affect performance on any behavioral tests.

Packham, C. L. (1995). "Setting limits on occupational skin exposure to chemical substances." Ann Occup Hyg **39**(1): 125-126.

Parmeggiani, L. (1973). "[Recent international developments concerning maximum permissible limits]." Med Lav **64**(5): 166-171.

Parmeggiani, L. (1988). "An international viewpoint on exposure limits." Am J Ind Med **14**(2): 213-214.

Pastino, G. M., A. A. Kousba, et al. (2003). "Derivation of occupational exposure limits based on target blood concentrations in humans." Regul Toxicol Pharmacol **37**(1): 66-72.

An approach for deriving occupational exposure limits (OEL) for pharmaceutical compounds is the application of safety factors to the most appropriate pre-clinical toxicity endpoint or the lowest therapeutic dose (LTD) in humans. Use of this methodology can be limited when there are inadequate pre-clinical toxicity data or lack of a well-defined therapeutic dose, and does not include pharmacokinetic considerations. Although some methods have been developed that incorporate pharmacokinetics, these methods do not take into consideration variability in response. The purpose of this study was to investigate how application of compartmental pharmacokinetic modeling could be used to assist in the derivation of OELs based on target blood concentrations in humans. Quinidine was used as the sample compound for the development of this methodology though the intent was not to set an OEL for quinidine but rather to develop an alternative approach for the determination of OELs. The parameters for the model include body weight, breathing rate, and chemical-specific pharmacokinetic constants in humans, data typically available for pharmaceutical agents prior to large scale manufacturing. The model is used to simulate exposure concentrations that would result in levels below those that may result in any undesirable pharmacological effect, taking into account the variability in parameters through incorporation of Monte Carlo sampling. Application of this methodology may decrease some uncertainty that is inherent in default approaches by eliminating the use of safety factors and extrapolation from animals to humans. This methodology provides a biologically based approach by taking into consideration the pharmacokinetics in humans and reported

therapeutic or toxic blood concentrations to guide in the selection of the internal dose-metric.

Pauli, G. and N. E. Birba (2003). "Recent developments in airway and nose occupational sensitizers." Curr Opin Allergy Clin Immunol **3**(2): 95-100.

PURPOSE OF REVIEW: To describe the latest developments in the field of occupational asthma and occupational rhinitis in 2001 and 2002. RECENT FINDINGS: Several surveillance programs of occupational diseases, such as Observatoire National des Asthmes Professionnels in France, Surveillance of work-related and Occupational Respiratory Diseases in South Africa (SORDSA), Surveillance of Work-related and Occupational Respiratory Diseases (SWORD) in UK, have reported on the frequency of occupational asthma. The causative agents were mainly flour, isocyanates and latex. The common methods of diagnosis - questionnaires, cutaneous tests, Peak Expiratory Flow Rate (PEFR), bronchial hyperresponsiveness - still create controversy. In addition, the specific bronchial challenge, the classical gold standard of diagnosis, has its limitations since it cannot be performed in every case. Other methods have been assessed as inflammatory markers in induced sputum. Occupational rhinitis appears to be a poorly diagnosed condition. SUMMARY: Further studies are expected to explore the effect of environmental control and medical surveillance. The key to successful management of occupational asthma and occupational rhinitis may be prospective surveillance of the occurrence of specific IgE antibodies before the onset of allergic symptoms.

Paull, J. M. (1984). "The origin and basis of threshold limit values." Am J Ind Med **5**(3): 227-238.

The concept of establishing a "threshold limit" for contaminants of industrial air is based on the principles of establishing: (1) quantitative relationships between the magnitude and duration of exposure to an industrial substance and the nature and magnitude of the response of the worker, and (2) a limiting level of exposure to potentially hazardous agents, when there exists no significant threat to health. This paper focuses on the origin of this concept, and traces the history and development of thought concerning the founding principles upon which it is based. The TLVs have undergone a remarkable evolution, from values denoting concentrations of contaminant producing overt signs of acute toxicity, to those concentrations to which nearly all workers may be exposed for their working lifetime without experiencing adverse health effects.

Paustenbach, D., Alarie, Yves, Kulle, Tom, Schacter, Neil, Smith, Ralph, Swenberg, James, Witschi, Hanspeter, and Horowitz, Susan (1997). "A Recommended Occupational Exposure Limit for Formaldehyde Based on Irritation." Journal of Toxicology and Environmental Health **50**: 217-263.

Paustenbach, D. (2001). "Approaches and considerations for setting occupational exposure limits for sensory irritants: Report of recent symposia." AIHA J **62**(6): 697-704.

Over the past 50 years significant strides have been made in reducing occupational exposure to airborne chemicals. To a large extent, the impetus behind the reductions has been the identification of presumably safe levels of exposure, or occupational exposure limits (OELs). Most of the reduction in exposure has been to chemicals such as hepatotoxins, neurotoxins, nephrotoxins, and carcinogens that cause frank toxic effects. Recently, however, a number of industrial hygiene and occupational medicine initiatives have sought to identify acceptable levels of exposure to sensory irritants and reduce exposure to this class of chemicals. This article presents an overview of the field with emphasis on the work presented at two symposia sponsored by the Chemical Manufacturers Association: "How Do We Set an Occupational Exposure Limit (OEL) for Irritation?" (1998) at the American Industrial Hygiene Conference and Exposition and "Respiratory Tract Irritation and Olfaction Conference" (1997). The two symposia reviewed clinical and experimental methods used to assess odor and sensory irritation, to increase understanding of the research needed to establish OELs for sensory irritants, and to discuss how to use this information to identify appropriate values. The symposia illustrated that research in this area is evolving quickly and that there is already sufficient understanding to permit scientists to identify chemicals likely to be sensory irritants. Further, there appears to be an ample number of research methods for identification of airborne concentrations that should protect most workers. This article summarizes some of the key points raised at these symposia and suggests areas deserving of future study.

Paustenbach, D., Y. Alarie, et al. (1997). "A recommended occupational exposure limit for formaldehyde based on irritation." J Toxicol Environ Health **50**(3): 217-263.

In recent years, several regulatory agencies and professional societies have recommended an occupational exposure limit (OEL) for formaldehyde. This article presents the findings of a panel of experts, the Industrial Health Foundation panel, who were charged to identify an OEL that would prevent irritation. To accomplish this task, they critiqued approximately 150 scientific articles. Unlike many other chemicals, a large amount of data is available upon which to base a concentration-response relationship for human irritation. A mathematical model developed by Kane et al. (1979) for predicting safe levels of exposure to irritants based on animal data was also evaluated. The panel concluded that for most persons, eye irritation clearly due to formaldehyde does not occur until at least 1.0 ppm. Information from controlled studies involving volunteers indicated that moderate to severe eye, nose, and throat irritation does not occur for most persons until airborne concentrations exceed 2.0-3.0 ppm. The data indicated that below 1.0 ppm, if irritation occurs in some persons, the effects rapidly subside due to "accommodation." Based on the weight of evidence from published studies, the panel found that persons exposed to 0.3 ppm for 4-6 h in chamber studies generally reported eye irritation at a rate no different than that observed when persons were exposed to clean air. It was noted that at a concentration of 0.5 ppm (8-h TWA) eye irritation was not

observed in the majority of workers (about 80%). Consequently, the panel recommended an OEL of 0.3 ppm as an 8-h time-weighted average (TWA) with a ceiling value (CV) of 1.0 ppm (a concentration not to be exceeded) to avoid irritation. The panel believes that the ACGIH TLV of 0.3 ppm as a ceiling value was unnecessarily restrictive and that this value may have been based on the TLV Committee's interpretation of the significance of studies involving self-reported responses at concentrations less than 0.5 ppm. The panel concluded that any occupational or environmental guideline for formaldehyde should be based primarily on controlled studies in humans, since nearly all other studies are compromised by the presence of other contaminants. The panel also concluded that if concentrations of formaldehyde are kept below 0.1 ppm in the indoor environment (where exposures might occur 24 h/d) this should prevent irritation in virtually all persons. The panel could not identify a group of persons who were hypersensitive, nor was there evidence that anyone could be sensitized (develop an allergy) following inhalation exposure to formaldehyde. The panel concluded that there was sufficient evidence to show that persons with asthma respond no differently than healthy individuals following exposure to concentrations up to 3.0 ppm. Although cancer risk was not a topic that received exhaustive evaluation, the panel agreed with other scientific groups who have concluded that the cancer risk of formaldehyde is negligible at airborne concentrations that do not produce chronic irritation.

Paustenbach, D. J. (1988). "Assessment of the developmental risks resulting from occupational exposure to selevt glycol ethers within the semiconductor industry." Journal of Toxicology and Environmental Health **23**: 29-75.

Paustenbach, D. J. (1989). "Important recent advances in the practice of health risk assessment: implications for the 1990s." Regulatory Toxicology and Pharmacology **10**: 204-243.

Paustenbach, D. J. (1990). "Health risk assessment and the practice of industrial hygiene." Am. Ind. Hyg. Assoc. J. **51**: 339-351.

Paustenbach, D. J. (1990). "Occupational exposure limits: Their critical role in preventive medicine and risk management." AIHAJ **51**: A332-A336.

Paustenbach, D. J. (1994). Occupational exposure limits, pharmacokinetics, and unusual work schedules. Patty's Industrial Hygiene, Third Edition. R. L. Harris, L. J. Cralley and L. V. Cralley, John Wiley & Sons, Inc. **3:** 191-237.

Paustenbach, D. J. (1997). "Updating OSHA's permissable expsoure limits: Putting politics aside." AIHAJ **58**: 845-489.

Paustenbach, D. J., Y. Alarie, et al. (1992). A review of sensory/respiratory irritation studies with formaldehyde from the standpoint of occupational exposure: conclusion of an expert panel. Pittsburgh, PA, Industrial Health Foundation.

Paustenbach, D. J., J. D. Jernigan, et al. (1990). "The current practice of health risk assessment: potential impact on standards for toxic air contaminants." J. Air Waste Manage. Assoc **40**(12): 1620-1630.

Paustenbach, D. J., A. K. Madl, et al. (2001). "Identifying an appppropriate occupational exposure limit (OEL) for beryllium: data gaps and current research initiatives." Appl Occup Environ Hyg **16**(5): 527-538.

The occupational exposure limit of 2.0 microg/m3 for beryllium has been used in the workplace since the late 1940s. In particular, the adequacy of the American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Value (TLV) for beryllium has recently come into question. The symposium "Beryllium: Effect on Worker Health" was convened in September 1999, to bring together leading scientists to present and discuss current research activities on beryllium exposure and chronic beryllium disease (CBD). One of the key questions to be resolved at the symposium was, "Is there a sufficient understanding of exposure and the cause of CBD that would allow us to develop a TLV that we believe would prevent disease?" Seven scientists presented information regarding the current understanding of the disease, possible causes, and ongoing research. The topics were (1) biomonitoring approaches and their relationship with clinical effects, (2) historical and current exposure assessments, (3) sampling methods and aerosol characterization, and (4) epidemiology. Six basic hypotheses regarding the relationship between exposure to beryllium and CBD were generated from the information presented at the symposium. The six hypotheses that are related to issues such as beryllium form, particle size, industrial hygiene practices, extrapulmonary routes of exposure, and genetic susceptibility also appear to be the focus of ongoing and likely future research initiatives. This article summarizes both the presentations made at the meeting and the hypotheses generated. It is expected that an understanding of these issues should explain the inconsistent dose-response relationship observed between exposure and CBD. The ongoing and planned research is anticipated to provide sufficient data within two to three years to develop one or more scientifically sound TLVs for the different chemical forms of beryllium.

Paustenbach, D. J., P. J. Sheehan, et al. (1992). "Review of the allergic contact dermatitis hazard posed by chromium-contaminated soil: identifying a "safe" concentration." J Toxicol Environ Health **37**(1): 177-207.

At least 200 sites in the United States contain soil with elevated levels of trivalent and hexavalent chromium [Cr(III) and Cr(VI)]. Although the potential cancer hazard posed by airborne Cr(VI) has been the primary concern for these sites, a soil cleanup standard based on the potential elicitation of allergic contact dermatitis has been proposed for sites in Hudson County, N.J. This paper

describes the rationale for identifying a soil concentration of Cr(VI) that should not pose an allergic contact dermatitis hazard-even in sensitized persons. A literature review of eight published patch test studies that evaluated the allergic response to potassium dichromate was conducted. These studies were evaluated for clinical and statistical relevance in establishing a threshold dose of Cr(VI) to which no more than 10% of the subpopulation sensitized to chromium would respond, and that would protect at least 99.84% of the general population. Although each of the studies had certain methodological limitations when evaluated against current test methods, the data set proved useful for deriving an estimated threshold. Using computer data-fitting techniques based on truncated lognormal distributions, a weighted mean 10% threshold of approximately 150 ppm potassium dichromate or 54 ppm Cr(VI) was identified for the eight studies. Due to the types of limitations noted for these studies, this threshold is likely to be somewhat conservative. Test results have shown that between 5 and 10% of the Cr(VI) at concentrations less than about 500 ppm are released from a soil matrix into an isotonic saline solution simulating sweat. Using human sweat as the extractant, it has been shown that only 0.1% of the CR(VI) at concentrations of approximately 1,000 ppm are released from a soil matrix into sweat. Based on 10% solubilization of soil-bound Cr(VI) and the results of our statistical analysis of previous threshold studies, a concentration of approximately 350 to 500 ppm Cr(VI) in soil should be sufficiently low to protect virtually all exposed people, including children, from chromium-induced allergic contact dermatitis.

Paustenback, D. and R. Langner (1986). "Corporate occupational exposure limits: the current state of affairs." Am Ind Hyg Assoc J **47**(12): 809-818.

It has been claimed that the implementation of occupational exposure limits has been instrumental for the near elimination of serious occupational disease in the Western world. Although exposure limits or guides for most large volume chemicals have been established, the majority of the 10,000 chemicals which are routinely used in industry do not have them. As a result, many firms have chosen to establish internal limits to protect their employees as well as the persons who purchase those chemicals. This paper reviews the most important issues discussed in a 2-day symposium on corporate exposure limits which was sponsored by the AIHA Workplace Environment Exposure Limits Committee (WEEL). Thirteen representatives of industry and professional organizations presented papers which addressed various aspects of the process for setting internal exposure limits. The various policies and methodologies used by large American companies which have set limits for many years and their benefits were discussed. The history and function of Threshold Limit Values (TLVs) Maximum Allowable Concentrations (MACs), Permissible Exposure Limits (PELs) and Workplace Environment Exposure Limits (WEELs) also were reviewed. Some of the legal aspects of setting corporate limits and their role in the Product Safety arena were discussed.

Paxman, D. and S. M. Rappaport (1990). "Analysis of OSHA's short-term-exposure limit for benzene." Regul Toxicol Pharmacol **11**(3): 275-287.

A review of the data cited by OSHA in its final standard for exposure to benzene provides no clear scientific basis for a short-term-exposure limit (STEL). While leukemia and bone marrow toxicity were related to cumulative exposures of benzene received by workers, no evidence was presented that the rate of exposure at a given cumulative exposure contributed to the effects. Likewise, animal experiments suggested that exposures of several hours duration at a given level of benzene induced more bone-marrow toxicity when administered 3 rather than 5 days/week but did not indicate that the rate of exposure over shorter time scales played any role. The toxicokinetics of benzene in humans were also studied to determine whether nonlinear dose-rate effects would be likely to result from peak exposures associated with an exposure dose of 8 ppm-hr, which is allowed under the permissible exposure limit. This led to three conclusions. First, the concentration of benzene in the bone marrow should be sufficiently damped that the impact of a peak exposure should be minimal. Second, the peak concentration of benzene in the liver should be within the capacity of the cytochrome P450 system to maintain first-order metabolism. And finally, the maximum blood concentration of metabolites should be well below levels which have been shown to induce toxic effects in vitro. Taken together, the toxicokinetic relationships and the absence of clear experimental dose-rate effects suggest that the current STEL for benzene is unwarranted, assuming that 8-hr average exposures are kept below 1 ppm. While the argument can be made, on the basis of health considerations, that the existing 8-hr limit for benzene is too high, the rate of exposure during short periods appears to be irrelevant. Thus, we recommend that health professionals focus upon long-term exposures to benzene received by large numbers of workers rather than devote scarce resources to evaluate transient air levels.

Pendergrass, J. A. (1969). "Screening of occupational environment: a critique of exposure limits." Am J Public Health Nations Health **59**(7): 1204-1208.

Penknovich, A. A. (2002). "[Length of employment and dosage in the evaluation of risk factors for chronic bronchitis among workers in contact with respiratory tract chemical irritants]." Med Tr Prom Ekol(2): 40-42.

Pieri, M., N. Miraglia, et al. (2003). "Determination of urinary S-phenylmercapturic acid by liquid chromatography-tandem mass spectrometry." J Chromatogr B Analyt Technol Biomed Life Sci **795**(2): 347-354.

Urinary S-phenylmercapturic acid (S-PMA) is considered a useful biomarker for the measurement of low levels of benzene exposure, related to occupational exposure, smoking habits or environmental pollution. S-PMA quantitative analysis requires highly sensitive and specific techniques and purification procedures, mainly based on liquid-liquid or solid-phase extraction, which result in time expensive analyses. A method was developed for the quantitative

determination of S-PMA in urine by using a simple, reproducible and easily automatizable HPLC purification followed by LC/ESI-NI/MS2 analysis. In order to reduce the cost of the analysis, related to the use of expensive labeled standards, p-bromo-S-phenylmercapturic acid (p-Br-S-PMA) was synthesized, characterized and used as internal standard. The feasibility and efficacy of the proposed method were examined by constructing calibration curves in the range from 6.2 to 200 microg/l and data were analyzed in terms of linearity and statistical parameters. The detection limit, related to the purification of 1 ml urine sample is 5 microg/l. The method was applied to the analysis of 12 urine samples from smoker subjects non-occupationally exposed to benzene. S-PMA urinary levels ranged from 13.6 to >200 microg/l, suggesting a high influence of life style in the S-PMA excretion. The proposed analytical method is suitable for the biological monitoring of both smoker and non-smoker workers, occupationally exposed to benzene. By processing at least 2 ml of urine samples, the method appears to be also useful for the evaluation of benzene uptake due to the environmental pollution.

Podlekareva, D., Z. Pan, et al. (2002). "Irritation of the human eye mucous membrane caused by airborne pollutants." Int Arch Occup Environ Health **75**(5): 359-364.

OBJECTIVES: The purpose of this study was to investigate the different irritative effects of carbon dioxide and n-butanol exposure on the ocular mucous membrane. MATERIAL AND METHODS: Provocation by the gases was at the same sensory level, which was 50% of maximum on a linear scale. The experiment was performed on nine healthy subjects with the aim of identifying the relationship between eye irritation and the human physiological response to this irritation. A goggle exposure system, invented at the Department of Occupational and Environmental Medicine, Aarhus University, was used for the experiment. The exposures lasted for 30 min each. RESULTS: There were no changes in tear film stability and conjunctival corrosion (lissamine staining) after carbon dioxide and n-butanol exposures leading to 50% sensory eye irritation. However, the study showed a delayed inflammatory response after carbon dioxide exposure when compared with clean air. The significant change was seen for tear fluid neutrophilic granulocytes 22 h after carbon dioxide (CO(2)) exposure only. CONCLUSIONS: It is concluded that the type of exposure made no difference to the elicited physiological responses and that tear film stability and epithelium damage were not affected by sensory irritation itself.

Posniak, M. and J. Skowron (2000). "Polish system of assessing occupational risk posed by chemical compounds." Int J Occup Saf Ergon **Spec No**: 103-109.

According to the Polish Labour Code &elpar;Ustawa, 1974) employers are legally obligated to provide workers with information about occupational health and safety risks. Maximum allowable concentrations (MAC) and the results of determining chemical compounds in workplace air are used for assessing occupational exposure and risk. A computer-assisted system STER, developed

in the Central Institute for Labour Protection, helps to register and document occupational risk assessment and all actions resulting from those assessments.

Prah, J. D. (1998). "1998 equivalence of sensory responses to single and mixed volatile organic compounds at equimolar concentrations." Environ Health Perspect **106**(11): 739-744.

Exposure to low levels of chemicals indoors is often to a mixture of volatile organic compounds (VOCs). It is of interest to determine if the symptomatic and sensory responses can be attributed to a single chemical or to a mixture of chemicals. To determine if sensory or symptomatic responses differ with exposure to single or mixed VOCs, 100 female subjects participated in a 6-hr exposure study. Subjects were exposed to one of six equimolar concentrations equivalent to 24 mg/m3 toluene, control, m-xylene, n-butyl acetate, m-xylene plus n-butyl acetate, a mixture of 21 chemicals including n-butyl acetate and m-xylene, and to the same mixture of chemicals without n-butyl acetate and m-xylene (19 chemicals). The results indicated that there was no difference in reporting of symptoms or sensory responses between the exposures. When the control group was added, some variables, primarily odor intensity and nasal irritation, attained significance.

Pratt, I. S. and T. Barron (2003). "Regulatory recognition of indirect genotoxicity mechanisms in the European Union." Toxicol Lett **140-141**: 53-62.

The European Union (EU) system for the regulation of chemicals includes approval systems for pharmaceuticals, pesticides and biocides, requirements for hazard classification and for risk assessment of industrial chemicals. Regulators have traditionally used the commonly accepted categorisation of chemicals into genotoxic (DNA-reactive) or non-genotoxic agents in their decision-making processes, and have generally considered that there is no threshold level for the former group. The recognition that a number of genotoxic agents operate by indirect genotoxicity mechanisms such as induction of aneuploidy, oxidative stress, inhibition of DNA synthesis or cytotoxicity presents new problems for the regulator. The dose-response relationship for a number of such agents is generally accepted to show a threshold, however, the degree of acceptance of the threshold effect differs in different EU regulatory systems. The classification system for mutagens is based primarily on intrinsic hazard rather than risk, and the classification criteria do not allow for a less stringent classification for chemicals operating by a threshold mechanism. In contrast, regulatory approval systems for plant protection products and therapeutic agents are based on a risk assessment approach, in which a demonstrated threshold effect for a genotoxic agent is likely to be an important factor in reaching a decision concerning authorisation of the product.

Rajan-Sithamparanadarajah, R., M. Roff, et al. (2004). "Patterns of dermal exposure to hazardous substances in European union workplaces." Ann Occup Hyg **48**(3): 285-297.

Workplace dermal exposure assessment is a complex task that aims to understand the dynamic interaction between the skin and the hazardous substances present in the surrounding environment. A European project known as RISKOFDERM gathered dermal exposure data in 85 workplaces (industrial and other types) in five countries in Europe. In order to optimize data collection and to develop a representative picture of dermal exposure, scenarios (tasks made up of a series of activities) were grouped together into dermal exposure operation units (DEOs). The allocation of scenarios to relevant DEOs was achieved on the basis of similarities of exposure routes, tasks and professional judgement. Sampling and quantification procedures were based on the approaches recommended by the OECD protocol. The laboratories involved in the analysis of the samples participated in quality assurance programmes. This exercise resulted in 419 body measurements and 437 measurements on hands expressed in terms of formulation (product) in use. Exposures for a given scenario varied by several orders of magnitude. The extent and patterns of exposure were found to be dependent on various exposure determinants, including inter- and intra-scenario variations. Hands were found to be the most contaminated parts of the body. Exposure patterns for liquid and solid contaminants were different. On the basis of the analysis of the data presented here, the averaged results (median and 95th percentile) for a given DEO unit should not be used as a representative measure of dermal exposure for all scenarios within that DEO without taking the exposure determinants into account. However, the data could be used to develop an exposure matrix (indicative exposure distributions) for different types of scenario and workplace, using determinants of exposure and a Bayesian approach to integrating expert opinion.

Randerath, K., K. L. Putman, et al. (1990). "Effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin on I-compounds in hepatic DNA of Sprague-Dawley rats: sex-specific effects and structure-activity relationships." Toxicol Appl Pharmacol **103**(2): 271-280.

The effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and related compounds on the specific patterns of age-dependent I-compound DNA adducts in the liver of male and female Sprague-Dawley rats were determined by the 32P-postlabeling assay. In female rats, TCDD causes a dose-dependent decrease of several individual and total hepatic I-compound levels after administration of 1 and 5 micrograms/kg per week for 4 weeks. In contrast, no such effects were observed in male Sprague-Dawley rats treated with the 5 micrograms/kg dose level of TCDD. The relative effects of TCDD, 1,2,3,7,8-pentachlorodibenzo-p-dioxin (PCDD) and 1,2,4,7,8-PCDD on hepatic I-compound levels in the susceptible female Sprague-Dawley rats were determined using a dose of 5 micrograms/kg per week for 4 weeks. The two compounds which are substituted in all four lateral positions, namely TCDD and 1,2,3,7,8-PCDD, caused a significant decrease in hepatic I-compound levels, whereas 1,2,4,7,8-PCDD which is substituted in only three lateral positions was inactive. The structure-activity relationships observed for the effects of these compounds on hepatic I-compounds correlated with their corresponding

structure-Ah receptor binding and structure-toxicity relationships. The results are therefore consistent with a role for the Ah receptor in the TCDD-mediated reduction in hepatic I-compound levels in female Sprague-Dawley rats. These results and data from previous studies demonstrate a correlation between the susceptibility of an organ/species to the carcinogenic effects of TCDD and the reduction of I-compound levels. The significance of this correlation in the development of TCDD-induced carcinogenesis has not been delineated.

Rappaport, S. M. (1993). "Threshold limit values, permissable exposure limits, and feasiblity: The bases for exposure limits in the United States." Am. J. Ind. Med. **23**: 683-694.

Rappaport, S. M. (1993). "Threshold limit values, permissible exposure limits, and feasibility: the bases for exposure limits in the United States." Am J Ind Med **23**(5): 683-694.

The development of exposure limits in the United States has always relied heavily upon the threshold limit values (TLVs) developed by the American Conference of Governmental Industrial Hygienists (ACGIH). In fact, the TLVs were adopted as official exposure limits by the Occupational Safety and Health Administration (OSHA) in 1972 and 1989. Given the continuing importance of the ACGIH limits, this paper compares the basis of the TLVs with that employed by OSHA de novo in its 12 new permissible exposure limits (PELs). Using benzene as an example, it is shown that OSHA's new PELs have been established following a rigorous assessment of the inherent risks and the feasibility of instituting the limit. The TLVs, on the other hand, have been developed by ad hoc procedures and appear to have traditionally reflected levels thought to be achievable at the time. However, this might be changing. Analysis of the historical reductions of TLVs, for 27 substances on the 1991-1992 list of intended changes, indicates smaller reductions in the past (median reduction of 2.0-2.5-fold between 1946 and 1988) compared to those currently being observed (median reduction of 7.5-fold between 1989 and 1991). Further analysis suggests a more aggressive policy of the ACGIH regarding TLVs for carcinogens but not for substances that produce effects other than cancer. Regardless of whether the basis of the TLVs has changed recently, it would take a relatively long time for the impact of any change to be felt, since the median age of the 1991-1992 TLVs is 16.5 years, and 75% of these limits are more than 10 years old. The implications of OSHA's continued reliance on the TLVs as a means of updating its PELs are discussed, and four alternatives are presented to the ACGIH regarding the future of its activities related to exposure limits. It is concluded that new mechanisms are needed for OSHA to update its PELs in a timely fashion so that the TLVs will not be adopted by default in the future.

Rappaport, S. M. (1995). "Biological monitoring and standard setting in the USA: a critical appraisal." Toxicol Lett **77**(1-3): 171-182.

Occupational exposure limits (OELs) issued in the US by the Occupational Safety and Health Administration (OSHA) require measurements of toxic substances in air rather than in biological samples. Most of OSHA's limits were adopted from the 1968 list of the American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Values (TLVs). Although there are no formal requirements to monitor exposures to these substances, it is implicit in the standards that air sampling will be performed. Of the 13 OELs which OSHA has set de novo, 2 (i.e., those for lead and cadmium) require biomonitoring after air sampling has identified the heavily exposed workers. OSHA appears to value biomonitoring in some circumstances but has apparently not found a consistent rationale for using biomarkers to set and enforce its standards. This paper discusses 2 valuable features of biomarkers which should be exploited by OSHA to further its regulatory agenda. The first relates to controversies associated with dose rate which have come into play in setting short-term exposure limits (STELs) when acute effects do not provide the necessary justification. OSHA has not provided evidence that its STELs are needed to reduce the risks of disease (as in the cases of benzene and ethylene oxide). By investigating the exposure-biomarker relationship, it is possible to determine whether the rate of exposure has any influence on the uptake and elimination of toxic substances and, therefore, whether STELs is needed. This is illustrated with data from 2 studies on styrene exposure. The second feature concerns biomonitoring as the primary means of exposure assessment in situations where the biomarker is accumulated over months or years (as in the cases of lead and cadmium). Using data from the lead-battery industry, it is shown that 'correct' compliance decisions are more likely to arise from evaluation of blood lead measurements than from traditional air monitoring.

Rennen, M. A., K. Nordheim, et al. (2002). "Prediction of local irritant effects after repeated dermal and respiratory exposure to chemicals." Regul Toxicol Pharmacol **36**(3): 253-261.

Health risks resulting from occupational exposure to chemicals are controlled by the establishment of acceptable dermal and respiratory exposure levels. Due to a lack of route-specific toxicity data, acceptable levels are frequently established by means of route-to-route extrapolation. A pitfall in route-to-route extrapolation is the occurrence of local effects. Often, the results of acute irritation studies are used to assess the likelihood of the occurrence of local effects also following repeated exposure and thereby the validity of route-to-route extrapolation. We questioned this working practice and considered whether local effects observed in a given study are of any predictive value with respect to the occurrence of local effects after repeated exposure. Our database analysis indicates that substances inducing skin and/or eye irritation frequently induce local effects after repeated respiratory exposure. In contrast, observations made in any type of study show little or no positive predictive value for the occurrence of local effects after repeated dermal exposure. Notably, the absence of any indication of local effects in any type of study does not exclude the occurrence of local effects on repeated

dermal or respiratory exposure. We conclude that the presumed reliability of route-to-route extrapolation in the absence of route-specific toxicity data can be questioned.

Riazanov, V., T. Kauppinen, et al. (2003). "[Using CAREX data base system for occupational exposure to carcinogens in Estonia]." Med Tr Prom Ekol(2): 17-22.
CAREX (CARcinogen EXposure) is international information system on occupational exposure to know and suspected carcinogens. The CAREX database provides selected exposure data and documented estimates of the number of exposed by workers by country, carcinogen, and industry. CAREX includes data on 139 agents evaluated by the International Agency for Research on Cancer, displayed across the 55 industrial classes of the United Nations system (ISIC Revision 2). In 1999-2000, CAREX approach was applied to Estonian, Latvian, Lithuanian and Czech exposure situation in 1997. According to the preliminary estimates, there were about 180,000 workers (29% of the employed) exposed to the agents covered by CAREX in Estonia in 1997. The number of the exposures was approximately 240,000. The most common exposure were solar radiation (62,000 workers), wood dust (34,000 exposed), environmental tobacco smoke (31,000), diesel engine exhaust (21,000 exposed), crystalline silica (19,000), radon and its decay products (14,000), formaldehyde (9000) benzene (7000), ethylene dibromide (6400), lead and inorganic compounds (6200), and glasswool (4300).

Richter, E. D. (1988). "On "Corporate influence on threshold limit values" by Castleman and Ziem." Am J Ind Med **14**(3): 365-368.

Rifkind, A. B. (2006). "CYP1A in TCDD toxicity and in physiology-with particular reference to CYP dependent arachidonic acid metabolism and other endogenous substrates." Drug Metab Rev **38**(1-2): 291-335.
Toxicologic and physiologic roles of CYP1A enzyme induction, the major biochemical effect of aryl hydrocarbon receptor activation by TCDD and other receptor ligands, are unknown. Evidence is presented that CYP1A exerts biologic effects via metabolism of endogenous substrates (i.e., arachidonic acid, other eicosanoids, estrogens, bilirubin, and melatonin), production of reactive oxygen, and effects on K(+) and Ca(2+) channels. These interrelated pathways may connect CYP1A induction to TCDD toxicities, including cardiotoxicity, vascular dysfunction, and wasting. They may also underlie homeostatic roles for CYP1A, especially when transiently induced by common chemical exposures and environmental conditions (i.e., tryptophan photoproducts, dietary indoles, and changes in oxygen tension).

Roach, S. A. (1978). "Threshold limit values for extraordinary work schedules." Am Ind Hyg Assoc J **39**(4): 345-348.

Roach, S. A. and S. M. Rappaport (1990). "But they are not thresholds: A critical analysis of the documentation of theshold limit values." Am. J. Ind. Med. **17**: 727-753.

Roach, S. A. and S. M. Rappaport (1990). "But they are not thresholds: a critical analysis of the documentation of Threshold Limit Values." Am J Ind Med **17**(6): 727-753.

Threshold Limit Values (TLVs) represent conditions under which the TLV Committee of the American Conference of Governmental Industrial Hygienists (ACGIH) believes that nearly all workers may be repeatedly exposed without adverse effect. A detailed research was made of the references in the 1976 Documentation to data on "industrial experience" and "experimental human studies." The references, sorted for those including both the incidence of adverse effects and the corresponding exposure, yielded 158 paired sets of data. Upon analysis it was found that, where the exposure was at or below the TLV, only a minority of studies showed no adverse effects (11 instances) and the remainder indicated that up to 100% of those exposed had been affected (8 instances of 100%). Although, the TLVs were poorly correlated with the incidence of adverse effects, a surprisingly strong correlation was found between the TLVs and the exposures reported in the corresponding studies cited in the Documentation. Upon repeating the search of references to human experience, at or below the TLVs, listed in the more recent, 1986 edition of the Documentation, a very similar picture has emerged from the 72 sets of clear data which were found. Again, only a minority of studies showed no adverse effects and TLVs were poorly correlated with the incidence of adverse effect and well correlated with the measured exposure. Finally, a careful analysis revealed that authors' conclusions in the references (cited in the 1976 Documentation) regarding exposure-response relationships at or below the TLVs were generally found to be at odds with the conclusions of the TLV Committee. These findings suggest that those TLVs which are justified on the basis of "industrial experience" are not based purely upon health considerations. Rather, those TLVs appear to reflect the levels of exposure which were perceived at the time to be achievable in industry. Thus, ACGIH TLVs may represent guides of levels which have been achieved, but they are certainly not thresholds.

Robinson, J. C. and D. G. Paxman (1991). "OSHA's four inconsistent carcinogen policies." Am J Public Health **81**(6): 775-780.

Robinson, J. C. and D. G. Paxman (1992). "The role of threshold limit values in U.S. air pollution policy." Am J Ind Med **21**(3): 383-396.

This paper analyzes the role of threshold limit values (TLVs) in national air pollution policy during the 1980s, a period in which the Environmental Protection Agency (EPA) sought to delegate to individual states the authority to evaluate and regulate airborne toxic substances. We focus on 20 carcinogens and 11 substances with non-genotoxic health effects that were regulated by local air toxics programs using TLVs. Data from EPA's National Air Toxics Information Clearinghouse indicate that maximum TLV-based Ambient Air Level guidelines

(AALs) frequently exceed minimum TLV-based AALs by a factor of greater than 1,000. Cancer potency data from EPA's Integrated Risk Information System suggest significant risks remain at TLV-based AALs. Cancer risks at the median TLV-based AAL exceed 1,000 cases per million exposed persons for cadmium (1,040), nickel and its compounds (1,420), propylene oxide (1,550), coke oven emissions (1,860), benzene (2,500), arsenic and its compounds (7,300), N-nitrosodimethylamine (21,000), asbestos (21,500), and ethylene dibromide (55,000). We also summarize published studies that report non-genotoxic health effects in workers exposed at levels near the TLV for 11 substances whose AALs were based on TLVs. Contrary to the assumption frequently made by state air toxics program, TLVs cannot be taken to represent no observed effect levels (NOELs) for regulatory purposes.

Robinson, J. C., D. G. Paxman, et al. (1991). "Implications of OSHA's reliance on TLVs in developing the air contaminants standard." Am J Ind Med **19**(1): 3-13.

This paper evaluates the decision by the Occupational Safety and Health Administration (OSHA) to base its Air Contaminants Standard on the threshold limit values (TLVs) of the American Conference of Governmental Industrial Hygienists. Contrary to the claim made by OSHA in promulgating the standard, the TLV list was not the sole available basis for a generic standard covering toxic air contaminants. The National Institute for Occupational Safety and Health (NIOSH) presented data indicating that the TLVs were insufficiently protective for 98 substances. NIOSH Recommended Exposure Limits (RELs) were available for 59 of these substances. The ratio of PEL to REL ranged up to 1,000, with a median of 2.5 and a mean of 71.4. OSHA excluded 42 substances from the standard altogether despite the availability of NIOSH RELs, solely because no TLV had been established.

Rosenkranz, H. S. and A. R. Cunningham (2003). "Environmental odors and health hazards." Sci Total Environ **313**(1-3): 15-24.

Using the recently developed and validated 'chemical diversity approach', the potential of chemicals, to be detected by the human olfactory system and to cause adverse health effects, was investigated. The analyses found no significant association between odor perceptibility and potential for inducing health effects.

Roy, D., Q. Cai, et al. (2007). "Estrogen-induced generation of reactive oxygen and nitrogen species, gene damage, and estrogen-dependent cancers." J Toxicol Environ Health B Crit Rev **10**(4): 235-257.

In addition to the direct effect of estrogen on mitochondria and the redox cycling of catechol estrogen, estrogen-induced proinflammatory cytokines, such as interleukin-1 beta (IL-1beta) and tumor necrosis factor alpha (TNF-alpha), also generate reactive oxygen and nitrogen species (RO/NS). Different cellular signaling pathways may operate in response to varying levels of estrogen-induced RO/NS, leading to genotoxic damage, cell apoptosis, or cell growth. At

high levels of RO/NS, cells receiving genotoxic insults, if not repaired, may engage the apoptotic pathways. There is increasing evidence supporting that estrogen-induced alterations in the genome of cells is produced by oxidative attack. Furthermore, ROS generated by estrogen exposure and/or active metabolites of estrogen in combination with receptor-mediated proliferation of genetically damaged cells may be involved in tumor development. This view is supported by the findings of DNA modifications produced in vitro or in vivo by natural and synthetic estrogens in the target organs of cancer both in experimental models and in humans. Interaction of estrogen-induced oxidants and estrogen metabolites with DNA was shown to generate mutations in genes. Cotreatment with an inhibitor of IL-1beta and TNF-alpha synthesis, pentoxifylline, decreased stilbene estrogen-induced levels of myeloperoxidase (MPO), 8-hydroxydeoxyguanosine formation, and gene mutations, and prevented stilbene estrogen-induced lesions. Stable MCF-7 clones overexpressing IL-1beta resulted in a high level of IL-1beta peptide secretion undergoing cell apoptosis, and an elevated level of p53 protein in response to high oxidative stress when compared to nontransfected cells, whereas MCF-7 clones overexpressing IL-1beta that resulted in a moderate level of IL-1beta secretion stimulated the clonal expansion of MCF-7 and TM3 cells. Estrogen-induced MCF-7 cell growth and cyclin D1 expression were suppressed by antioxidants and mitochondrial blockers. These studies support that in addition to ovarian estrogen-mediated ER signaling, mitogenic signals may also come from estrogen-induced RO/NS. Further validation of this concept that the concentration of the RO/NS within the cellular microenvironment determines its stimulatory or inhibitory growth signals as well as its genotoxic effects regulating the growth of estrogen-dependent tumors may result in novel preventive strategies.

Rozman, K. K. (2002). "Comments on the Jayjock et al. paper." Hum Exp Toxicol **21**(7): 405-406.

Establishing hormesis as an evolution-based biological phenomenon requires a broad discussion of its implications for currently used risk paradigms. The Jayjock et al. papers provide an industrial hygienist's perspective and, as such, represent a valuable contribution to this discussion. Our comments outline a toxicologist's view on the limits and practicability of the Jayjock et al. suggestions. The arguments are primarily based on the shape of dose and time responses and associated variabilities and uncertainties.

Rozman, K. K. and J. Doull (2002). "Derivation of an occupational exposure limit (OEL) for n-propyl bromide using an improved methodology." Appl Occup Environ Hyg **17**(10): 711-716.

n-Propyl bromide is an industrial solvent with increasing production volume due to its use as a replacement for fluorohydrocarbons. Therefore, the number of occupationally exposed workers is growing accordingly. This manuscript presents a thorough evaluation of available animal and human data to derive an occupational exposure limit (OEL) for n-propyl bromide. In addition, structure

activity relationship within the homologous series of methyl, ethyl, and n-propyl bromide and an identical spectrum of effects caused by similar doses of 2-propyl bromide are used to increase the confidence of the analysis. The structure activity relationship was entirely consistent for acute and subchronic (neurologic, reproductive, and hematopoietic) toxicities and for mutagenic potency in that CH3Br was more toxic than CH3CH2Br, which in turn was more toxic than CH3CH2CH2Br in every case in all species studied, including humans. Animals appeared to be similarly susceptible as, or slightly more susceptible than, humans to n-propyl bromide's toxicity. An OEL (60-90 ppm) was derived from a limited human study and supported by an across-the-toxic-spectrum comparison of animal and human data for both n-propyl and 2-propyl bromide. A carcinogenic classification was not deemed necessary at the recommended OEL based on very low mutagenic potency and the consistent structure activity relationship across the homologous series of these alkyl bromides.

Ruden, C. (2003). "Scrutinizing ACGIH risk assessments: the trichloroethylene case." Am J Ind Med **44**(2): 207-213.

BACKGROUND: The American Conference of Governmental Industrial Hygienists (ACGIH) threshold limit values (TLVs) for occupational exposure to chemicals and physical agents have been very influential in the setting of occupational exposure limits in many countries. METHODS: Three ACGIH risk assessments of the chlorinated solvent trichloroethylene (TCE) [ACGIH (1989): 5th edition; ACGIH (1992): 5th edition. Revised Vol II; ACGIH (1996): Suppl. 6th edition] are compared to 26 other risk assessments made of the same chemical substance. The documents are compared in terms of their overall conclusions and the data selected for assessment. RESULTS: It is shown that these ACGIH risk assessment documents were based on incomplete and biased data sets. CONCLUSIONS: The data on which the ACGIH [ACGIH (1996): Suppl. 6th edition] base their TCE risk assessment do not adequately reflect the available scientific knowledge about TCE toxicity and carcinogenicity. This may have influenced their conclusion that TCE is not carcinogenic in either animals or humans which stand out compared to contemporary risk assessments.

Rusch, G. M., R. Garrett, et al. (2002). "The development of acute exposure guideline levels for hazardous substances." Drug Chem Toxicol **25**(4): 339-348.

The National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances (NAC/AEGL) was created to develop guideline levels for short-term exposures to airborne concentrations for approximately 400-500 high priority, acutely hazardous substances. The program should be completed within the next 10 years. These Acute Exposure Guideline Levels (AEGLs) are being applied to a wide range of planning, response, and prevention applications both within the United States and abroad. The NAC/AEGL Committee seeks to develop the most scientifically credible, acute (short-term) exposure guideline levels possible within the constraints of data availability, resources and time. The program begins with comprehensive data gathering, data evaluation and data

summarization. The resulting Technical Support Documents (TSD) are first reviewed by a small review committee; (chemical manager, two chemical reviewers and the author), then by the full AEGL committee. After that review, a summary is published in the Federal Register for Public comment. When these comments have been addressed, the TSDs are sent to the National Research Council's (NRC) Subcommittee on AEGLs for a peer review. Following acceptance by the NRC, they are published by the Academy. The NAC/AEGL Committee currently comprises representatives of federal, state, and local agencies and representatives from France, Germany, and the Netherlands, private industry, medicine, academia and other organizations in the private sector that will derive programmatic or operational benefits from the existence of the AEGL values. AEGL values are determined for three different health effect end-points. These values are intended for the general public where they are applicable to emergency (accidental) situations. Threshold exposure values are developed for five exposure periods (10 and 30 min, 1 h, 4 h, 8 h). Each threshold value is distinguished by varying degrees of severity of toxic effects, as initially conceived by the American Industrial Hygiene Association's Emergency Response Planning Committee, subsequently defined in the NAS' National Research Council publication of the Guideline for Developing Community Emergency Exposure Levels for Hazardous Substances and further categorized in the Standing Operating Procedures of the NAC/AEGL Committee. To date, the committee has reviewed almost 100 chemicals.

Russell, R. M., S. C. Maidment, et al. (1998). "An introduction to a UK scheme to help small firms control health risks from chemicals." Ann Occup Hyg **42**(6): 367-376.

The Control of Substances Hazardous to Health Regulations 1994 (COSHH), provide the main British legislation to protect against health risks arising from hazardous substances used at work. Under the regulations, employers have a duty to carry out a suitable and sufficient risk assessment and take steps to ensure exposure is adequately controlled. The paper by Topping et al. (1998) concluded that small firms need more basic, readily available advice on how to effectively control hazardous substances. To meet this need the Health and Safety Executive (HSE) and the Advisory Committee on Toxic Substances (ACTS) have developed a new scheme for the UK. It involves a simple system of generic risk assessments to identify appropriate control strategies and a series of control guidance sheets providing good-practice examples of those strategies for common operations. The approach builds on earlier industry risk banding schemes and HSE's general approach to risk assessment and risk management. To help ensure the advice reaches small firms, HSE is seeking to involve key intermediaries in its dissemination. This paper describes the rationale for the new UK scheme, how it sits in the legal framework, and proposals for its dissemination. The papers by Brooke (1998) and Maidment (1998) set out in detail the technical basis for the scheme.

Ruth, J. H. (1986). "Odor thresholds and irritation levels of several chemical substances: a review." Am Ind Hyg Assoc J **47**(3): A142-151.

A collation of odor threshold data for approximately 450 chemical substances is presented. The range of odor thresholds reported in the literature is shown along with any reported threshold of irritation to humans. These data can assist the industrial hygienist in determining when an "odor" may be in excess of the Threshold Limit Value, when an organic vapor respirator is not acceptable due to the lack of an odor warning at the end of a cartridge life, and where odors may not indicate a hazard due to extremely low odor thresholds which may be well below the respective TLVs.

Rydzynski, K. and R. Jedrychowski (1994). "Sensory irritating properties of cyanuric chloride as revealed with plethysmographic method." Int J Occup Med Environ Health **7**(2): 149-154.

Sensory respiratory irritation properties of cyanuric chloride (2,4,6-trichlorotriazine; CC) were studied in mice. For this purpose, the respiratory rate was measured in Balb/C male mice by means of the whole body plethysmographic method. Each animal was placed in a body plethysmograph attached to a small (0.25 m3) dynamic inhalation chamber and exposed to various concentrations (2.1, 6.7, 9.1, 11.7 and 14.6 mg/m3) of CC. Respiratory rates were recorded before, during and after termination of the exposure. It was found that exposure to CC caused a concentration-dependant decrease of respiratory rates in mice. After termination of exposure fast and full recovery of respiratory rates were observed within 5 minutes. RD50 value calculated with probit method was established as 5.9 (1.3-13.9 for 95% confidence limits) mg/m3. The slope of the dose response curve was 1.366 (0.78). It is concluded that cyanuric chloride is a strong respiratory irritant.

Sakurai, H. (2000). "Carcinogenicity and other health effects of acrylonitrile with reference to occupational exposure limit." Ind Health **38**(2): 165-180.

The occupational exposure limit for acrylonitrile (AN) has been set by many organizations on the basis of its carcinogenicity. However, recent epidemiological studies do not afford evidence supporting the hypothesis that AN is carcinogenic to humans. Review of the 18 published cohort studies revealed that, although there is not adequate evidence in humans for carcinogenicity of AN, the possibility of a causal association between high exposure to AN and lung cancer in humans cannot be excluded. It was pointed out that carcinogenic potential of AN may be weak, if any, to humans, and the current occupational exposure limit (OEL) for AN of 2 ppm was evaluated as appropriate in view of AN exposure levels reported by epidemiological studies. Based also on review of the literature on health effects other than carcinogenicity, it was concluded that the current OEL for AN is a reasonable value and there is no need for a revision at present.

Saltzman, B. E. (2001). "Recent risk rates of occupational fatalities, injuries, and illnesses in U.S. industries and their use in planning environmental controls." Appl Occup Environ Hyg **16**(7): 742-744.

Cost/benefit justifications are now required for new environmental regulations. The benefit is related to the difference between the currently existing health risk rate and the rate corresponding to the proposed permissible exposure limit. The adoption of many permissible exposure limits has been delayed by the lack of supporting human data and the use of animal data instead. This has resulted in difficulties and controversies not likely to be resolved soon. Meanwhile, a review of currently existing occupational risk rates can provide a perspective for best use of available funds. Tables and text are presented summarizing published occupational risk data for 1996. Transportation incidents cause 42 percent of occupational fatalities. Proper selection and training of workers and proper work rules should be cost-effective, also especially in other listed dangerous industries. Annual risk rates per hundred workers for occupational nonfatal injuries and illness were surprisingly high: for manufacturing 10.6, and for the entire private sector, 7.4. Seven worst industries ranged from 25.8 to 30.3. The benefit from controlling such high rates is almost the same whether the final rate is 10(-3) or 10(-6). Thus, specifying a good low-cost procedure that reduces most of the initial risk can provide the lowest cost/benefit ratio, eligible for priority use of available funds.

Sargent, E. V. and D. G. Kirk (1988). "Establishing airborne exposure control limits in the pharmaceutical industry." Am. Ind. Hyg. Assoc. J. **49**(6): 309-313.

Sartorelli, P. (2000). "[Dermal risk assessment in occupational medicine]." Med Lav **91**(3): 183-191.

The importance of dermal exposure has increased during the last few years mainly because of the reduction of respiratory exposure to toxicants. Pesticides, aromatic amines and polycyclic aromatic hydrocarbons are considered to be the chemicals with highest dermal risk. In the occupational exposure limit lists of the ACGIH and of many countries compounds that can be absorbed through the skin are identified by a skin notation. Usually the skin notation indicates that the percutaneous absorption of the chemical can contribute to the body burden. However, a generally accepted criterion for assigning skin notation does not exist. When it is possible to make standardized measurements of dermal exposure, it will be possible to develop Dermal Occupational Exposure Limits (DOEL) with which such measurements can be compared to enable a regulatory approach in the risk assessment field. However, the recent attempts to develop health-based DOELs have not been accepted, thus in practice their use has been limited.

Sartorelli, P. (2002). "Dermal exposure assessment in occupational medicine." Occup Med (Lond) **52**(3): 151-156.

The importance of dermal exposure has increased during the last few years, mainly because of the reduction of respiratory exposure to toxicants. Pesticides, aromatic amines and polycyclic aromatic hydrocarbons are considered to be the chemicals at highest dermal risk. In the occupational exposure limit lists of the American Conference of Governmental Industrial Hygienists (ACGIH) and of many countries, compounds that can be absorbed through the skin are identified by a skin notation. However, a generally accepted criterion for assigning skin notation does not exist. The recent attempts to develop health-based dermal occupational exposure limits (DOELs) have not been accepted, thus in practice their use has remained limited. To predict the systemic risk associated with dermal exposure and to enable agencies to set safety standards, penetration data are needed. Moreover, there is a need for a practical risk assessment model, particularly for small and medium-sized enterprises.

Sass, R. (1988). "What's in a name? The occupational hygienist's problem with threshold limit values." Am J Ind Med **14**(3): 355-363.

Sayli, B. S. (2001). "Assessment of fertility and infertility in boron-exposed Turkish subpopulations: 3. Evaluation of fertility among sibs and in "borate families"." Biol Trace Elem Res **81**(3): 255-267.

As a part of a work to reveal the health effects of boron and its compounds, fertility and infertility states of sibs of probands, contacted and interviewed in the field, and of their spouses were given. The purposes were to prevent duplications seemingly inevitable in a relatively small community with prevailing consanguinity while analyzing marriages over respective generations and to reveal if there occurred an aggregation of infertile couples. Any family without offspring after about the second year of marriage was considered primary infertile as adopted throughout the study and such families were ascertained through the individual pedigree charts set up according to the instructions of the proband, he (she) himself (herself) being excluded. The rates of childless families of this type were 0.0-3.4% among male and 0.9-3.8% among female sibs of the participant, and 2.3-10.0% among male and 0.0-5.6% among female sibs of his (her) spouse with averages of 2.3% of 1589, 2.6% of 1589, 4.0% of 1314, and 3.3% of 1436 instances, respectively. The differences were insignificant and the rates were not different from those concerning probands themselves and that of a comparable segment of the Turkish population. "Borate families/kindreds" with two or more members engaged in the borate industry were also assessed in order to detect if there was a significant clustering of infertiles within the kindred. Although it was difficult to compare with a matched group, few couples were examples of familial concentration of infertility. These results provided further support that boron exposure does not affect human reproduction primarily and most probably secondarily.

Sayli, B. S. (2003). "Low frequency of infertility among workers in a borate processing facility." Biol Trace Elem Res **93**(1-3): 19-30.

In order to rule out the possibility of omitting some individuals in the study at field visits described in previous articles, either because of the reluctance of the subject or because of his appointment elsewhere, fertility and infertility states of borate workers of the Borax and Acid Plants in Bandirma, Balikesir are given. Balikesir is one of the four provinces with large borate deposits of Turkey, and Bandirma is 1 of its 19 districts. This county is relatively far away from borate deposits, and drinking water piped out through the springs has a boron amount between 0.10 and 0.82 ppm B. That the participants are occupationally exposed to the mineral in essence is therefore conceivable. At the first phase of the investigation, 191 workers were interviewed, as detailed previously. Among these, there were six infertiles of the primary type with a rate 3.1%. Boron-unrelated infertile couples among sibs were found to be 2.6-3.6%, and 3.2% for three generation marriages-none being higher than those revealed in different sets of controls. In the second stage of work, computerized files of all workers of the facility and all employees of the general management sharing the same location were checked without an interview. Twenty-four subjects (3.4%) out of 712 workers were childless versus 2.7% among 108 employees, and 2.2% among 91 workers of a distantly located sulfuric acid plant of the same complex. The differences were not significant, and these recent findings support the conclusion already reached almost unambiguously that boron exposure at the present levels does not interfere with human reproduction.

Scala, R. A. (1992). "Major issues in traditional workplace exposure limits." Am Ind Hyg Assoc J **53**(9): A438-439.

Schaper, M. (1993). "Development of a database for sensory irritants and its use in establishing occupational exposure limits." AIHA J **54**(9): 488-544.

A database was developed for chemicals whose sensory-irritating properties had been investigated using a previously described animal bioassay. In this bioassay, mice were exposed to an airborne chemical, and changes in their respiratory pattern were determined. For each chemical tested, the concentration capable of producing a 50% decrease in respiratory rate (RD50) was obtained and its relative potency estimated. For the current study, 295 such airborne materials, including single chemicals and mixtures, were found in the literature. A total of 154 RD50 values were obtained in male mice of various strains for the 89 chemicals in the database for which there were also TLVs. An examination of the TLVs and RD50 values demonstrated, as previously with the smaller dataset (n = 40), a high correlation (R2 = 0.78) of the TLVs with 0.03 x RD50. This supports the continued use of the animal bioassay for establishing exposure limits to prevent sensory irritation in the workplace. No other bioassay provides this type of information or has been used so extensively to suggest guidelines for occupational exposures.

Schiffman, S. S. and C. M. Williams (2005). "Science of odor as a potential health issue." J Environ Qual **34**(1): 129-138.

Historically, unpleasant odors have been considered warning signs or indicators of potential risks to human health but not necessarily direct triggers of health effects. However, citizen complaints to public health agencies suggest that odors may not simply serve as a warning of potential risks but that odor sensations themselves may cause health symptoms. Mal-odors emitted from large animal production facilities and wastewater treatment plants, for example, elicit complaints of eye, nose, and throat irritation, headache, nausea, diarrhea, hoarseness, sore throat, cough, chest tightness, nasal congestion, palpitations, shortness of breath, stress, drowsiness, and alterations in mood. There are at least three mechanisms by which ambient odors may produce health symptoms. First, symptoms can be induced by exposure to odorants (compounds with odor properties) at levels that also cause irritation or other toxicological effects. That is, irritation--rather than the odor--is the cause of the health symptoms, and odor (the sensation) simply serves as an exposure marker. Second, health symptoms from odorants at non-irritant concentrations can be due to innate (genetically coded) or learned aversions. Third, symptoms may be due to a co-pollutant (such as endotoxin) that is part of an odorant mixture. Objective biomarkers of health symptoms must be obtained, however, to determine if health complaints constitute health effects. One industry that is receiving much attention, worldwide, related to this subject is concentrated animal production agriculture. Sustainability of this industry will likely necessitate the development of new technologies to mitigate odorous aerial emissions. Examples of such "environmentally superior technologies" (EST) developed under the initiative sponsored through agreements between the Attorney General of North Carolina and Smithfield Foods and Premium Standard Farms are described.

Schnuch, A., H. Lessmann, et al. (2002). "["When should a substance be designated as sensitizing for the skin ("sh") or for the airways ("sa")"?"]." Pneumologie **56**(5): 304-308.

SCOEL (1999). Methodology for the derivation of occupational exposure limits: Key documentation. Luxembourg, European Union: Scientific Committee on Occupational Exposure Limits.

Seeber, A., C. van Thriel, et al. (2002). "Psychological reactions related to chemosensory irritation." Int Arch Occup Environ Health **75**(5): 314-325.

OBJECTIVES: For risk assessments of solvents the knowledge on chemosensory irritation effects is important, but the methodological base for that is incomplete. The psychological approach measuring chemosensory irritations leans on perceived symptoms and self-reported changes of well being. Characteristics assessing the validity of such psychological approaches are presented. METHODS: The article is based on 14 experimental inhalation studies with (mostly) 4-h exposures to acetone, 2-butanone, ethanol, ethyl acetate, ethyl benzene, iso-propanol, 1-octanol, and styrene. The profiles of exposure include constant and changing concentrations using the range of the German maximum concentrations at the workplace (MAK) list. Irritations (eyes

and nose), olfactory symptoms (odour), and annoyance are the dependent variables measured by ratings. Young and healthy subjects (n=160), - partially, subjects with self-reported odour sensitivity (measured by items from the questionnaire on chemical and general environmental sensitivity) - were investigated. RESULTS: The reliability of ratings is sufficient. Dose-response relationships for perceived odour and annoyance are stronger than those for irritations. A ranked order of the size of effect (related to the values before exposure) for the substances investigated shows correspondence between odour and annoyance; that for irritation differs. Within the limits of the MAK list, perceived irritations are not correlated to annoyance, whereas perceived bad smell correlates significantly to annoyance. Reversibility of the self-reported effects to approximately the pre-exposure level can be shown 1 h after cessation of the experimental exposure for the "normal" subjects. Influences of trait anxiety and chemical sensitivity on reports of annoyance, bad odour or irritation are only weak. CONCLUSION: The psychological approach of repeated measurements for self-reported irritation includes distinctive advantages compared with other methods, the simple and repeated availability during exposure, the sufficient reliability and dose-response relationship, and the comparability between substances by means of effect size. The extension of the concept of "chemosensory irritations" on reports for annoyance and bad smell can be recommended.

Seeley, M. R., L. E. Tonner-Navarro, et al. (2001). "Procedures for health risk assessment in europe." Reg Tox Pharm **34**: 153-169.

Selevan, S. G. (1981). "Design considerations in pregnancy outcome studies of occupational populations." Scand J Work Environ Health **7 Suppl 4**: 76-82.
Increased attention has been focused on the relationship between adverse pregnancy outcomes and occupational exposures to parents of both sexes. However, the characteristics and dynamics of working populations impose limitations on potential study populations. These limitations result from the combined effects of workforce size, exposure, age distribution, and marital status, which limit the number of pregnancies available for study. The smaller populations available typically result in retrospective studies covering extended time periods. Potential data sources for these studies include interview data, medical records, vital statistics data, and insurance records. All sources may have biased ascertainment of certain pregnancy outcomes such as early fetal loss due to errors in recall in interview data, legal requirements for recording vital statistics data, and differences in medical care patterns.

Semple, S. (2004). "Dermal exposure to chemicals in the workplace: just how important is skin absorption?" Occup Environ Med **61**(4): 376-382.

Senft, A. P., T. P. Dalton, et al. (2002). "Dioxin increases reactive oxygen production in mouse liver mitochondria." Toxicol Appl Pharmacol **178**(1): 15-21.

Dioxin (2,3,7,8-tetrachlorodibenzo-p-dioxin; TCDD) causes an oxidative stress response in liver and several extrahepatic tissues. The subcellular sources and underlying mechanisms of dioxin-induced reactive oxygen, however, are not well understood. In this study, we examined whether mitochondria, organelles that consume the majority of cellular oxygen, might be a source of dioxin-induced reactive oxygen. Female C57BL/6 mice were treated with dioxin (15 microg/kg body wt ip) on 3 consecutive days, and liver mitochondria were examined at 1, 4, and 8 weeks after the first treatment. Mitochondrial aconitase activity, an enzyme inactivated by superoxide, was decreased by 44% at 1 week, 22% at 4 weeks, and returned to control levels at 8 weeks. Dioxin elevated succinate-stimulated mitochondrial H2O2 production twofold at 1 and 4 weeks; H2O2 production remained significantly elevated at 8 weeks. The enhanced H2O2 production was due to neither increased Mn-superoxide dismutase activity nor decreased mitochondrial glutathione peroxidase activity. Dioxin treatment augmented mitochondrial glutathione, but not glutathione disulfide levels, a result that might be explained by increased mitochondrial glutathione reductase activity. Liver ATP levels were significantly lowered at 1 and 4 weeks, the peak times of mitochondrial reactive oxygen production. Increased dioxin-stimulated reactive oxygen at 1 and 4 weeks did not appear to be related to the observed decrease in cytochrome oxidase activity, since State 3 and State 4 respiration were not diminished. To our knowledge, this is the first report to show that dioxin increases mitochondrial respiration-dependent reactive oxygen production, which may play an important role in dioxin-induced toxicity and disease.

Shen, D., T. P. Dalton, et al. (2005). "Glutathione redox state regulates mitochondrial reactive oxygen production." J Biol Chem **280**(27): 25305-25312.

Oxidative stress induced by 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD; dioxin) is poorly understood. Following one dose of TCDD (5 microg/kg body weight), mitochondrial succinate-dependent production of superoxide and H2O2 in mouse liver doubled at 7-28 days, then subsided by day 56; concomitantly, levels of GSH and GSSG increased in both cytosol and mitochondria. Cytosol displayed a typical oxidative stress response, consisting of diminished GSH relative to GSSG, decreased potential to reduce protein-SSG mixed disulfide bonds (type 1 thiol redox switch) or protein-SS-protein disulfide bonds (type 2 thiol redox switch), and a +10 mV change in GSSG/2GSH reduction potential. In contrast, mitochondria showed a rise in reduction state, consisting of increased GSH relative to GSSG, increases in type 1 and type 2 thiol redox switches, and a -25 mV change in GSSG/2GSH reduction potential. Comparing Ahr(-/-) knock-out and wild-type mice, we found that TCDD-induced thiol changes in both cytosol and mitochondria were dependent on the aromatic hydrocarbon receptor (AHR). GSH was rapidly taken up by mitochondria and stimulated succinate-dependent H2O2 production. A linear dependence of H2O2 production on the reduction potential for GSSG/2GSH exists between -150 and -300 mV. The TCDD-stimulated increase in succinate-dependent and thiol-stimulated production of reactive oxygen paralleled a four-fold increase in formamidopyrimidine DNA N-

glycosylase (FPG)-sensitive cleavage sites in mitochondrial DNA, compared with a two-fold increase in nuclear DNA. These results suggest that TCDD produces an AHR-dependent oxidative stress in mitochondria, with concomitant mitochondrial DNA damage mediated, at least in part, by an increase in the mitochondrial thiol reduction state.

Shertzer, H. G. (2010). "Protective effects of the antioxidant 4b,5,9b,10-tetrahydroindeno[1,2-b]indole against TCDD toxicity in C57BL/6J mice." Int J Toxicol **29**(1): 40-48.

The protection against 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD; 5 microg/kg body weight) toxicity by the antioxidant 4b,5,9b,10-tetrahydroindeno[1,2-b]indole (THII) was examined in female C57BL/6J mice. TCDD produced increases in the levels of hepatic lipid-derived aldehydes, rates of mitochondrial production of hydrogen peroxide and superoxide, and the oxidation state of cytosolic GSH. In contrast, mitochondrial GSH increased in reduction state, correlating with an increase in mitochondrial membrane potential. Systemically, TCDD lowered body weight gain, percentage body fat, and hepatic ATP levels, parameters prevented by concomitant administration of 100 microM THII in drinking water. However, TCDD-induced increases in mitochondrial respiration and decreased mitochondrial membrane fluidity were not prevented by THII. These results suggest that TCDD-mediated oxidative stress was not responsible for changes in mitochondrial respiration or membrane fluidity. Furthermore, although TCDD produced a large increase in mitochondrial oxygen consumption, this was not associated with the poor gain in weight produced by TCDD.

Shertzer, H. G., M. B. Genter, et al. (2006). "TCDD decreases ATP levels and increases reactive oxygen production through changes in mitochondrial F(0)F(1)-ATP synthase and ubiquinone." Toxicol Appl Pharmacol **217**(3): 363-374.

Mitochondria generate ATP and participate in signal transduction and cellular pathology and/or cell death. TCDD (2,3,7,8-tetrachlorodibenzo-p-dioxin) decreases hepatic ATP levels and generates mitochondrial oxidative DNA damage, which is exacerbated by increasing mitochondrial glutathione redox state and by inner membrane hyperpolarization. This study identifies mitochondrial targets of TCDD that initiate and sustain reactive oxygen production and decreased ATP levels. One week after treating mice with TCDD, liver ubiquinone (Q) levels were significantly decreased, while rates of succinoxidase and Q-cytochrome c oxidoreductase activities were increased. However, the expected increase in Q reduction state following TCDD treatment did not occur; instead, Q was more oxidized. These results could be explained by an ATP synthase defect, a premise supported by the unusual finding that TCDD lowers ATP/O ratios without concomitant changes in respiratory control ratios. Such results suggest either a futile cycle in ATP synthesis, or hydrolysis of newly synthesized ATP prior to release. The TCDD-mediated decrease in Q, concomitant with an increase in respiration, increases complex 3 redox cycling. This acts in concert with glutathione to increase membrane potential and reactive

oxygen production. The proposed defect in ATP synthase explains both the greater respiratory rates and the lower tissue ATP levels.

Sherwood, R. J. and G. C. Sinclair (1999). "New PBPK model applied to old occupational exposure to benzene." Am Ind Hyg Assoc J **60**(2): 259-265.

An intensive program of benzene monitoring using new techniques was undertaken in Western Europe in the late 1960s and early 1970s. Significant exposure was found in the transport of benzene and gasoline, particularly during the loading of barges, and during the loading and operation of sea-going vessels. The ceiling threshold limit value of 25 ppm recommended at that time generated problems in assessing exposure, so alternative criteria were proposed. During that period some shore-based exposures were reported, and their significance was discussed in several articles. The information gained at that time is reexamined by physiologically based pharmacokinetic (PBPK) modeling and is used to help validate an improved PBPK model, which is described and tested on results from experimental exposure in a companion article. The old field data, comprising five specific studies, confirm the relevance of modeling to assessment of occupational exposure, and demonstrate its value for interpretation of field data, which is seldom as complete, systematic, or accurate as that obtained in experimental work. The model suggests that metabolism of benzene in humans may not be restricted to the liver. Sites and processes of metabolism merit further investigation.

Shusterman, D. (1992). "Critical review: the health significance of environmental odor pollution." Arch Environ Health **47**(1): 76-87.

Environmental odor pollution problems generate a significant fraction of the publicly initiated complaints received by air pollution control districts. Such complaints can trigger a variety of enforcement activities under existing state and local statutes. However, because of the frequently transient timing of exposures, odor sources often elude successful abatement. Furthermore, because of the predominantly subjective nature of associated health complaints, air pollution control authorities may predicate their enforcement activities upon a judgment of the public health impact of the odor source. Noxious environmental odors may trigger symptoms by a variety of physiologic mechanisms, including exacerbation of underlying medical conditions, innate odor aversions, aversive conditioning phenomena, stress-induced illness, and possible pheromonal reactions. Whereas relatively consistent patterns of subjective symptoms have been reported among individuals who live near environmental odor sources, documentation of objective correlates to such symptoms would require as-yet unproven research tools. Therefore, given our current state of knowledge, any differential regulatory response to environmental odor pollution, which is based upon the distinction between community "annoyance reactions" and "health effects," is a matter of legal--not scientific--interpretation.

Shusterman, D. (2001). "Odor-associated health complaints: competing explanatory models." Chem Senses **26**(3): 339-343.

Physical symptoms may be reported in workplace and community settings in which odorous airborne chemicals are present. Despite the relative frequency of such reports, clinicians, public health authorities and sensory scientists often experience difficulty interpreting odor-associated symptoms. The approach to interpretation advocated in this review involves: (i) understanding the toxicology of the agent(s) involved (in particular their relative irritant and odorant potencies); (ii) assessing exposure parameters (i.e. concentration and duration). Depending upon exposure concentration, duration and relative irritant and odorant potencies, a variety of pathophysiological mechanisms may be invoked in explaining odor-associated health symptoms. Some of these imputed mechanisms fall under the traditional scope of toxicology and others involve attitudinal and/or behavioral responses to odors.

Shusterman, D. (2003). "Toxicology of nasal irritants." Curr Allergy Asthma Rep **3**(3): 258-265.

The upper airway, including nasal cavities, naso-, oro-, and hypopharynx, is the portal of entry for air pollutants. Upper airway (as well as eye) irritation figures prominently in symptom reporting in so-called problem buildings and with exposure to environmental tobacco smoke. Large particles and water-soluble gases and vapors are likely to have their initial irritant effects in the mucous membranes of the upper airway and eyes, giving warning to the exposed individual to minimize further exposure. The spectrum of irritant-related upper airway health effects is reviewed in this article.

Shusterman, D. and P. C. Avila (2003). "Real-time monitoring of nasal mucosal pH during carbon dioxide stimulation: Implications for stimulus dynamics." Chem Senses **28**(7): 595-601.

Carbon dioxide is a commonly employed irritant test compound in nasal chemesthetic studies because it is essentially free of olfactory stimulus properties. CO(2) is thought to act via hydration to H(2)CO(3) and dissociation to H(+) in nasal mucus, with resulting activation of acid sensors. However, transient changes in nasal mucosal pH have not been documented during CO(2) stimulation in humans. We placed a small pH probe on the floor of the right anterior nasal cavity during CO(2) stimulation in eight human subjects with historically high (>30%) and low (< or =20%) CO(2) detection thresholds. Three second pulses of CO(2) (15-45% v/v) paired with air in random order (12-15 s inter-stimulus interval; 60 s inter-trial interval) were administered by nasal cannula at 5 l/min. in an ascending series. For each subject, both a CO(2) detection threshold and suprathreshold psychophysical ratings [psi; labeled magnitude scale] were generated. All subjects showed phasic drops in pH associated with CO(2) stimulation (DeltapH). For all subjects combined, a positive correlation was apparent between applied [CO(2)] and both DeltapH and psi, as well as between DeltapH and psi themselves ($P < 0.0001$ for each

comparison). Subjects with historically low CO(2) thresholds showed steeper dose-response curves for psi as a function of both applied [CO(2)] and DeltapH, but not for DeltapH as a function of applied [CO(2)]. For the six of eight subjects with measurable pH changes at threshold, DeltapH was positively related to log [CO(2) threshold] ($P < 0.01$). These data imply that variability in CO(2) detection thresholds and suprathreshold rating may derive from intrinsic differences in neural sensitivity, rather than differences in stimulus activation to hydrogen ion.

Shusterman, D., J. Lipscomb, et al. (1991). "Symptom prevalence and odor-worry interaction near hazardous waste sites." Environ Health Perspect **94**: 25-30.

Retrospective symptom prevalence data, collected from over 2000 adult respondents living near three different hazardous waste sites, were analyzed with respect to both self-reported "environmental worry" and frequency of perceiving environmental (particularly petrochemical) odors. Significant positive relationships were observed between the prevalence of several symptoms (headache, nausea, eye and throat irritation) and both frequency of odor perception and degree of worry. Headaches, for example, showed a prevalence odds ratio of 5.0 comparing respondents who reported noticing environmental odors frequently versus those noticing no such odors and 10.8 comparing those who described themselves as "very worried" versus "not worried" about environmental conditions in their neighborhood. Elimination of respondents who ascribed their environmental worry to illness in themselves or in family members did not materially affect the strength of the observed associations. In addition to their independent effects, odor perception and environmental worry exhibited positive interaction as determinants of symptom prevalence, as evidenced by a prevalence odds ratio of 38.1 comparing headaches among the high worry/frequent-odor group and the no-worry/no-odor group. In comparison neighborhoods with no nearby waste sites, environmental worry has been found to be associated with symptom occurrence as well. Potential explanations for these observations are presented, including the possibility that odors serve as a sensory cue for the manifestation of stress-related illness (or heightened awareness of underlying symptoms) among individuals concerned about the quality of their neighborhood environment.

Shusterman, D., M. A. Murphy, et al. (2003). "Differences in nasal irritant sensitivity by age, gender, and allergic rhinitis status." Int Arch Occup Environ Health **76**(8): 577-583.

OBJECTIVES. Sensory (eye, nose, and throat) irritation is an important component of non-specific building-related illness ("sick-building syndrome"). Inter-individual variability in susceptibility to upper airway/mucous membrane irritants is suspected epidemiologically, but has been neglected experimentally. We wished to document population variability in nasal irritant sensitivity, as indexed by threshold measurements of sensory acuity. We hypothesized that younger subjects, women, and allergic rhinitis sufferers would display lower sensory thresholds than would older subjects, men, and rhinitis non-sufferers. METHODS. We evaluated Sixty human subjects (stratified by age, gender, and

seasonal allergy status), using two different test systems: (1) carbon dioxide (detection) and (2) n-propanol (localization). We obtained carbon dioxide (CO2) detection thresholds using an ascending concentration series, presenting 3-s pulses of CO2, paired with air in random order, by nasal cannula. Localization thresholds were obtained by the simultaneous presentation of n-propanol vapor (ascending concentrations in air) and blanks (saturated water vapor in air) to opposite nostrils, with laterality randomized. Threshold data were log-transformed to satisfy normality and analyzed by population marker via ANOVA and linear regression. RESULTS. Test-retest variability was greater for volatile organic compound (VOC) localization than for CO2 detection (r=0.50 and 0.75, respectively); the two measurements were, however, positively correlated (r=0.48; P<0.001). Age predicted both (log-transformed) VOC localization thresholds (P<0.0001) and (log-transformed) CO2 thresholds (P<0.01), with younger age predicting lower thresholds. Female gender predicted lower CO2 detection (P<0.05) but not VOC localization thresholds (P=0.10). Nasal allergies predicted lower VOC localization (P<0.05) but not CO2 detection thresholds (P=0.52). CONCLUSIONS. Consistent with epidemiological reporting patterns in so-called problem buildings, nasal irritant sensitivity appears to be non-randomly distributed in the population, with significant variability predicted by age, gender, and the presence of allergic rhinitis.

Silaev, A. A. (1981). "[Experimental studies on calcium borate toxicity]." Gig Tr Prof Zabol(6): 53-54.

Silk, S. J. (1987). "Setting recommended limits for occupational exposure." Ann Occup Hyg **31**(1): 91-93.

Silverman, K. C., B. D. Naumann, et al. (1999). "Establishing data-derived uncertainty factors from published pharmaceutical clinical trial data."

Siracusa, A., A. Marabini, et al. (2002). "Occupational rhinitis." Monaldi Arch Chest Dis **57**(2): 127-129.

Occupational rhinitis (OR), a very frequent disease caused by several occupations, tends to share etiological agents and to be three times more prevalent than occupational asthma (OA). Exposure, which can be reliably estimated by means of job description or mean week exposure, may be the single most important determinant of occupational sensitization and OR. Atopy is a controversial risk factor for OR and a major risk factor for occupational sensitization when high molecular weight agents are involved. The role of smoking in OR and occupational sensitization is not clear and has yet to be explained in full.

Slavin, R. G. (2003). "Occupational rhinitis." Ann Allergy Asthma Immunol **90**(5 Suppl 2): 2-6.

OBJECTIVE: To define occupational rhinitis, classify its various causes, review the steps in diagnosis, and describe the nonpharmacologic and pharmacologic management principles. DATA SOURCES: A review of MEDLINE articles in English on occupation rhinitis for January 1, 1970, through December 31, 2001, was performed. In addition, references were identified from bibliographies of relevant articles and books. STUDY SELECTION: The expert opinion of the author was used to select the relevant articles for the review. RESULTS: Occupational rhinitis is the episodic, work-related occurrence of sneezing, nasal discharge, and nasal obstruction. It frequently coexists with asthma but may present alone. Occupational rhinitis can be caused by heightened olfactory awareness, nonspecific inflammation of the nose, exposure to a high concentration of irritating and soluble chemical gases, or IgE mechanisms. The history and physical examination are the most important components to the workup of the patient. A site visit to the specific work area may give helpful insights to the patients' exposure. In the case of IgE-mediated allergic occupational rhinitis, skin testing or serologic testing may be useful. Greater objectivity to the diagnosis can be obtained through nasal challenge and the rapidly developing technique of rhinomanometry. Nonpharmacologic management (environmental control) and pharmacotherapy, such as that used in allergic rhinitis, should both be instituted. CONCLUSIONS: Although it does not have the same impact as occupational asthma, occupational rhinitis causes distress, discomfort, and work inefficiency. Attention to principles of management involving nonpharmacologic and pharmacologic measures will spare the patient the symptoms of occupational rhinitis.

Smeets, M. and P. Dalton (2002). "Perceived odor and irritation of isopropanol: a comparison between naive controls and occupationally exposed workers." Int Arch Occup Environ Health **75**(8): 541-548.

OBJECTIVES: To assess sensory irritation levels from isopropanol (IPA) unconfounded by subjective evaluations of odor for comparison against the recommended exposure limits (400 ppm threshold limit value (TLV); American Conference of Governmental Industrial Hygienists). METHOD: The lateralization method was used to assess intra-nasal irritation thresholds for IPA, while odor detection thresholds were also measured. Thresholds for 1-butanol and phenyl ethyl alcohol (PEA) were obtained as positive and negative irritant controls. To compare potency and hedonic characteristics, subjects provided subjective ratings of odor, irritation and annoyance intensity for three concentrations of each chemical. Workers occupationally exposed to IPA (n=26) were compared with previously unexposed controls (n=26). RESULTS: The (geometric) mean odor detection threshold for IPA was slightly higher among exposed workers than controls (39 ppm vs. 11 ppm). Lateralization thresholds measuring intra-nasal irritation were elevated when compared with controls (6,083 ppm in exposed workers vs. 3,361 ppm in naive controls), with a significantly higher proportion of phlebotomists being unable to lateralize the maximum concentration regarded as safe, than controls. Calculations of the 6th percentile for lateralization thresholds

revealed that 95% of the sample did not experience sensory irritation below 512 ppm. Thus, while odor detection thresholds were well below the current recommended exposure limits, the irritation thresholds were well above these values. The odor, irritation and annoyance from IPA was perceived, on average, as between weak and almost strong, from lowest to highest concentration. CONCLUSIONS: The results indicate that current exposure guidelines would be adequately protective of the acute adverse effect of nasal sensory irritation, as operationally defined by the intra-nasal lateralization threshold. Exposures to higher concentrations should perhaps be evaluated on the basis of existing knowledge about systemic, rather than local (e.g., irritation), toxic effects. IPA appears to be a weak sensory irritant and occupational exposure to IPA appears to elicit small changes in sensitivity that do not generalize to other odorants (e.g., PEA and 1-butanol) and are likely to be reversible.

Smeets, M. A., C. Maute, et al. (2002). "Acute sensory irritation from exposure to isopropanol (2-propanol) at TLV in workers and controls: objective versus subjective effects." Ann Occup Hyg **46**(4): 359-373.

OBJECTIVES: Phlebotomists occupationally exposed to isopropanol (IPA) (2-propanol) and naive controls (n = 12 per group) were exposed to the time-weighted average threshold limit value of 400 p.p.m. IPA for 4 h in an environmental chamber to investigate: (i) acute effects of sensory irritation using subjective health symptom reports and objective, physiological end-points; and (ii) differences in measured effects in relation to exposure history. METHODS: Before, during and after exposure subjects gave self-reports of health complaints. During exposure subjects rated the intensity of the odor, sensory irritation and annoyance. Objective end-points of ocular hyperemia, nasal congestion, nasal secretion and respiration were obtained at various times before, during and after exposure. Results were compared with exposure to phenylethyl alcohol (PEA), a negative control for irritation, and to clean air (CA), a negative control for odor and irritation, using a within-subjects design. RESULTS: Significantly higher intensity ratings of odor, irritation and annoyance were reported during the exposure to IPA, when compared with exposure to CA or PEA. Nevertheless, the overall level of reported sensory irritation to IPA was low and perceived as 'weak' on average. Health symptom ratings were not significantly elevated for IPA as compared with PEA or CA exposure. The only physiological end-point that showed a change exclusively in the IPA condition was respiration frequency: relative to baseline, respiration frequency increased in response to IPA in both groups. No differences were encountered between the occupationally exposed and the control groups. CONCLUSIONS: The increase in respiration frequency in response to IPA may reflect either a reflexive change due to sensory irritation (an autonomic event) or a voluntary change in breathing in response to perception of an unpleasant, solvent-like odor (a physiological event caused by cognitive mediation). Our findings on objective end-points, including nasal and ocular sensory irritation, did not confirm subjective irritation reports. Irritation reports and odor intensity decreased, rather than increased,

over time, lending credence to the cognitive argument and suggesting that the elevated subjective responses to IPA may be mediated by responses to its odor.

Smith, J. S. and J. M. Mendeloff (1999). "A quantitative analysis of factors affecting PELs and TLVs for carcinogens." Risk Analysis **19**(6): 1223-1234.

Smith, R. A. and F. M. Ascherl (1998). "Measurement of borate in occupational environments." Biol Trace Elem Res **66**(1-3): 55-58.

The hydration stability for inhalable borate particles has been characterized as a function of temperature and relative humidity when collected by a field personnel monitor. The rate of hydration was measured for boric acid (B[OH]3); Neobor borax 5 mol (Na2O x 2B2O3 x 5H2O); borax 10 mol (Na2O x 2B2O3 x 10H2O); anhydrous boric acid (B2O3); and anhydrous borax (Na2O x 2B2O3). The particle size is large in bulk commercial products, such that they can be handled and stored without problems. However, inhalable dust particles, in the range of 20 microm (MMD), undergo hydration/dehydration rapidly owing to their high surface-to-volume ratio. The hydration state of a collected air sample was found to be strongly dependent on the conditions of relative humidity and temperature during its collection. As a consequence, the actual chemical species of dust being inspired cannot be identified accurately. Inhalable particles of borax 10 mol placed in a field personal monitoring cartridge and exposed to dry air at 2.0 L/min at 70 degrees F for 7 h undergo rapid dehydration, producing a sodium borate residue having significantly less than four waters of hydration. Likewise, inhalable particles of anhydrous boric acid and anhydrous borax were found to hydrate under normal atmospheric conditions. Borax 5 mol and boric acid were found to be stable to dehydration. In most cases, the specific borate species or borate compounds collected in a field monitor cannot be accurately characterized other than by their boron (B) content.

Smith, R. A. and F. M. Ascherl (1999). "Issues concerning the measurement of borate in occupational environments." Am Ind Hyg Assoc J **60**(5): 651-658.

Borates are susceptible to weight change due to uptake or loss of water and this hydration instability can lead to gravimetric and interpretation errors in occupational hygiene field sampling of dust. The hydration stability for inhalable borate dust particles (mean diameter 7-22 microns) was characterized over a range of ambient temperature and relative humidity conditions simulating field sampling. Borax 10 mol (Na2O.2B2O3.10H2O), a fully hydrated borate, has a relatively high vapor pressure to water that led to rapid dehydration with significant weight change. Low hydrate borates, Neobor borax 5 mol (Na2O.2B2O3.5H2O), anhydrous boric acid (B2O3), and anhydrous borax (Na2O.2B2O3) were found to hydrate rapidly with an increase in weight. In contrast, boric acid (B[OH]3) and borax 5 mol were found to be stable to dehydration under all conditions. Boron can be measured with high analytical accuracy, but because the specific borate species or borate compounds collected in a 37-mm dust sampler cannot be accurately identified, it is argued

that occupational exposure values should be revised to reflect exposure to boron and exposure values for these borates should be the same based on equivalent boron content.

Smith, R. G. (1985). "Cummings Award address. Occupational health standard setting in the United States." Am Ind Hyg Assoc J **46**(10): 541-546.

Socha, G. E. (1975). "Dow's approach to toxicity and exposure guideline development in industrial hygiene." J Occup Med **17**(4): 251-253.

Sorahan, T., L. Hamilton, et al. (1998). "Short communication-Quantitative risk assessments derived from occupational cancer epidemiology: A worked example." Ann. Occup. Hyg. **42**(5): 347-352.

Spear, R. C. and S. Selvin (1989). "OSHA's permissible exposure limits: regulatory compliance versus health risk." Risk Anal **9**(4): 579-586.

Workplace exposures to airborne chemicals are regulated in the U.S. by the Occupational Safety and Health Administration (OSHA) via the promulgation of permissible exposure limits (PELs). These limits, usually defined as eight-hour time-weighted average values, are enforced as concentrations never to be exceeded. In the case of chronic or delayed toxicants, the PEL is determined from epidemiological evidence and/or quantitative risk assessments based on long-term mean exposures or, equivalently, cumulative lifetime exposures. A statistical model was used to investigate the relation between the compliance strategy, the PEL as a limit never to be exceeded, and the health risk as measured by the probability that an individual's long-term mean exposure concentration is above the PEL. The model incorporates within-worker and between-worker variability in exposure, and assumes the relevant distributions to be log-normal. When data are inadequate to estimate the parameters of the full model, as it is in compliance inspections, it is argued that the probability of a random measurement being above the PEL must be regarded as a lower bound on the probability that a randomly selected worker's long-term mean exposure concentration will exceed the PEL. It is concluded that OSHA's compliance strategy is a reasonable, as well as a practical, means of limiting health risk for chronic or delayed toxicants.

Spirtas, R., M. Steinberg, et al. (1986). "Identification and classification of carcinogens: procedures of the Chemical Substances Threshold Limit Value Committee, ACGIH. American Conference of Governmental Industrial Hygienists." Am J Public Health **76**(10): 1232-1235.

The Chemical Substances Threshold Limit Value Committee of the American Conference of Governmental Industrial Hygienists has refined its procedures for evaluating carcinogens. Types of epidemiologic and toxicologic evidence used are reviewed and a discussion is presented on how the Committee evaluates data on carcinogenicity. Although it has not been conclusively determined

whether biological thresholds exist for all types of carcinogens, the Committee will continue to develop guidelines for permissible exposures to carcinogens. The Committee will continue to use the safety factor approach to setting Threshold Limit Values for carcinogens, despite its shortcomings. A compilation has been developed for lists of substances considered to be carcinogenic by several scientific groups. The Committee will use this information to help to identify and classify carcinogens for its evaluation.

Sprague, G. and T. Sutton (1997). "Occupational toxicology: test methods and approaches for the pharmaceutical industry." Occup Med **12**(1): 119-129.

Occupational toxicologists consider the intended pharmacologic effects of active substances to be adverse and undesirable in healthy workers, because of the absence of any therapeutic benefit. This chapter covers testing of finished agents as well as intermediates and related materials for determining exposure routes and potential toxicity.

Srivasstava, A. K. and B. M. Gupta (1989). "Oculotoxins: Effects, Implications, and Importance in Occupational Health." American Journal of Industrial Medicine **16**: 723-726.

Stadler, J. C. and G. L. Kennedy, Jr. (1996). "Evaluation of the sensory irritation potential of volatile organic chemicals from carpets--alone and in combination." Food Chem Toxicol **34**(11-12): 1125-1130.

Some individuals have reported burning or painful sensations in the eyes or upper respiratory tract when they enter certain indoor environments. Recently, carpets have been suggested as a potential source of organic chemicals that could contribute to this irritation. The sensations are generally termed 'sensory irritation' or 'pungency', and result from stimulation of trigeminal nerve endings. Indoor air quality is typically evaluated based on the concentrations of individual airborne materials, and rarely do concentrations of potentially offending materials exceed levels expected to cause adverse human health effects. In particular, volatile organic chemicals are measured at low levels (ppb) in the indoor environment. Sources of these organics vary considerably, but concentrations of the individual chemicals do not ordinarily exceed irritating levels. It is possible that the chemical mixture may cause effects not predicted by the present data available on individual chemicals. A list of approximately 50 chemicals identified in carpet emissions was developed for the study. Chemicals were selected from over 200, based on the highest frequency of occurrence and/or highest rate of emission. A mouse model of sensory irritation was used to examine the individual chemicals. In this model, mice are exposed to airborne chemicals by inhalation and evaluated for changes in respiratory function parameters. The model relies on chemical stimulation of the trigeminal nerve endings to elicit a response identified by a decrease in respiratory frequency and an alteration in the breathing pattern. Chemicals are compared quantitatively by measuring the airborne concentration required to elicit a 50% depression in respiratory rate

(RD50). Some of the chemicals were previously evaluated by this method, while others were recently examined. The emission chemicals tested individually to date have had RD50 values that generally range from 100 ppm to more than 1000 ppm, indicating that human respiratory irritation would not be expected from the individual chemicals at levels measured in the indoor environment. Differences observed in timing of response from one chemical to another and experimental variability will be important considerations for mixtures testing. The potential for combinations of these emission chemicals to cause sensory irritation at low concentrations, resulting in additivity, synergy, or antagonism of the response, will be addressed. These results should have general application for assessing the risk of causing respiratory irritation in humans exposed to combinations of organic chemicals.

Stamm, R. (2001). "MEGA-database: one million data since 1972." Appl Occup Environ Hyg **16**(2): 159-163.

MEGA is the chemical workplace exposure database of the Institute for Occupational Safety (BIA) of the German Berufsgenossenschaften (BG) (statutory accident institutions for insurance and prevention). On the legal basis of the social insurance law the inspectorates of the BGs conduct workplace measurements of chemical and biological agents. The BGs have cooperated with BIA within the Berufsgenossenschaftliches Messsystem Gefahrstoffe--BGMG since 1972: measurements are done by the BGs, analyses and data processing are the tasks of BIA. In 1999 31,000 measurements with 68,000 analyses were taken in 4,000 enterprises. All data are stored in the MEGA-database with up to 150 pieces of information (describing type of workplace, working conditions, measured substances, sampling strategy, sampling duration, sampling and analytical method etc.), for each result. MEGA contains today about 1,000,000 measurements of more than 400 substances starting in 1972. MEGA is used by BIA and the BGs for the following purposes: prevention (e.g., identification of hazards, efficiency of exposure reducing measures, determination of technical criteria for exposure limit values), epidemiological questions, and investigations of occupational diseases. In the framework of the measuring and inspection activities and tasks of the inspectorates of the BGs the locations for measurements are not randomly selected, but are based on criteria such as supposed critical exposure situations or testing the efficiency of exposure reducing measures. Nevertheless, a statistical appraisal of the data is possible for different purposes considering the specific determinants of the results, as, for example, classification of enterprises (sectors), workplaces (activities, tasks), used materials, and products. The MEGA-database will be further developed into a multifactorial exposure database with additional data on biological exposure to bacteria and funghi, but also noise and other data.

Stayner, L. and R. Hornung (1994). Assessing the risks of occupational hazards. Occupational Medicine. C. Zenz, O. B. Dickerson and E. P. Horvath. St. Louis, Mosby-Year Book**:** 1145-1148.

Stayner, L., R. Smith, et al. (1995). "Modeling epidemiolgic studies of occupational cohorts for the quantitative assessment of carcinogenic hazards." American Journal of Industrial Medicine **27**: 155-170.

Steenland, K. and D. Brown (1995). "Silicosis among gold miners: Exposure-response analyses and risk assessment." Am. J. Pub. Health **85**(10): 1372-1377.

Stelljes, M. E. and R. R. Wood (2004). "Development of an occupational exposure limit for n-propylbromide using benchmark dose methods." Regul Toxicol Pharmacol **40**(2): 136-150.

This paper presents the development of an occupational exposure level (OEL) for n-propylbromide (nPB) using benchmark dose methods. nPB is a non-ozone depleting solvent, proposed under the Significant New Alternatives Policy (SNAP) for use as a precision vapor degreaser. OELs have generally been developed on the basis of a NOAEL or LOAEL and application of uncertainty factors; this paper represents a departure from historic methods. Six recently completed toxicological studies were critically reviewed to identify (1) toxicologically significant endpoints, (2) dose-response information on these endpoints, and (3) uncertainties and limitations associated with the studies. Dose-response data were compiled and entered into the USEPA's benchmark dose software for calculation of a benchmark dose (BMD) and a benchmark dose low (BMDL). Once values were estimated for all relevant studies, they were then incorporated into a weight-of-evidence approach to develop a single BMD and BMDL representative of nPB. This approach is similar to that recently taken by USEPA to develop their own recommended OEL for nPB. USEPA's approach is compared and contrasted with ours, particularly in relation to the application of uncertainty factors (UFs) to generate a final OEL. There are no published criteria for application of UFs in developing an OEL. Although USEPA recommends utilizing a UF of 9, based on intraspecies variability and pharmacokinetic differences between rats and humans, to meet the goal of protecting healthy adult in a workplace setting, no uncertainty factor was deemed necessary for nPB in this paper. Therefore, the BMDL was recommended as the OEL.

Stewart, P. and M. Stenzel (2000). "Exposure assessment in the occupational setting." Appl Occup Environ Hyg **15**(5): 435-444.

Exposure assessment, the first step in risk assessment, has traditionally been performed for a variety of purposes. These include compliance determinations; management of specific programs that are implemented by comparison with an occupational exposure limit (such as medical surveillance, training, and respiratory protection programs); task/source investigations for determination of exposure control strategies; epidemiologic studies; worker compensation/toxic tort cases; health complaint or problem investigations; risk assessment and management; and evaluation of future changes in the workplace (e.g., introduction of a new chemical). Each purpose requires slightly different

approaches, but there are also many similarities. The goal of this paper is to identify a general approach to assessing exposures that can be used for all purposes with only slight modifications. Five components of exposure assessments are identified: collection of data, identification of the hazard, selection of exposure metrics, definition of exposure groups and estimation of the exposures. The characteristics of these components for each type of assessment are discussed. From this review, it is clear that there is substantial overlap across the types of assessment. A single exposure assessment program is suggested that encompasses all the needs of these assessments and incorporates assessment of exposures for an entire workforce at a site at minimal cost by using prediction models and validation with measurements.

Stijkel, A. and L. Reijnders (1995). "Implementation of the precautionary principle in standards for the workplace." Occup Environ Med **52**(5): 304-312.

The objectives were to describe and discuss the current and proposed European occupational health policy on two categories of substances that pose serious effects: those potentially carcinogenic or genotoxic and those with toxic effects on reproduction. The precautionary principle was applied to setting standards for the workplace for those two categories of substances, to give an impression of the resulting limit values and the consequences of the implementation of this precautionary principle. A pragmatic approach was chosen as this starts with substantial indications of health risks. For the suspected carcinogenic or genotoxic substances 0.1 mg/m3 as a precautionary occupational exposure limit (precautionary OEL) is proposed. For the substances suspected of causing reproductive toxicity the precautionary OEL was derived in three ways, depending on the availability of data and of a current Dutch workplace standard (MAC, maximum accepted concentration): (a) by calculation based on available inhalatory animal data on the risks of reproductive toxicity; (b) by adding a safety factor of 10 to the current MAC, if no inhalatory animal data on reproductive toxicity are available; (c) by using 0.1 mg/m3 as precautionary OEL for substances suspected of having reproductive toxicity but without inhalatory animal data on reproductive toxicity and without a MAC.

Stijkel, A., J. C. van Eijndhoven, et al. (1996). "Drafting guidelines for occupational exposure to chemicals: the Dutch experience with the assessment of reproductive risks." Am J Ind Med **30**(6): 705-717.

The Dutch procedure for standard setting for occupational exposure to chemicals, just like the European Union (EU) procedure, is characterized by an organizational separation between considerations of health on the one side, and of technology, economics, and policy on the other side. Health considerations form the basis for numerical guidelines. These guidelines are next combined with technical-economical considerations. Standards are then proposed, and are finally set by the Ministry of Social Affairs and Employment. An analysis of this procedure might be of relevance to the US, where other procedures are used and criticized. In this article we focus on the first stage of the standard-setting

procedure. In this stage, the Dutch Expert Committee on Occupational Standards (DECOS) drafts a criteria document in which a health-based guideline is proposed. The drafting is based on a set of starting points for assessing toxicity. We raise the questions, "Does DECOS limit itself only to health considerations? And if not, what are the consequences of such a situation?" We discuss DECOS' starting points and analyze the relationships between those starting points, and then explore eight criteria documents where DECOS was considering reproductive risks as a possible critical effect. For various reasons, it will be concluded that the starting points leave much interpretative space, and that this space is widened further by the manner in which DECOS utilizes it. This is especially true in situations involving sex-specific risks and uncertainties in knowledge. Consequently, even at the first stage, where health considerations alone are intended to play a role, there is much room for other than health-related factors to influence decision making, although it is unavoidable that some interpretative space will remain. We argue that separating the various types of consideration should not be abandoned. Rather, through adjustments in the starting points and aspects of the procedure, clarity should be guaranteed about the way the interpretative space is being employed.

Stjarne, P. (1991). "Sensory and motor reflex control of nasal mucosal blood flow and secretion; clinical implications in non-allergic nasal hyperreactivity." Acta Physiol Scand Suppl **600**: 1-64.

1. Co-localization of SP and CGRP was observed in a dense intraepithelial and perivascular network of capsaicin-sensitive sensory nerves in the nasal mucosa of different species, including man. The morphological similarity in the distribution of these nerves among various experimental animals and man indicates that animal experimental data may be used for the understanding of sensory mechanisms in the human nasal mucosa. 2. Release of CGRP into the venous effluent of the nasal mucosa in parallel with vasodilatation was demonstrated in vivo upon antidromic stimulation of the maxillary division of the trigeminal nerve or local i.a. capsaicin injection. 3. Infusion of capsaicin induced concentration-dependent increase in arterial, venous and superficial blood flow as well as V in the pig nasal mucosa. Exogenous SP, CGRP and VIP displayed concentration-dependent, but partly separate, vasodilatory profiles in the nasal mucosa. SP was more potent regarding maximal blood flow increase, whereas the vasodilatation induced by CGRP infusion was more long-lasting on an equimolar basis. Although VIP caused an increase in ABF and VBF as well as V, the LDF signal (i.e. superficial blood flow) was decreased, possibly due to a stealing phenomenon. 4. Local i.a. capsaicin infusion induced a bilateral chlorisondamine-sensitive atropine-resistant vasodilatation. However, i.a. capsaicin in higher doses also induced a chlorisondamine-resistant vasodilatation in the superficial vascular compartment of the nasal mucosa, presumably via the release of sensory neuropeptides. Thus, the vasodilatory effect of capsaicin may be due to a complex interaction of local effects on the sensory nerve terminals close to blood vessels in the nasal mucosa and a main parasympathetic central reflex. 5.

Capsaicin, but not nicotine, induced a concentration dependent increase in irritation or pain upon local application to the human nasal mucosa. Since both agents evoked secretion, this indicates that capsaicin and nicotine activate different populations of sensory neurons. Local application onto the nasal mucosa of capsaicin and nicotine as well as metacholine induced a concentration dependent muscarinic antagonist sensitive increase in the secretory response. The capsaicin or nicotine-induced secretion was bilateral and could be markedly reduced by combined pretreatment with a local anaesthetic and a vasoconstrictor. Our findings suggest that the secretory effect of capsaicin and nicotine in the human nasal mucosa is mediated via a central parasympathetic reflex arc with a final muscarinic receptor mechanism. No clear-cut contribution seemed to be exerted by locally released tachykinins and CGRP as direct trigger substances for the secretory response to capsaicin.(ABSTRACT TRUNCATED AT 400 WORDS)

Stokinger, H. E. (1988). "Threshold limit values: any alternative?" Am J Ind Med **14**(2): 231-232.

Storm, J. E. and K. K. Rozman (1998). "Derivation of an occupational exposure limit (OEL) for methylene chloride based on acute CNS effects and relative potency analysis." Reg. Toxicol. Pharmacol. **27**: 240-250.

Storm, J. E., K. K. Rozman, et al. (2000). "Occupational exposure limits for 30 organophosphate pesticides based on inhibition of red blood cell acetylcholinesterase." Toxicology **150**(1-3): 1-29.

Toxicity and other relevant data for 30 organophosphate pesticides were evaluated to suggest inhalation occupational exposure limits (OELs), and to support development of a risk assessment strategy for organophosphates in general. Specifically, the value of relative potency analysis and the predictability of inhalation OELs by acute toxicity measures and by repeated oral exposure NOELs was assessed. Suggested OELs are based on the prevention of red blood cell (RBC) acetylcholinesterase (AChE) inhibition and are derived using a weight-of-evidence risk assessment approach. Suggested OEL values range from 0.002 to 2 mg/m(3), and in most cases, are less than current permissible exposure levels (PELs) or threshold limit values(R) (TLVs(R)). The available data indicate that experimental data for most organophosphates evaluated are limited; most organophosphates are equally potent RBC AChE inhibitors in different mammalian species; NOELs from repeated exposure studies of variable duration are usually equivalent; and, no particular grouping based on organophosphate structure is consistently more potent than another. Further, relative potency analyses have limited usefulness in the risk assessment of organophosphates. The data also indicated that equivalent relative potency relationships do not exist across either exposure duration (acute vs. repeated) or exposure route (oral vs. inhalation). Consideration of all variable duration and exposure route studies are therefore usually desirable in the development of an OEL, especially when data

are limited. Also, neither acute measures of toxicity nor repeated oral exposure NOELs are predictive of weight-of-evidence based inhalation OELs. These deviations from what is expected based on the common mechanism of action for organophosphates across exposure duration and route - AChE inhibition - is likely due to the lack of synchrony between the timing of target tissue effective dose and the experimental observation of equivalent response. Thus, comprehensive interpretation of all toxicity data in the context of available toxicokinetic, toxicodynamic and exposure information for each individual organophosphate in a weight-of-evidence based risk assessment is desirable when deriving inhalation OELs.

Sucker, K., R. Both, et al. (2001). "Adverse effects of environmental odours: reviewing studies on annoyance responses and symptom reporting." Water Sci Technol **44**(9): 43-51.

Air pollution control authorities dealing with odourous emissions from industrial, municipal and agricultural activities are often faced with many complaints from the public. In Germany, the Directive on Odour in ambient air provides a regulation system for the abatement of odour annoyance. Ambient air quality standards have been established based on investigations of the relationship between ambient odour load and community annoyance reaction. This paper describes a tool for the assessment of annoyance reactions, whereby degree of annoyance is correlated with ambient odour load. Systematic exposure response relations have been established for odour annoyance responses and symptom reporting for a variety of industrial sources. However, the precision of annoyance prediction from odour exposure measures rarely exceeds r2 = 0.17 in such studies. This is partly due to the fact that person-related factors, such as age, perceived health or stress coping styles, modify exposure response relations. The contribution of intensity and unpleasantness (hedonic tone) of ambient odours as modifying the annoyance reaction is currently investigated.

Suda, M., H. Tsuruta, et al. (1999). "The contribution of acute toxicity in animals to occupational exposure limits of chemical substances." Ind Health **37**: 22-27.

Sussman, R. G., T. A. Kimmel, et al. (1997). "Health hazard labeling for hazard communication in the pharmaceutical industry." Occup Med **12**(1): 107-117.

Company health and safety professionals must advise workers of the potential hazards of workplace chemicals. Yet it is difficult to develop one, consistent corporate labeling strategy for worldwide use. This chapter describes one company's approach to devising a corporate policy satisfying all criteria.

Sweeney, L. M. (2000). "Comparing occupational and evironmental risk assessment methodologies using pharmacokinetic modeling." Hum Ecol Risk Assess **6**(6): 1101-1124.

Sweeney, L. M., T. R. Tyler, et al. (2001). "Proposed occupational exposure limits for select ethylene glycol ethers using PBPK models and Monte Carlo Simulations." Tox. Sci. **62**: 124-139.

Swuste, P., A. Hale, et al. (2003). "Solbase: a databank of solutions for occupational hazards and risks." Ann Occup Hyg **47**(7): 541-547.

Several attempts have been made to develop strategies for an effective control of workplace hazards. This paper will focus on the results of a European project called Solbase, which is a databank for solutions to occupational hazards and risks. The Safety Science Group of Delft University of Technology in collaboration with TNO Work and Organisation (formerly NIA-TNO) designed Solbase in a series of projects funded by the Dutch Ministry of Social Affairs and Employment and the European Commission. It consists of the design of and software for a databank with an intelligent navigation system allowing users two principal entry points, which correspond to two basic types of solutions. The first entry point is based on the production process, subdivided into the production principle and production function. This entry point provides the dissemination of solutions within and between branches of industry. The second entry point includes the hazard and its emission and transmission as an access point for more conventional occupational hygiene control measures. With the partners of the consortium, from Spain, Italy, Ireland, Germany, the UK and The Netherlands, 535 new and existing solutions throughout Europe and the world were gathered to test the software and the solutions during a field study. Despite the relatively small number of 'test solutions' used, 54% of the search actions in the field study resulted in a useful and suitable solution which the company could actually put into practice. The companies characterized the software as very user friendly. The reproducibility of the coding system for solutions, the classification tree, was satisfactory. Most coders chose the same keywords from the classification tree to describe a corresponding solution. Solbase is a good searching machine for workplace solutions. Especially, the classification of production processes is an inherent guarantee of an exchange of information across the borders of a specific company or branch of industry.

Tait, K. (1992). "The workplace exposure assessment expert system (WORKSPERT)." Am Ind Hyg Assoc J **53**: 84-98.

Tait, K. (1993). "The workplace exposure assessment workbook (WORKBOOK)." App Occ Env Hyg **8**(1): 55-68.

Tait, K. and M. Mchta (1997). "Validation of the workplace exposure assessment expert system (WORKBOOK)." Am Ind Hyg Asso J **58**: 592-602.

Tarlo, S. M. (2003). "Workplace irritant exposures: do they produce true occupational asthma?" Ann Allergy Asthma Immunol **90**(5 Suppl 2): 19-23.

OBJECTIVE: To describe the features of irritant-induced asthma and discuss the diagnosis in relation to differing workplace irritant exposures and symptomatic responses. DATA SOURCES: A review of MEDLINE articles on this topic from January 1, 1985, through December 31, 2001 was performed. STUDY SELECTION: The author selected relevant articles for inclusion in the review. RESULTS: Many reports indicate that unintentional high-level respiratory irritant exposures can induce the new onset of asthma. Cases that meet strict criteria for a syndrome of irritant-induced asthma, termed reactive airways dysfunction syndrome, can be diagnosed with relative certainty. Several reports of irritant-induced asthma, especially prevalence studies, have relied on historical data or have otherwise modified the reactive airways dysfunction syndrome criteria for diagnosis (eg, expanding the definition to include the symptom onset several days after exposure). Such modifications, or inclusion of cases with incomplete documentation, likely increase diagnostic sensitivity but may reduce the certainty of diagnosis for individual cases. Expanding exposure criteria to moderate or long-term low-level irritant exposures causes difficulty in excluding transient irritant exacerbation of underlying asthma or coincidental onset of asthma during working life. Although recent population studies suggest a greater relative risk of asthma in occupations with expected low-to-moderate respiratory irritant exposures, currently no objective laboratory tests exist to exclude coincidental asthma in such patients. CONCLUSIONS: Irritant-induced asthma can be produced by high-level unintentional respiratory irritant exposures at work or outside the workplace. Lower levels of exposure to respiratory irritants at work are more common, and additional studies are needed to determine the airway effects of such exposures.

Tarlo, S. M. and G. M. Liss (2003). "Occupational asthma: an approach to diagnosis and management." Cmaj **168**(7): 867-871.

Tas, S., R. Lauwerys, et al. (1996). "Occupational hazards for the male reproductive system." Crit Rev Toxicol **26**(3): 261-307.

The etiology of male infertilities is largely undetermined, and our knowledge of exogenous factors affecting the male reproductive system is still limited. In particular, the role of specific environmental and occupational factors is incompletely elucidated. Various occupational (physical and chemical) agents have been shown to affect male reproductive functions in animals, but large differences in reproductive function and/or xenobiotic handling between species limit extrapolation to humans. When available, human data are often conflicting and, except in a few instances, usually refer to broad and heterogenous occupational categories or to groups of agents (e.g., solvents). It is often difficult to elucidate the role of a single agent because occupational exposure conditions are often complex and various confounding factors related to lifestyle (smoking, alcohol, and diet) or socioeconomic state may also affect sperm quality, fertility, or pregnancy outcomes. The objective of this work is to summarize the main epidemiological and, where relevant, experimental findings pertaining to agents

(physical and chemical) encountered in the occupational environment that might affect the male reproductive system (sperm count, motility and morphology, libido, and fertility) and/or related pregnancy outcomes (spontaneous abortion, stillbirth, low birth weight, and birth defects and childhood malignancy in offspring). Some methodological issues related to research on the reproductive effects of toxicants are also discussed briefly.

Tearle, P. (2002). "Occupational exposure limits: options for change." Commun Dis Public Health **5**(3): 262-264.

The Health and Safety Commission's (HSC) Advisory Committee on Toxic Substances has produced a discussion document on the future of occupational exposure limits for hazardous chemicals. The HSC wish to see changes made in the way standards which determine the amount of substance allowable in workplace air are implemented. The objective of the review and change is to ensure that protection of workers' health is continually improved as new and changing standards are announced. This article looks at the problems associated with the implementation of the current standards and the options proposed for change.

ten Berge, W. F., A. Zwart, et al. (1986). "Concentration-Time mortality response relationship of irritant and systemically acting vapours and gases." J. Haz. Mat. **13**: 301-309.

Tharmmaphornphilas, W., B. Green, et al. (2003). "Applying mathematical modeling to create job rotation schedules for minimizing occupational noise exposure." AIHA J (Fairfax, Va) **64**(3): 401-405.

This research developed worker schedules by using administrative controls and a computer programming model to reduce the likelihood of worker hearing loss. By rotating the workers through different jobs during the day it was possible to reduce their exposure to hazardous noise levels. Computer simulations were made based on data collected in a real setting. Worker schedules currently used at the site are compared with proposed worker schedules from the computer simulations. For the worker assignment plans found by the computer model, the authors calculate a significant decrease in time-weighted average (TWA) sound level exposure. The maximum daily dose that any worker is exposed to is reduced by 58.8%, and the maximum TWA value for the workers is reduced by 3.8 dB from the current schedule.

Thier, R. and H. M. Bolt (2001). "European aspects of standard setting in occupational hygiene and medicine." Rev Environ Health **16**(2): 81-86.

Occupational standards concerning the allowable concentrations of chemical compounds in the ambient air of workplaces have been established in several countries at national levels. With the integration of the European Union, a need exists for establishing harmonized Occupational Exposure Limits. For analytical developments, it is apparent that methods for speciation or fractionation of

carcinogenic metal compounds will be of increasing practical importance for standard setting. Criteria of applicability under field conditions, cost-effectiveness, and robustness are practical driving forces for new developments. When the European Union issued a list of 62 chemical substances with Occupational Exposure Limits in 2000, 25 substances received a 'skin' notation. The latter indicates that toxicologically significant amounts may be taken up via the skin. Similar notations exist on national levels. For such substances, monitoring concentrations in ambient air will not be sufficient; biological monitoring strategies will gain further importance in the medical surveillance of workers who are exposed to such compounds. Proceedings in establishing legal frameworks for a biological monitoring of chemical exposures within Europe are paralleled by scientific advances in this field. A new aspect is the possibility of a differential adduct monitoring, using blood proteins of different half-life or lifespan. This technique allows differentiation between long-term mean exposure to reactive chemicals and short-term episodes, for example, by accidental overexposure. For further analytical developments, the following issues have been addressed as being particularly important: New dose monitoring strategies, sensitive and reliable methods for detection of DNA adducts, cytogenetic parameters in biological monitoring, methods to monitor exposure to sensitizing chemicals, and parameters for individual susceptibilities to chemical toxicants.

Thomas, R. S., P. L. Bigelow, et al. (1996). "Variability in biological exposure indices using physiologically based pharmacokinetic modeling and Monte Carlo simulation." Am Ind Hyg Assoc J **57**(1): 23-32.

By using physiologically based pharmacokinetic (PBPK) modeling coupled with Monte Carlo simulation, the interindividual variability in the concentrations of chemicals in a worker's exhaled breath and urine were estimated and compared with existing biological exposure indices (BEIs). The PBPK model simulated an exposure regimen similar to a typical workday, while exposure concentrations were set to equal the ambient threshold limit values (TLVs) of six industrial solvents (benzene, chloroform, carbon tetrachloride, methylene chloride, methyl chloroform, and trichloroethylene). Based on model predictions incorporating interindividual variability, the percentage of population protected was derived using TLVs as the basis for worker protection. Results showed that current BEIs may not protect the majority or all of the workers in an occupational setting. For instance, current end-expired air indices for benzene and methyl chloroform protect 95% and less than 10% of the worker population, respectively. Urinary metabolite concentrations for benzene, methyl chloroform, and trichloroethylene were also estimated. The current BEI recommendation for phenol metabolite concentration at the end-of-shift sampling interval was estimated to protect 68% of the worker population, while trichloroacetic acid (TCAA) and trichloroethanol (TCOH) concentrations for methyl chloroform exposure were estimated to protect 54% and 97%, respectively. The recommended concentration of TCAA in urine as a determinant of trichloroethylene exposure protects an estimated 84% of the workers. Although many of the existing BEIs considered appear to protect a

majority of the worker population, an inconsistent proportion of the population is protected. The information presented in this study may provide a new approach for administrative decisions establishing BEIs and allow uniform application of biological monitoring among different chemicals.

Thun, M. J., C. G. Elinder, et al. (1991). "Scientific basis for an occupational standard for cadmium." Am J Ind Med **20**(5): 629-642.

The U.S. Occupational Safety and Health Administration (OSHA) has proposed a revised 8-hour permissible exposure limit (PEL) for cadmium in air of either 1 or 5 micrograms/m3, based upon the prevention of lung cancer and kidney dysfunction. To evaluate the scientific basis for these alternative standards, we compare the OSHA estimates of risk, derived from mathematical modelling of selected studies, to empirical data on lung cancer and kidney dysfunction in the published literature. At least seven epidemiologic studies examine renal tubular proteinuria by cumulative cadmium exposure. Three suggest increased proteinuria at cumulative exposures below 500 micrograms/m3-year (equivalent to a PEL of 11.1 micrograms/m3 over 45 working years). One shows prevalence increasing at cumulative exposures between 100 and 299 micrograms/m3 (equivalent to a PEL between 2.2 and 6.6 micrograms/m3). Insufficient data exist to estimate a no-effect level for kidney toxicity. For lung cancer, qualitative evidence of carcinogenicity in humans is seen in four of five occupational cohorts. Quantitative estimates of risk based on epidemiologic data provide lower and more plausible estimates of lifetime risk than do estimates from a rodent bioassay. The data overall suggest that the PEL for cadmium should not exceed 5 micrograms/m3 to protect workers from kidney dysfunction and lung cancer over a working lifetime.

TNO (1996). Methods for the establishment of health-based recommended occupational exposure limits for existing substances. The Netherlands, TNO Nustrition and Food Research Institute.

Tolentino, D., E. Zenari, et al. (2003). "Application of statistical models to estimate the correlation between urinary benzene as biological indicator of exposure and air concentrations determined by personal monitoring." AIHA J (Fairfax, Va) **64**(5): 625-629.

This study evaluated the correlation between benzene in urine and in workplace air at low airborne benzene levels (below 1 ppm). Eleven workers were monitored over a period of 1-4 days at a petrochemical plant in Italy; samples of end-of-shift urine and workplace air were analyzed for benzene. A significant correlation, with a coefficient of determination R(2)=0.63, was found between urine and airborne benzene, confirming the results of previous studies. Two different statistical models were utilized to estimate urine benzene values of 9-16 microg/L corresponding to the American Conference of Governmental Industrial Hygienists' threshold limit value (TLV) of 0.5 ppm in workplace air. Not withstanding the variability inherent to biological monitoring, the results suggest

application of biomonitoring as a trigger for identification of lower exposure level below, but approaching the TLV. Additionally, the proposed benzene biomonitoring may be useful in evaluating PPE effectiveness and use characteristics as well as dermal contribution to total exposure.

Topping, M. (2001). "Occupational exposure limits for chemicals." Occup. Environ. Med **58**: 138-144.

Topping, M. D., C. R. Williams, et al. (1998). "Industry's perception and use of occupational exposure limits." Ann Occup Hyg **42**(6): 357-366.

Market research was carried out to determine industry's perception of occupational exposure limits (OELs) and the extent to which they influence the selection of measures to control exposure. Telephone interviews were carried out with 1000 randomly selected users of chemicals, 400 from establishments with some use of chemicals and 600 from establishments with chemicals in daily use. 150 interviews were also carried out with Trade Union Health and Safety Representatives. The interviews covered basic information on chemicals used, sources of information, risk reduction measures used and understanding of COSHH and OELs. Most respondents came from firms with 10 employees or less (75%, all user group; 57%, heavy user group), closely reflecting the profile of British industry. In contrast, most (77%) Trade Union Health and Safety Representatives came from firms with at least 100 employees. Respondents in the all user group were drawn from across the whole range of industrial activity, whereas the heavy users were concentrated in manufacturing. The results showed that in making decisions on what control measures to use most users rely heavily on information from suppliers and personal experience and rather less on information from sources such as Trade Associations and HSE. Most respondents reported that steps were taken to protect employees. The use of personal protective equipment featured highly, followed by process controls. Little consideration was given to the possibility of substitution. Awareness of COSHH was limited with 65% of the all user group and 53% of the heavy user group being unaware of any legal requirements for establishments which manufacture or work with chemicals. Awareness of OELs was similarly limited with 19% of the all user group and 32% of the heavy user group having any real understanding. The results from Trade Union Representatives showed that overall they are somewhat better informed than chemical users in the small firms surveyed.

Tornero-Velez, R., E. Symanski, et al. (1997). "Compliance versus risk in assessing occupational exposures." Risk Anal **17**(3): 279-292.

Assessments of occupational exposures to chemicals are generally based upon the practice of compliance testing in which the probability of compliance is related to the exceedance [gamma, the likelihood that any measurement would exceed an occupational exposure limit (OEL)] and the number of measurements obtained. On the other hand, workers' chronic health risks generally depend upon

cumulative lifetime exposures which are not directly related to the probability of compliance. In this paper we define the probability of "overexposure" (theta) as the likelihood that individual risk (a function of cumulative exposure) exceeds the risk inherent in the OEL (a function of the OEL and duration of exposure). We regard theta as a relevant measure of individual risk for chemicals, such as carcinogens, which produce chronic effects after long-term exposures but not necessarily for acutely-toxic substances which can produce effects relatively quickly. We apply a random-effects model to data from 179 groups of workers, exposed to a variety of chemical agents, and obtain parameter estimates for the group mean exposure and the within- and between-worker components of variance. These estimates are then combined with OELs to generate estimates of gamma and theta. We show that compliance testing can significantly underestimate the health risk when sample sizes are small. That is, there can be large probabilities of compliance with typical sample sizes, despite the fact that large proportions of the working population have individual risks greater than the risk inherent in the OEL. We demonstrate further that, because the relationship between theta and gamma depends upon the within- and between-worker components of variance, it cannot be assumed a priori that exceedance is a conservative surrogate for overexposure. Thus, we conclude that assessment practices which focus upon either compliance or exceedance are problematic and recommend that employers evaluate exposures relative to the probabilities of overexposure.

Triebig, G. (2002). "Chemosensory irritation and the setting of occupational exposure limits." Int Arch Occup Environ Health **75**(5): 281-282.

Truhaut, R. (1968). "[On setting a tolerance limit for benzene in work environments]." Arch Mal Prof **29**(1): 5-22.

Truhaut, R. (1980). "The problem of thresholds for chemical carcinogens--its importance in industrial hygiene, especially in the field of permissible limits for occupational exposure." Am Ind Hyg Assoc J **41**(10): 685-692.

Tsuchiya, K. (1988). "Significance and use of threshold limit values with reference to "Corporate Influence on Threshold Limit Values" by Castleman and Ziem." Am J Ind Med **14**(2): 215-216.

Tuggle, R. M. (2000). "The relationship between TLV-TWA compliance and TLV-STEL compliance." Appl Occup Environ Hyg **15**(4): 380-386.

The purpose of this study was to investigate the relationship between the American Conference of Governmental Industrial Hygienists' (ACGIH) time-weighted average (TLV-TWA) and short-term exposure limit (TLV-STEL) Threshold Limit Values (TLVs). It is of value to determine if one or the other of these exposure limits is inherently more stringent so that exposure monitoring strategies may be devised which efficiently use available resources and

effectively control exposures to meet both exposure limits. The ACGIH short-term exposure limit (TLV-STEL) imposes three conditions on short-term (15-minute) exposures. These conditions involve exceeding the TLV-TWA and TLV-STEL levels and the time-separation of those short-term exposures that exceed the TLV-TWA level. These conditions were analyzed to produce eight unique component probabilities for TLV-STEL non-compliance. The sum of these eight components is the total probability of TLV-STEL non-compliance. Mathematical expressions for the eight probability components are derived in terms of the probability that a single 15-minute exposure exceeds the time-weighted average threshold limit value (TLV-TWA) and the geometric standard deviation of these 15-minute exposures. These expressions were applied to various hypothetical workplaces, and the relationship between TLV-TWA and TLV-STEL compliance is presented. The results showed that non-compliance of 15-minute exposures with the TLV-STEL level is only one part of overall TLV-STEL non-compliance. The additional ACGIH provisions for TLV-STEL compliance--the number of 15-minute exposures exceeding the TLV-TWA level and the number of clean periods separating such exposures--can be important factors in determining TLV-STEL compliance. It is concluded that compliance with all provisions of the ACGIH TLV-STEL adds a degree of stringency that greatly enhances the likelihood of TLV-TWA compliance for most workplace environments.

Turteltaub, K. W., J. S. Felton, et al. (1990). "Accelerator mass spectrometry in biomedical dosimetry: relationship between low-level exposure and covalent binding of heterocyclic amine carcinogens to DNA." Proc Natl Acad Sci U S A **87**(14): 5288-5292.

Accelerator mass spectrometry (AMS) is used to determine the amount of carcinogen covalently bound to mouse liver DNA (DNA adduct) following very low-level exposure to a 14C-labeled carcinogen. AMS is a highly sensitive method for counting long-lived but rare cosmogenic isotopes. While AMS is a tool of importance in the earth sciences, it has not been applied in biomedical research. The ability of AMS to assay rare isotope concentrations (10Be, 14C, 26Al, 41Ca, and 129I) in microgram amounts suggests that extension to the biomedical sciences is a natural and potentially powerful application of the technology. In this study, the relationship between exposure to low levels of 2-amino-3,8-dimethyl[2-14C]imidazo[4,5-f]quinoxaline and formation of DNA adducts is examined to establish the dynamic range of the technique and the potential sensitivity for biological measurements, as well as to evaluate the relationship between DNA adducts and low-dose carcinogen exposure. Instrument reproducibility in this study is 2%; sensitivity is 1 adduct per 10(11) nucleotides. Formation of adducts is linearly dependent on dose down to an exposure of 500 ng per kg of body weight. With the present measurements, we demonstrate at least 1 order of magnitude improvement over the best adduct detection sensitivity reported to date and 3-5 orders of magnitude improvement over other methods used for adduct measurement. An additional improvement of 2 orders of magnitude in sensitivity is suggested by preliminary experiments to develop bacterial hosts depleted in radiocarbon. Expanded applications involving

human subjects, including clinical applications, are now expected because of the great detection sensitivity and small sample size requirements of AMS.

Turteltaub, K. W., M. G. Knize, et al. (1990). "Metabolism of 2-amino-1-methyl-6-phenylimidazo[4,5-b] pyridine (PhIP) by liver microsomes and isolated rabbit cytochrome P450 isozymes." Carcinogenesis **11**(6): 941-946.

The cytochrome P450-dependent metabolism of the heterocyclic amine mutagen 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP) has been determined. We investigated the in vitro metabolism of PhIP by polycyclic hydrocarbon-induced mouse and rabbit liver microsomes, and by purified rabbit liver P450 isozymes. Following a 60 min incubation, 3-methylcholanthrene-induced mouse microsomes converted 36% of the PhIP to two major metabolites, N-hydroxy-PhIP and 4'-hydroxy-PhIP, with 43% total metabolism. Rabbit P450 form 6 and form 4 produced the same two major metabolites (20 and 5% total metabolism respectively). Additional metabolites were produced in low yields and amounts varied depending on the isozyme used (1-5%). Metabolites were not detected in incubations of PhIP with P450 forms 2 and 3C. N-Hydroxy-PhIP was found to be directly mutagenic to Salmonella TA98, while the 4'-hydroxy-PhIP was not mutagenic either with or without additional metabolic activation. These data suggest that the cytochrome P450IA isozymes are involved in the metabolism of PhIP by rabbit liver and that formation of N-hydroxy-PhIP is involved in the mutagenicity of PhIP.

Turteltaub, K. W., B. E. Watkins, et al. (1990). "Role of metabolism on the DNA binding of MeIQx in mice and bacteria." Carcinogenesis **11**(1): 43-49.

We report the effects of several inducers of P450 metabolizing enzymes on DNA adduct formation by 2-amino-3,8-dimethylimidazo[4,5-f]quinoxaline (MeIQx) in C57BL/6 mice. We also examined the role of N:O-acetylation and the nitrenium ion in the genotoxicity of MeIQx, since these have been implicated in the activation of other aminoimidazoazaarenes (AIA) to DNA reactive species. Mice were given phenobarbital (PB), Aroclor 1254, beta-naphthoflavone (BNF) or corn oil, i.p., followed 3-5 days later with oral administration of MeIQx. Induction of Aroclor and BNF produced DNA with 8-fold more adducts than either the corn oil-alone or PB-treated animals. Both corn oil-alone and PB-treated animals were similar. Four major adducts were found in all cases with no differences among inducers as judged by co-chromatography. Azido-MeIQx induced calf-thymus-DNA adducts produced identical adduct profiles to those seen for the mouse DNA. Similar adduct profiles were obtained from Salmonella TA98, and the nitroreductase deficient strains (TA98NR and TA98/1,8-DNP6) exposed to MeIQx in the presence of Aroclor-induced-mouse-liver S9. Adduct frequencies in TA98/1,8-DNP6 were significantly lower than in TA98 and TA98NR. The data described in this report demonstrate that induction quantitatively increases adduct numbers but does not affect the types of DNA damage. These data also suggest that the same DNA reactive intermediates are formed in vivo as in vitro and support the hypothesis that the metabolism of MeIQx involves the P450I

family of isozymes, N:O-acetyltransferases and possibly a nitrenium ion. The application of radioanalytic scanners for quantitation of 32P-postlabelling adduct maps is described.

U.S.EPA (1998). Methods for exposure-response analysis for acute inhalation exposure to chemicals. Washington, D.C., United States Environmental Protection Agency, Office of Research and Development.

Ueda, A. (1992). "[Evaluation of allergic reaction and setting for occupational exposure limits]." Sangyo Igaku **34**(7): 674-676.

Ulanova, I. P., N. G. Ivanov, et al. (1980). "Development of methodological approaches to the determination of safe levels of activity of harmful substances in the air of the working environment." J Hyg Epidemiol Microbiol Immunol **24**(3): 332-337.

1. An experiment study was carried out to substantiate fundamental approaches to the determination of shift-average and maximum instantaneous concentration of highly cumulative substances in the air of the working environment. 2. The determination of maximum instantaneous concentrations in the air of the working environment is maintained for some groups of chemical compounds (irritant poisons, substances having acute effect, etc). An express, method of determining MAC in the air of the working environment has been developed for the purpose of hygienic norm-setting for irritant substances.

Ulfvarson, U. (1987). "Assessment of concentration peaks in setting exposure limits for air contaminants at workplaces, with special emphasis on narcotic and irritative gases and vapors." Scand J Work Environ Health **13**(5): 389-398.

In various countries, concentration peaks of gaseous air contamination are assessed by a standard formula. Toxicologic data are not sufficient to warrant occupational short-term exposure limits for the majority of substances. In this article the literature on exposure to concentration peaks is reviewed, and the problem is analyzed from general toxicokinetic and physicochemical points of view. Several ways are suggested to achieve better standards. One straightforward and reasonably simple method is summarized in the following three points, which should be considered in the setting of occupational exposure limits: (i) For substances with fast or moderately fast action, only ceiling limits should be considered; (ii) when structure analogy is justified for narcotic and irritating gases, the correct way is to set the limits at the same thermodynamic activity (relative saturation) of the substances in question and not at the same concentration; (iii) for substances absorbed and eliminated slowly time-weighted exposure limits, combined with rules for excursions, or short-term exposure limits derived from such rules are appropriate, but the possible accumulation of large absolute quantities of the substances should be considered. This point is particularly important when the critical effect is narcosis or irritation, as the thermodynamic equipotency means that the effective concentration of water-

soluble gases and vapors is higher than that of substances with low water solubility.

Ulm, K. and G. Salanti (2003). "Estimation of the general threshold limit values for dust." Int Arch Occup Environ Health **76**(3): 233-240.

In 1997 the German MAK Commission set new general threshold limit values for dust. The procedure has recently been assessed (McLaughlin et al. 2001). One of the points raised was the use of inappropriate statistical methods. We want to address this point to a greater extent by discussing several alternatives implied by the already established threshold models, and we present results from a new approach that has been refined in the meantime: the use of the additive isotonic model. The underlined assumption of monotonicity regarding the dose-response relationship has been extensively investigated. One very flexible model, based on smoothing splines, shows in some of the samples a decline in the risk over a certain range of the exposure compared to the risk at baseline. Another approach with fractional polynomials and segmented regression lines shows that this result can be explained by chance. These methods show an increasing risk with increasing exposure. Additionally, permutation tests are used to prove the trend within the isotonic framework. The results from the additive isotonic model confirm previous assessments of the general threshold limit value.

Van Dyke, M. V., A. D. LaMontagne, et al. (2001). "Development of an exposure database and surveillance system for use by practicing OSH professionals." Appl Occup Environ Hyg **16**(2): 135-143.

This report summarizes the development of an occupational exposure database and surveillance system for use by health and safety professionals at Rocky Flats Environmental Technology Site (RFETS), a former nuclear weapons production facility. The site itself is currently in the cleanup stage with work expected to continue into 2006. The system was developed with the intent of helping health and safety personnel not only to manage and analyze exposure monitoring data, but also to identify exposure determinants during the highly variable cleanup work. Utilizing a series of focused meetings with health and safety personnel from two of the major contractors at RFETS, core data elements were established. These data elements were selected based on their utility for analysis and identification of exposure determinants. A task-based coding scheme was employed to better define the highly variable work. The coding scheme consisted of a two-tiered hierarchical list with a total of 34 possible combinations of work type and task. The data elements were incorporated into a Microsoft Access database with built-in data entry features to both promote consistency and limit entry choices to enable stratified analyses. In designing the system, emphasis was placed on the ability of end users to perform complex analyses and multiparameter queries to identify trends in their exposure data. A very flexible and user-friendly report generator was built into the system. This report generator allowed users to perform multiparameter queries using an intuitive system with very little training. In addition, a number of automated

graphical analyses were built into the system, including exposure levels by any combination of building, date, employee, job classification, type of contaminant, work type or task, exposure levels over time, exposure levels relative to the permissible exposure limit (PELS), and distributions of exposure levels. Both of these interfaces, allow the user to "drill down" or gradually narrow query criteria to identify specific exposure determinants. A number of other industrial hygiene processes were automated by the use of this database. Exposure calculations were coded into the system to allow automatic calculation of time-weighted averages and sample volumes. In addition, a table containing all the PELs and other relevant occupational exposure limits was built into the system to allow automatic comparisons with the current standards. Finally, the process of generating reports for employee notification was automated. The implementation of this system demonstrates that an integrated database system can save time for a practicing hygienist as well as provide useful and more importantly, timely information to guide primary prevention efforts.

van Hemmen, J. J., J. Auffarth, et al. (2003). "RISKOFDERM: risk assessment of occupational dermal exposure to chemicals. An introduction to a series of papers on the development of a toolkit." Ann Occup Hyg **47**(8): 595-598.

Dermal exposure to industrial chemicals during work is of major concern in the risk assessment of chemicals. Current approaches in procedures for European legislation are not based on experimental data on dermal exposures in workplaces because these are lacking. A large project, with four interrelated work parts, was funded by the European Commission (DG Research) in order to overcome large parts of this problem. The 4 year project is now in its final year and an overview is given of an important part of the project: the development of a risk assessment and risk management toolkit for dermal exposure. Five other papers in this issue deal with various aspects of this development.

van Thriel, C., E. Kiesswetter, et al. (2003). "Neurobehavioral effects during experimental exposure to 1-octanol and isopropanol." Scand J Work Environ Health **29**(2): 143-151.

OBJECTIVES: The study examined acute neurobehavioral effects provoked by controlled exposure to 1-octanol and isopropanol among male volunteers. METHODS: In a 29-m3 exposure laboratory, 24 male students (mean age 25.8 years) were exposed to 1-octanol and isopropanol. Each substance was used in two concentrations (0.1 and 6.4 ppm for 1-octanol; 34.9 and 189.9 ppm for isopropanol:). In a crossover design, each subject was exposed for 4 hours to the conditions. Twelve subjects reported enhanced chemical sensitivity; the other 12 were age-matched controls. At the onset and end of the exposures neurobehavioral tests were administered and symptoms were rated. RESULTS: At the end of the high and low isopropanol exposures the tiredness ratings were elevated, but no dose-dependence could be confirmed. For both substances and concentrations, the annoyance ratings increased during the exposure, but only for isopropanol did the increase show a dose-response relation. The subjects

reported olfactory symptoms during the exposure to the high isopropanol and both 1-octanol concentrations. Isopropanol provoked no sensory irritation, whereas high 1-octanol exposure slightly enhanced it. Only among the subjects with enhanced chemical sensitivity were both 1-octanol concentrations associated with a stronger increase in annoyance, and lower detection rates were observed in a divided attention task. CONCLUSIONS: Previous studies reporting no neurobehavioral effects for isopropanol (up to 400 ppm) were confirmed. The results obtained for 1-octanol lacked dose-dependency, and their evaluation, is difficult. The annoying odor of 1-octanol may mask sensory irritation and prevent subjects with enhanced chemical sensitivity from concentrating on performance in a demanding task.

van Thriel, C., A. Seeber, et al. (2003). "Physiological and psychological approaches to chemosensory effects of solvents." Toxicol Lett **140-141**: 261-271.

Workplace related standard settings for solvents are based in a remarkable extent on information about sensory irritations. However, data from controlled human exposure studies are seldom available. Therefore, the aim of this study was to present the association of self-reported symptoms and physiological processes leading to sensory irritations. Three series of laboratory experiments each with 24 young male subjects were performed. Ethyl benzene (EB), 2-butanone (methyl ethyl ketone or MEK), isopropyl alcohol (IPA), 1-octanol (OCT), and 2-ethylhexanol (EHEX) were investigated in low and high concentrations. Ratings for sensory irritations (eyes and nose), olfactory symptoms, and annoyance were assessed repeatedly before, during and after the 4-h-exposures. The anterior active rhinomanometry (AAR) was employed measuring the nasal flow. The nasal lavage was used for the analysis of the neuropeptide substance P as indicator of nasal chemosensory irritations. Goodness-of-fit was calculated for non-linear regression analyses by fitting the sine function on the data of the ratings given during the 4-h-exposure. In general, ratings for annoyance and odor symptoms were fitted on a higher level than those for sensory irritations. However, a high fit could be shown for nasal irritations due to EHEX. In these experiments, a significant reduction of the nasal flow and a significant increase of substance P could be proved.

Verma, D. K. (2000). "Adjustment of occupational exposure limits for unusual work schedules." Aihaj **61**(3): 367-374.

A review of literature relating to the issue of adjustments of occupational exposure limits for unusual work shifts and unusual work schedules is described. The important issues relating to various adjustment models are discussed, and a number of conclusions are drawn. Tables of adjustment factors for 34 specific contaminants for 2 unusual schedules are given. A simple approach for use by industrial hygienists is proposed.

Vincent, J. H. (1995). Chapter 8. The inhalation of aerosols. Aerosol Science for Industrial Hygienists. New York, Elsevier Science Inc.

Vincent, J. H. (1999). "Occupational hygiene science and its application in occupational health policy, at home and abroad." Occup. Med. **49**: 27-35.

Vincent, J. H., V. P. Tchachtchine, et al. (1999). "A study of exposure standards in Russia and the role of occupational hygiene." J. Environ. Monit **1**: 497-501.

Vincent, R. and B. Jeandel (2001). "COLCHIC-occupational exposure to chemical agents database: current content and development perspectives." Appl Occup Environ Hyg **16**(2): 115-121.

Set up in 1987, COLCHIC is a database for occupational exposure to chemical agents. Eight French regional health insurance fund (Caisse Regionale d'Assurance Maladie-CRAM) interregional laboratories and the French national research and safety institute (Institut National de Recherche et de Securite-INRS) laboratories have stored results and information from chemical agent exposure measurements on this database. More than 10 years later, 400,000 measurement results of exposure to 600 substances are now stored on COLCHIC. Utilization of data from this base is limited by the quality and absence of certain information, so a working group has been formed to develop a new data retrieval system, which takes into account recommendations formulated by the AIHA-ACGIH and European working groups. Utilization of this new coding system should allow improved description of workplace exposure conditions in the near future. This data retrieval system is currently being validated and should be used by the laboratories concerned during the course of 2001.

Vinzents, P. S., Y. Thomassen, et al. (1995). "A method for establishing tentative occupational exposure limits for inhalable dust." Ann Occup Hyg **39**(6): 795-800.

Four-fold classification tables are used on five datasets containing 112 parallel personal measurements of total dust and inhalable dust. The classification are carried out in such a way that the frequency of non-compliance is equal for total dust and inhalable dust. The results can be used as tentative occupational exposure limits (OELs) for inhalable dust, and the results range from 0.7 to 3.4 of OELs for total dust. The results depend on the industry and the content of the dust.

Volturo, E. (1990). "[The value and limits of limit values: the viewpoint of a district physician]." G Ital Med Lav **12**(5-6): 223-227.

Vu-Duc, T., C. K. Huynh, et al. (1997). "[Do the isocyanate monomer standards still protect against attacks of occupational asthma? Should a standard including polyisocyanates be evolved?]." Schweiz Med Wochenschr **127**(48): 2000-2007.

Field surveys of diisocyanates at the workplaces in Switzerland and particularly in car repair shops, where HDI was the most used, showed that the monomer levels comply with the Swiss permissible exposure limit (PEL) in the great number of situations. Cases of medical surveillance associated with industrial

hygiene measurements demonstrate that occupational asthma was also observed in situations where the monomer concentrations are low although high peaks of prepolymers are often recorded. From the statistical data on compensations, the annual incidence of occupational asthma over the period 1988 to 1992 remains around 54 cases with a mean cost of 21,000 sFr. per case per year. It is suggested that a PEL on the prepolymers should be introduced in the Swiss PEL list to enhance the efficiency of prevention policy.

Waickman, F. J. and A. Vojdani (1998). "Putting Chemical and Environmental Sensitivities in Perspective." Otolaryngologic Clinics Of North America **31**(1): 55-67.
Biosis copyright: biol abs. rrm literature review human patient allergy toxicology allergy chemical sensitivity environmental sensitivity immune system disease toxicity

Walker, J. C., M. Kendal-Reed, et al. (2001). "Human breathing and eye blink rate responses to airborne chemicals." Environ Health Perspect **109 Suppl 4**: 507-512.
Increased levels of air pollution have been linked with morbidity and mortality, but mechanisms linking physiologic responses to quality of life and productivity issues remain largely unknown. Individuals often report irritation of the nose and/or eyes upon exposures to environmental contaminants. Evaluation of these self-reports would be greatly aided by the development of valid physiological markers. Chamber studies (unencumbered exposures) of nonsmoker responses to environmental tobacco smoke offer two candidate end points: (a) Tidal volume increases and breathing frequency declines with stimuli that elicit only moderate irritation. (b) Eye blink rate increases only with a concentration sufficiently high to cause progressive worsening of eye irritation with prolonged exposure. Experiments with very brief nasal-only presentations also suggest the value of breathing changes as sensitive markers of irritation: (a) Tidal volume is inversely related to perceived nasal irritation (NI) intensity in both normal and anosmic (lacking olfactory input) individuals, although normals exhibit greater NI sensitivity. (b) Inhalation duration, in both groups, declines only with trigeminal activation sufficient to cause readily perceptible NI in anosmics. Changes in eye blink rate and breathing may be useful in the investigation of irritation and other effects of air pollution, and could be quite useful in investigations of mixtures of volatile organic compounds.

Wambach, P. F. and R. M. Tuggle (2000). "Development of an eight-hour occupational exposure limit for beryllium." Appl Occup Environ Hyg **15**(7): 581-587.
This article recommends an 8-hour occupational exposure limit (OEL) for beryllium. It responds to growing concerns about the continuing incidence of chronic beryllium disease despite the long-standing OEL for beryllium: 2 micrograms of beryllium per cubic meter of air (microgram/m3), 8-hour time-weighted average (TWA). Current 8-hour TWA beryllium OELs are not based on chronic beryllium disease toxicology and an increasing number of studies report incidence of chronic beryllium disease at exposure levels apparently below 2

micrograms/m3. The experience of the beryllium-exposed population of Lorain, Ohio, in the late 1940s, and the ambient air regulatory standards derived from that event provide evidence that establishing a protective level is possible. These levels are used as the basis for a new recommended beryllium exposure standard. A correspondingly protective 8-hour TWA level of 0.1 microgram/m3 has been derived, which, for commonly encountered workplace conditions (in terms of geometric standard deviation and percent-compliance), should provide long-term mean exposure protection comparable to that received by the unaffected Lorain subpopulation and provided by the Environmental Protection Agency (EPA) ambient standard. It is concluded that an exposure limit of 0.1 microgram/m3 combined with exposure monitoring to assure a high rate of day-to-day compliance would provide better control of both long-term mean exposure levels and short-term levels than do current occupational exposure limits. The health data available, while certainly not conclusive, support further reductions in exposure levels to help minimize the incidence of chronic beryllium disease.

Wegman, D. H. and E. A. Eisen (1990). "Acute irritants. More than a nuisance." Chest **97**(4): 773-775.

Wegman, D. H., E. A. Eisen, et al. (1994). "Acute and chronic respiratory effects of sodium borate particulate exposures." Environ Health Perspect **102 Suppl 7**: 119-128.

This study examined work-related chronic abnormality in pulmonary function and work-related acute irritant symptoms associated with exposure to borate dust in mining and processing operations. Chronic effects were examined by pulmonary function at the beginning and end of a 7-year interval. Time-specific estimates of sodium borate particulate exposures were used to estimate cumulative exposure during the study interval. Change in pulmonary function over the 7 years was found unrelated to the estimate of cumulative exposure during that interval. Exposure-response associations also were examined with respect to short-term peak exposures and incidence of five symptoms of acute respiratory irritation. Hourly measures of health outcome and continuous measures of particulate exposure were made on each subject throughout the day. Whenever a subject reported one of the irritant symptoms, a symptom intensity score was also recorded along with the approximate time of onset. The findings indicated that exposure-response relationships were present for each of the specific symptoms at several symptom intensity levels. The associations were present when exposure was estimated by both day-long and short-term (15-min) time-weighted average exposures. Associations persisted after taking account of smoking, age, and the presence of a common cold. No significant difference in response rate was found between workers exposed to different types of sodium borate dusts.

Welch, A. R., J. P. Birchall, et al. (1995). "Occupational rhinitis--possible mechanisms of pathogenesis." J Laryngol Otol **109**(2): 104-107.

Occupational rhinitis has been a prescribed industrial disease in the UK since 1907. It has only relatively recently received significant attention from

otorhinolaryngologists although numerous studies have been performed in the past by occupational and industrial health physicians. At the present time the precise mechanisms of pathogenesis are unclear and would appear to be multiple. Recently interest has arisen because of compensation claims. Diagnosis made on the basis of the clinical history is subject to two problems: firstly, there is difficulty in differentiating between occupational and nonoccupational rhinitis, and secondly, clinical histories can easily be feigned. Physical signs would be a more reliable indicator of occupational damage to the nasal mucosa if they differ from the signs normally found in allergic or vasomotor rhinitis. In a series of 100 shipyard workers dry atrophic nasal mucosa was found in 66 and septal ulceration in two. From their clinical histories 78 individuals complained of nasal obstruction, 28 of epistaxis, 42 of hyposmia, 10 of anosmia and 90 of rhinorrhoea. Possible pathogenesis is described.

Welsch, F. (2005). "The mechanism of ethylene glycol ether reproductive and developmental toxicity and evidence for adverse effects in humans." Toxicol Lett **156**(1): 13-28.

Numerous experimental studies have established that only a few among the large family of ethylene glycol ethers (EGEs) elicit toxicity on reproduction in either gender. Notable are the monomethyl (EGME) and monoethyl (EGEE) ethers and their respective acetate esters whose production volumes have dramatically declined. Oxidation to the respective monoalkoxy acids is a prerequisite for toxicity. The most potent EGE reproductive toxicant is EGME (via 2-methoxyacetic acid; MAA), which elicits developmental phase-specific insults on either conceptus or on testes. Toxicity at either target site is markedly attenuated by simple physiological compounds such as acetate, formate, glycine, D-glucose and serine. Lack of solid EGME occupational exposure data and the need to improve the scientific foundations for animal data extrapolations, prompted the development of physiologically based pharmacokinetic (PBPK) models for pregnancy application. Interspecies (mouse-rat) and different exposure routes (including inhalation) were experimentally validated. Such PBPK models were then extrapolated to potential occupational exposures, using rather limited human MAA pharmacokinetic data. PBPK model predictions of human blood levels upon simulated inhalation exposure to the 5 ppm threshold limit value (TLV) for 8 h were approximately 60 microM were well below those causing adverse effects in pregnant mice or rats. This conclusion concurs with the lack of objective analytical chemistry data for EGME/MAA in occupational settings, regardless of the potential route of exposure. There are no exposure data that can be linked in a cause-and-effect association to adverse human reproductive outcomes.

Wennig, R. (2000). "Threshold values in toxicology - useful or not?" Forensic Sci Int **113**(1-3): 323-330.

In many fields of toxicology, numbers are used as threshold values, e.g. as "acceptable daily intake values" resulting in maximum permissible concentrations

in food or in animal feed by using "safety factors"; maximal admissible concentrations of toxic substances in the air at the workplace; cut-off values in analytical toxicology; limit values for biological specimens in the case of driving under the influence of drugs, guidance values for environmental specimens, etc. The philosophy behind these values must be well understood and they should only be applied to real cases by persons with enough toxicological background. The bad use of these numbers in toxicology can have dramatic consequences. Especially in regulatory toxicology their use should be made with great care. Moreover, tremendous improvements in analytical methodology, e.g. the decreasing of the limits of detection for many potentially toxic substances in recent years, should not end up in an overestimation of risks to humans. To avoid these abuses careful interpretations of analytical findings by qualified toxicologists are of paramount importance. The use and abuse of some of these threshold values will be outlined in several applications from analytical toxicology, risk assessment issues, forensic toxicology in post-mortem cases, as well as from the drugs and driving cases. Generally, if threshold values are considered as guidance values and not as the "absolute truth" in toxicology, they may be very useful in the interpretation of toxicology data.

Western, N. J. (1986). "Hygiene assessment of new products--a company view." Ann Occup Hyg **30**(2): 237-240.

Whaley, D. A., M. D. Attfield, et al. (1999). "Regression method to estimate provisional TLV/WEEL-equivalents for non-carcinogens." Ann Occup Hyg **44**: 361-374.

Whaley, D. A., M. D. Attfield, et al. (2000). "Regression method to estimate provisional TLV/WEEL-equivalents for non-carcinogens." Ann. Occup. Hyg. **44**(5): 361-374.

Williams, N. R. (2002). "Occupational voice disorders due to workplace exposure to irritants--a review of the literature." Occup Med (Lond) **52**(2): 99-101.
The medical literature contains relatively few examples of reports of voice disorders that could be attributed to chemical exposure at work. General medical conditions such as gastro-oesophageal reflux and the use of medication such as inhaled steroids are well-recognized causes of laryngitis, but the occupational causes are less well documented. This paper describes the results of a literature review looking at the reporting of cases of occupationally acquired voice disorders due to exposure to irritants in the workplace.

Wilson, D. A. (2005). "Odor Perception is Dynamic: Consequences for Interpretation of Odor Maps." Chem Senses **30 Suppl 1**: i105-i106.

Winneke, G. (1992). "Structure and determinants of psychophysiological response to odorant/irritant air pollution." Ann N Y Acad Sci **641**: 261-276.
From a psychophysiological point of view, acute effects of indoor air pollution with odorant/irritant properties can be evaluated in terms of sensory/perceptual

factors, in terms of objective eye/mucous membrane irritation or systemic responses of the orienting reflex, as well as in terms of either specific or systemic psychological responses. Formaldehyde and hydrogen sulfide are used to illustrate sensory evaluation in terms of detection (absolute thresholds), suprathreshold intensity, and hedonic tone. Dose-response contingencies are exemplified for ETS-induced eye irritation in terms of eyeblinks and lacrymal flow. Orienting responses to odorant stimuli are illustrated using peripheral vasoconstriction and pupil dilation as outcome measures. Specific (descriptive statements and symptoms) as well as systemic psychological responses (annoyance) exhibited clear-cut dose-response association in chamber studies using ETS and hydrogen sulfide exposures. It is, furthermore, shown that environmental annoyance to different environmental stressors exhibits both trait and state characteristics, and that age, perceived health, and (to a smaller degree) gender moderate the response. Based on this information proposals for research needs are given.

Wise, P. M., C. J. Wysocki, et al. (2003). "Time-intensity ratings of nasal irritation from carbon dioxide." Chem Senses **28**(9): 751-760.

In three experiments, subjects tracked intensity of nasal irritation during sustained presentation of carbon dioxide in the nose. Experiment 1 showed that: (i). functions of peak intensity vs. concentration and latency to first non-zero ratings agreed with published literature, thereby supporting the validity of the technique; (ii). on average, rated intensity peaked approximately 3-4 s after stimulus-onset and began to fall rapidly thereafter; (iii). large and stable individual differences in temporal dynamics occurred. Experiment 2 replicated experiment 1 with some methodological refinements. In experiment 3, application of the technique revealed that the nose regains sensitivity with very brief (300-500 ms) interruptions in presentation of carbon dioxide. In short: (i). the method developed here provides a temporally fine-grained tool to study the time-course of nasal irritation, and (ii). nasal irritation from carbon dioxide shows relatively rapid temporal dynamics.

Wiwanitkit, V., J. Suwansaksri, et al. (2001). "Feasibility of urinary trans, trans-muconic acid determination using high performance liquid chromatography for biological monitoring of benzene exposure." J Med Assoc Thai **84 Suppl 1**: S263-268.

Benzene is an important carcinogenic substance used in many industrial processes. Inhalation of this substance can cause both acute and chronic toxicity. In this study, monitoring of benzene exposure by high-performance liquid chromatography (HPLC) for urine trans, trans-muconic acid (ttMA) determination was adapted. We described a new adapted sensitive and specific HPLC method. We mixed 0.5 mL of urine sample with 2 mL of Tris Buffer containing vanillic acid as internal standard (IS) and percolate this through a preconditioned ion-exchange column. After rinsing the column with phosphoric acid solution, acetate buffer, and deionized water, we eluated the analytes with 2 mL of an equivolume solution of 1.5 mol/L sodium chloride and methanol. Of this, 10 microliter was

injected into the HPLC column. The mobile phase consisted of, per liter, 10 ml of acetic acid, 100 ml of methanol, and 5 mmol/L sodium acetate. The flow rate was started at 1.2 ml/min. The ttMA and IS were detected at 4.2 to 4.4 and 12.6-13.3 minutes, respectively. The lowest detection limit was 0.05 mg/L.

Wojcik, A. and I. Luterek (2003). "Analysis of occupational risk due to exposure to carcinogenic factors in the work environment of a chemical plant." Ann Univ Mariae Curie Sklodowska [Med] **58**(2): 185-193.

The evaluation of exposure to some carcinogenic chemicals and seemingly carcinogenic chemicals, e.g. mist of sulphuric acid, benzene, chromium (VI) and formaldehyde among employees of some departments of a chemical plant was carried out. The study was carried out in the years 1999--2002. The analysis of concentration of the studied substances revealed the highest risk of exposure in the Cyclohexanon Department and The Maintenance Services Department in Caprolactam department. No direct relationship between the exposure to the studied chemicals and the development of cancer in the working population was found.

Wolkoff, P., P. Skov, et al. (2003). "Eye irritation and environmental factors in the office environment--hypotheses, causes and a physiological model." Scand J Work Environ Health **29**(6): 411-430.

The study reviews eye irritation using a multidisciplinary approach. Potential risk factors and objective gender differences are identified, and possible hypotheses for eye irritation caused by indoor air pollution are discussed. Eye irritation depends somewhat on destabilization of the outer-eye tear film. An integrated physiological risk model with blink frequency, destabilization, and break-up of the eye tear film as inseparable phenomena may explain eye irritation among office workers in terms of occupational, climate, and eye-related physiological risk factors. Certain volatile organic compounds that are both chemically reactive and airway irritants may cause eye irritation. If airborne particles alone should destabilize the tear film and cause eye irritation, their content of surface-active compounds must be high. Personal factors (eg, use of contact lenses, eye make-up, and certain medication) may also affect destabilization of the tear film and possibly result in more eye symptoms.

Woskie, S. R., E. E. Eisen, et al. (1998). "Worker sensitivity and reactivity: indicators of worker susceptibility to nasal irritation." Am J Ind Med **34**(6): 614-622.

This study examines the determinants of susceptibility to the irritant effects of sodium borate in 18 responsive workers identified through repeated self-reports of nasal irritation. For each worker, susceptibility was characterized by two features; reactivity and sensitivity, as estimated from the slope and intercept parameters from their individual exposure-response regression model. Individual estimates of reactivity and sensitivity were then examined to evaluate the importance of personal and environmental characteristics in determining susceptibility. The use of nasal sprays, current smoking and allergies were

associated with lower reactivity, while high exposures to borate dust were associated with higher sensitivity. To examine possible biologic mechanisms for the irritant response, a toxicokinetic dose model was used to calculate nasal osmolarity during symptom intervals. The estimated levels suggest that osmolar activation of mast cells to release histamine and other mediators is a plausible mechanism by which these workers may experience nasal irritation.

Woskie, S. R., P. Shen, et al. (1994). "The real-time dust exposures of sodium borate workers: examination of exposure variability." Am Ind Hyg Assoc J **55**(3): 207-217.

As part of an epidemiologic study of acute respiratory irritation, an assessment of the short term (TWA-0.25 hr) and daily (TWA-6 hr) dust and boron exposures of workers in a sodium borate production facility was undertaken. A real-time continuous aerosol monitor was used in an active mode with an in-line filter to collect a TWA-6 gravimetric sample with a datalogger to store the continuous aerosol measurements. Over 430 person-days of personal exposure measurements were made, resulting in more than 10,000 15-minute average (TWA-0.25) dust concentration measurements. The arithmetic mean total dust concentrations for the 13 job groups exposed to sodium borate dust ranged from 0.29 to 18.95 mg/m3. The geometric standard deviation of the TWA-6 total dust exposures within the sodium borate exposed job groups had a median of 2.78. The geometric standard deviation of the TWA-0.25 total dust exposures had a median of 3.97. In most jobs the "within-day" variability accounted for over 50% of the total variability in exposure levels. In jobs with constant exposure to sodium borate, the second most important source of exposure variability was attributable to "between worker" differences. Where there was only intermittent exposure, the second most important source of exposure variability was "within-worker" variability. The implications of these findings for control strategies are discussed. Based on boron measurements, a substantial portion of a total dust air sample is nonborate material such as cigarette smoke, vehicle exhaust, ambient dust, or hydration mass. Thus, even in an environment where sodium borate is being packaged, total dust measurements are an overestimate of the actual borate exposure level.

Woudenberg, F. and P. van der Torn (1992). "Emergency exposure limits: a guide to quality assurance and safety." Qual Assur **1**(4): 249-293.

Emergency exposure limits (EELs) are necessary in disaster prevention, preparation, and repression. Occupational EELs are available for many chemicals, but are of low toxicological adequacy. An animal experimental EEL of high toxicological adequacy available for many irritant chemicals is the concentration causing a 50% decrease in respiratory rate (RD50). The most outstanding EELs for the general population are the emergency response planning guidelines (ERPGs). A theoretical framework for a three-limit system is developed by the European Chemical Industry Ecology and Toxicology Center (ECETOC). ECETOC found over one order of magnitude variation between assessments of several companies. Nine selected EELs were classified in three

clusters of increasing degrees of seriousness of health effects. There was little consistency within clusters, making it impossible to combine EELs. It is recommended to develop a toxicologically adequate EEL in an intercontinental context with cooperation of industry and (supra)national regulatory bodies. ERPGs can be taken as a start. The framework developed by ECETOC can be used to improve the limit setting procedure. A 5- to 10-year update should become part of the procedure. Attention should be devoted to the use of expert judgment. The minimal uncertainty in EELs should be expressed by presenting ranges instead of single values.

Wyde, M. E., T. Cambre, et al. (2002). "Promotion of altered hepatic foci by 2,3,7,8-tetrachlorodibenzo-p-dioxin and 17beta-estradiol in male Sprague-Dawley rats." Toxicol Sci **68**(2): 295-303.

The determination of differences in hormonal regulation of tumor promotion-related response to 2,3,7,8-tetrachlorodibenzop-dioxin (TCDD) between males and females may identify factors contributing to the female-specific hepatocarcinogenicity of TCDD in rats. In the current study, diethylnitrosamine-initiated male Sprague-Dawley rats were exposed to TCDD or corn oil vehicle in the presence and absence of 17beta-estradiol (E2), and cell proliferation and development of preneoplastic altered hepatic foci (AHF) were determined. After 30 weeks of exposure, gamma-glutamyltranspeptidase (GGT)-positive AHF and the number of placental glutathione-s-transferase (PGST)-positive AHF were significantly higher in TCDD-treated rats than in control rats. Both the number and volume fraction of GGT-positive AHF were significantly lower in rats cotreated with E2 regardless of TCDD exposure compared with corresponding non-E2-treated groups and were unaffected by TCDD. In contrast, the number of PGST-positive AHF was significantly higher in E2-treated rats in the absence of TCDD treatment. In addition, whereas E2 had no effect on the volume fraction of PGST-positive foci, the levels in rats cotreated with both E2 and TCDD were significantly higher than in controls. No differences were observed in cell proliferation between TCDD-treated and control rats, although cell proliferation was lower in rats exposed to E2 compared with placebo controls. The weaker potency of tumor promotion and lack of induction of cell replication and DNA damage in male rats likely explain the female-specific hepatocarcinogenicity of TCDD in chronic bioassays.

Wyde, M. E., S. R. Eldridge, et al. (2001). "Regulation of 2,3,7,8-tetrachlorodibenzo-p-dioxin-induced tumor promotion by 17 beta-estradiol in female Sprague--Dawley rats." Toxicol Appl Pharmacol **173**(1): 7-17.

2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) is a potent hepatocarcinogen in female but not in male rats. In an initiation-promotion model, ovariectomy inhibits TCDD-induced cell replication and reduces both TCDD-induced tumor formation and the promotion of enzyme-altered hepatocellular foci (AHF). The aim of this study was to determine the involvement of the ovarian hormone 17 beta-estradiol in the induction of cell proliferation and development of putative preneoplastic

AHF following chronic exposure to TCDD. Diethylnitrosamine (DEN)-initiated ovariectomized (OVX) female rats were treated with TCDD for 20 or 30 weeks in the presence and absence of 17 beta-estradiol administered continuously by implanted 90-day release pellets. Following 20 weeks of treatment, cell proliferation in TCDD-treated rats was decreased regardless of ovarian hormones. Following 30 weeks of exposureTCDD, only significantly induced cell proliferation in OVX rats receiving supplemental 17 beta-estradiol. These data demonstrate that the the transitory mitoinhibition of cell replication by TCDD is not hormonally responsive, but that induction of cell replication at later time points is. TCDD exposure resulted in elevated AHF expressing gamma-glutamyltranspeptidase (GGT) in intact, but not OVX rats at both time points. TCDD also induced GGT-positive AHF in 17 beta-estradiol-supplemented OVX rats. TCDD induced AHF expressing the placental form of glutathione-S-transferase (PGST) in both intact and OVX rats regardless of 17 beta-estradiol exposure, indicating that the modulating effect of 17 beta-estradiol on AHF was specific to the GGT-positive phenotype.

Wyde, M. E., V. A. Wong, et al. (2001). "Induction of hepatic 8-oxo-deoxyguanosine adducts by 2,3,7,8-tetrachlorodibenzo-p-dioxin in Sprague-Dawley rats is female-specific and estrogen-dependent." Chem Res Toxicol **14**(7): 849-855.

2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) is a hepatocarcinogen that induces sex-specific hepatic neoplastic alterations in female, but not male, rats. It has been hypothesized that TCDD-induced alterations in estrogen metabolism lead to increased generation of reactive oxygen species. The resulting oxidative damage to DNA may contribute to TCDD-induced tumor promotion and hepatocarcinogenesis. This hypothesis is supported by previous observations of increased 8-oxo-deoxyguanosine (8-oxo-dG) adduct formation in the livers of intact, but not ovariectomized (OVX), rats following chronic exposure to TCDD. The aim of the current study was to more clearly define the roles of hormonal regulation, gender, dose-response, and exposure duration in TCDD induction of 8-oxo-dG adducts. Diethylnitrosamine (DEN)-initiated male and female (both intact and OVX) rats were exposed to TCDD in the presence or absence of 17 beta-estradiol. Following 30 weeks of exposure, hepatic 8-oxo-dG adduct levels were significantly higher in TCDD-treated intact female rats, and TCDD-treated OVX female rats receiving supplemental 17 beta-estradiol, when compared to respective corn oil vehicle controls. In DEN-initiated female rats exposed to a range of TCDD concentrations for 30 weeks, TCDD induced 8-oxo-dG adduct levels in a dose-dependent manner. However, 8-oxo-dG adduct levels were not altered in TCDD-treated male or OVX female rats following 30 weeks of exposure. In noninitiated female rats, the level of 8-oxo-dG adducts 4 days following a single dose of TCDD was not significantly different than in control rats. Additionally, 8-oxo-dG adduct formation was not affected by exposure to TCDD for 20 weeks in intact female rats. These data suggest that the induction of 8-oxo-dG adduct levels by TCDD is likely a response to chronic oxidative

imbalance. These studies provide strong evidence that the induction of 8-oxo-dG by TCDD occurs via a chronic, sex-specific, estrogen-dependent mechanism.

Wysocki, C. J., P. Dalton, et al. (1997). "Acetone odor and irritation thresholds obtained from acetone-exposed factory workers and from control (occupationally unexposed) subjects." Am Ind Hyg Assoc J **58**(10): 704-712.

Sensitivity of olfaction (smell) and chemesthesis (irritation) was evaluated for 2-propanone (acetone) and 1-butanol in acetone-exposed workers (AEW; N = 32) during a workday and unexposed subjects (microES; N = 32). Irritation sensitivity was assessed using a method that relies on the ability of individuals to localize irritants on the body. When a volatile compound is inhaled into one nostril and air into the other, the stimulated side can be determined (lateralized) only after the concentration reaches a level that stimulates the trigeminal nerve (irritation); compounds stimulating olfaction alone cannot be lateralized. Intranasal lateralization thresholds offer an objective measure of sensory irritation elicited by volatile compounds. Test results indicated that neither olfactory nor lateralization thresholds for butanol differed between AEW and microES. Olfactory thresholds to acetone in AEW (855 ppm) were elevated relative to those of microES (41 ppm), as were lateralization thresholds (36,669 ppm and 15,758 ppm, respectively). Within AEW, level of occupational exposure was not correlated with thresholds. Other measures revealed that microES used more irritation descriptors than did AEW on trials where the acetone concentration was below the lateralization threshold. This is noteworthy because microES received lower concentrations of acetone to evaluate than did AEW. These results suggest that exposures to acetone induce changes in acetone sensitivity that are specific to acetone. The acetone concentrations eliciting sensory irritation using the lateralization technique were all well above current occupational exposure standards. The current study indicates that acetone is a weak sensory irritant and that sensory adaptation is an important factor affecting its overall irritancy.

Yeates, D. B. and J. L. Mauderly (2001). "Inhaled environmental/occupational irritants and allergens: mechanisms of cardiovascular and systemic responses. Introduction." Environ Health Perspect **109 Suppl 4**: 479-481.

The articles in this monograph focus on the mechanisms whereby ambient particulate matter (PM) and co-pollutants deposited in the respiratory tract cause cardiovascular and systemic effects, especially in persons with preexisting conditions such as allergic hyperresponsiveness and pulmonary, cardiac, and vascular diseases. During the past few years, it has become clear that inhaled pollutants cause adverse effects outside the respiratory tract and that these effects may in some cases be more important than respiratory effects. Investigators pursuing traditional approaches to understanding mechanisms of air pollution effects need to be brought together with those outside that community who have expertise in pathogenetic mechanisms by which deposited air pollutants might affect nonrespiratory organs. To this end, a workshop was held and papers were developed from a broad range of scientists having

specialized expertise in allergic and cardiovascular physiology. The overall goal of this monograph is to benchmark current thinking and enhance progress toward identifying and understanding the mechanisms by which nonrespiratory health effects occur and, by extension, to facilitate the appropriate management of relationships between air quality and health. This monograph contains a compilation of multidisciplinary research that forms a framework for generating and testing plausible new research hypotheses. Not only will this information stimulate the thinking of researchers, but it will also provide an improved foundation for funding agencies and advisory groups to frame research strategies, programs, and priorities.

Yodaiken, R. E. (1984). "Occupational disease. Problems of risk assessment." Clin Lab Med **4**(3): 475-482.

Aspects of risk assessment are discussed as an integral part of the regulation of occupational health standards. Events that lead to risk estimates and factors to consider in the assessment of risk management are examined. Some aspects of estimating the risk of exposure to benzene are considered as an example of the process.

Yodaiken, R. E. and D. Bennett (1986). "OSHA work-practice guidelines for personnel dealing with cytotoxic (antineoplastic) drugs. Occupational Safety and Health Administration." Am J Hosp Pharm **43**(5): 1193-1204.

Work-practice guidelines for personnel dealing with cytotoxic drugs (CDs) are presented. Current practices in the preparation, storage, administration, and disposal of CDs may expose pharmacists, nurses, physicians, and other health-care workers to high environmental levels of these drugs. OSHA has developed these guidelines to protect health-care workers from unnecessary exposure to CDs. A brief summary of the short-term and long-term hazards known to be associated with these drugs is presented. The risks to workers handling CDs are a combined result of the drugs' inherent toxicity and the extent to which workers are directly exposed to CDs via inhalation, absorption, and ingestion. Work-practice guidelines that can limit the exposure of workers to CDs and the equipment necessary to carry out these practices properly are described.

York, M. and W. Steiling (1998). "A critical review of the assessment of eye irritation potential using the Draize rabbit eye test." J Appl Toxicol **18**(4): 233-240.

Traditionally, the eye irritation potential of substances and products has been assessed using the Draize eye test. While this procedure has been criticized in terms of its scientific validity and its ethical acceptability, it remains the only official, government-recognized procedure for predicting the irritant effect of substances in the eye. The relative absence of serious human accidents testifies to the success of the predictions. With the development of alternative non-animal procedures to replace the Draize test, the data generated in the Draize procedure are also being used as a 'gold standard' against which the performance of alternative procedures is measured. The major sources of

variability are small group size and inability of existing scoring systems to reflect the complexities of the total in vivo response. In addition, the use of algorithms to simplify the in vivo data (for comparison with in vitro data) also misrepresents the in vivo data. Addressing the above issues would inevitably increase the use of animals. This would go against the general public demand for a reduction in the use of animals. Therefore the issue is to decide upon a simple parameter (for comparison with in vitro data) that encompasses the complexity of the irritation response and accurately reflects irritation without requiring the use of additional test animals. Such a parameter could be the recovery time. In addition, controlled human testing to benchmark the Draize data would be invaluable. The future use of Draize data in the validation of in vitro alternatives is undisputed, but the utility of these data will only be enhanced by a proper understanding of the shortcomings of the Draize test.

Yu, I. J., H. Y. Kim, et al. (1999). "The occupational exposure level (OEL) for 2-bromopropane: the first OEL established by Korea." Appl Occup Environ Hyg **14**(6): 356-358.

Zhuang, J. G., Y. J. Cheng, et al. (1993). "The setting of an occupational exposure limit for phosphamidon in the workplace--a Chinese approach." Ann Occup Hyg **37**(1): 89-99.

This paper describes the approach of setting an occupational exposure limit for phosphamidon, an organophosphorus pesticide, in the workplace in China. Apart from a general review of the literature relating to various toxicological studies, special emphasis has been placed on the results of a systematic occupational health survey on the workers exposed to phosphamidon. As a result of the survey, together with the literature review, a 'maximum allowable concentration' (MAC) for phosphamidon in the air of workplace is suggested as 0.02 mg m-3 but on the condition that the route of skin entry be blocked effectively. In addition, based on the description of the standard-setting process in China, a comparison has been made to the current U.K. approach.

Ziegler-Skylakakis, K. (2004). "Approaches for the development of occupational exposure limits for man-made mineral fibres (MMMFs)." Mutat Res **553**(1-2): 37-41.

Occupational exposure limits (OELs) are an essential tool in the control of exposure to hazardous chemical agents, and serve to minimise the occurrence of occupational diseases associated with such exposure. The setting of OELs, together with other associated measures, forms an essential part of the European Community's strategy on health and safety at work, upon which the legislative framework for the protection of workers from risks related to chemical agents is based. The European Commission is assisted by the Scientific Committee on Occupational Exposure Limits (SCOEL) in its work of setting OELs for hazardous chemical agents. The procedure for setting OELs requires information on the toxic mechanisms of an agent that should allow to differentiate between thresholded and non-thresholded mechanisms. In the first case, a no-

observed adverse effect level (NOAEL) can be defined, which can be the basis for a derivation of an OEL. In the latter case, any exposure is correlated with a certain risk. If adequate scientific data are available, SCOEL estimates the risk associated with a series of exposure levels. This can then be used for guidance, when setting OELs at European level. Man-made mineral fibres (MMMFs) are widely used at different worksites. MMMF products can release airborne respirable fibres during their production, use and removal. According to the classification of the EU system, all MMMF fibres are considered to be irritants and are classified for carcinogenicity. EU legislation foresees the use of limit values as one of the provisions for the protection of workers from the risks related to exposure to carcinogens. In the following paper, the research requirements identified by SCOEL for the development of OELs for MMMFs will be presented.

Zielhuis, R. L. (1971). "Threshold limit values and total work load." J Occup Med **13**(1): 30-34.

Zielhuis, R. L. (1974). "Permissible limits for occupational exposure to toxic agents. A discussion on differences in approach between US and USSR." Int Arch Arbeitsmed **33**(1): 1-13.

Zielhuis, R. L. (1994). "Yant Memorial Award Lecture, 1992. A more informative list of occupational exposure limits with a supplement." Am Ind Hyg Assoc J **55**(2): 102-111.

Dr. Reinier Zielhuis was presented with the Yant Memorial Award by the American Industrial Hygiene Association in 1992. The award recognizes outstanding contributions in industrial hygiene or allied fields made by an individual residing outside the United States. Dr. Zielhuis was chair of occupational and environmental health, medical faculty, at Coronel Laboratory of the University of Amsterdam from 1964-1987. Since 1987 he has been advisor to the Department of Toxic Substances of the Dutch Directorate-General of Labour. In 1990-1991 he was also advisor to the European Community on occupational standard setting. For personal reasons Dr. Zielhuis was unable to present the Memorial Award Lecture at the 1992 American Industrial Hygiene Conference & Exposition, but prepared the following article for publication in the Journal.

Zielhuis, R. L., P. C. Noordam, et al. (1991). "Harmonization of criteria documents for standard setting in occupational health: A report of a workshop." Reg Tox Pharmacol **13**: 241-262.

Zielhuis, R. L., P. C. Noordam, et al. (1988). "Short-term occupational exposure limits: a simplified approach." Int Arch Occup Environ Health **61**(3): 207-211.

This paper presents a simplified proposal for setting health standards based on short-term exposure limits (STEL). It presents an alternative to the approach by the German MAC Commission: with only three instead of five categories, no fixed

excursion factors, but ranges; more restrictive duration of sampling; no fixed frequencies of the number of accepted excursions per workshift.

Zielhuis, R. L. and A. A. E. Wibowo (1989). "Standard setting in occupational health: "philosophical" issues." American Journal of Industrial Medicine **16**: 569-598.

Zielhus, R. L. and F. W. van der Kreek (1979). "Calculation of a safety factor in setting health based permissible levels for occupational exposure." Int. ARc. Occup. Health **42**: 203-215.

Zielhus, R. L. and F. W. van der Kreek (1979). "The use of a safety factor in setting health based permissable levels for occupational exposure." Int. Arch. Occup. Environ. Health **42**: 191-201.

Ziem, G. E. and B. I. Castleman (1989). "Threshold limit values: historical perspectives and current practice." J Occup Med **31**(11): 910-918.

A 1989 Occupational Safety and Health Administration standard mandates that workplace air concentrations be held below new permissible exposure limits for 376 substances. As more than 350 of these limits came from the 1987 list of "Threshold Limit Values" (TLVs), the medical basis of the TLVs is of direct importance to the health of millions of workers. However, the TLV development process has been gravely flawed by lack of scientific rigor, inadequate medical input, and lack of attention to financial conflicts of interest. The adoption by the Occupational Safety and Health Administration of many poorly supported values as permissible exposure limits reflects also the underutilization of industrial medicine in identifying health effects of exposures below the TLVs. It is thus the responsibility of the medical profession to act on the presumption that the TLV permissible exposure limits are unsafe limits until a sound underlying body of medical and scientific literature exists for the substances on the list. It is industry's responsibility to commit itself seriously to medical and exposure monitoring and to begin to remedy the knowledge deficit that exists about the less immediate health effects of most industrial materials.