Chapter 3.0 Views on Key Issues Facing the Chemical Industry

3.3   Risk Assessment
     3.3.1   Chemical risk assessment as used in setting regulatory levels or standards. [Bernard Gadagbui, Lynne Haber and Michael Dourson, Toxicology Excellence for Risk Assessment]
     3.3.2   The limits of a risk assessment-based approach to sustainability in the chemicals industry and the need for a new paradigm based on precaution. [Joel Tickner (Lowell Center for Sustainable Production, University of Massachusetts Lowell)]

3.4   The Limits of Risk Management and New Chemicals Policies [Ken Geiser (Toxics Use Reduction Institute)]

3.5   Impacts to Human Health and the Environment
     3.5.1   The challenge to the chemical industry of PBTs. [Joanna Underwood (Inform)]
     3.5.2   Why endocrine disruptors and the associated human health effects have become a high research and policy priority [Rich Liroff (World Wildlife Fund)]

3.6   Impacts of, and Issues Associated with, Chemical Production from Manufacture to Final Use and Disposal [Richard Sigman (OECD)]

3.7   Closing the Gap on Chemical Plant Security [Agnes Shanley (Pharmaceutical Manufacturing Magazine)]

3.8   Economic Issues and Competitiveness [Peter Spitz (Chemical Advisory Partners)]

3.3 Risk Assessment

3.3.1 Chemical Risk Assessment As Used In Setting Regulatory Levels Or Standards

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Risk assessment is a process where the magnitude of a specific risk is characterized so that decision makers can conclude whether the potential hazard is sufficiently great that it needs to be managed or regulated, reduced or removed. The National Research Council (NRC, 1983) of the National Academy of Sciences (NAS) first described the process of human health risk assessment, with an update in 1994 and 1996, as a four-component paradigm (i.e., hazard identification, dose-response assessment, exposure assessment, and risk characterization), with risk communication as a fifth area of study. The first four components are described briefly below.

Four Components of Human Health Risk Assessment

1. Hazard identification explores potential concerns of a chemical. It involves an evaluation of the nature, quality, and relevance of scientific data on the specific chemical, the characteristics and relevance of the experimental routes of exposure, and the nature and significance of the observed effects. In this step, scientific studies are reviewed to determine if exposure to an agent could cause increased incidence of adverse health effects (noncancer or cancer effects) in humans, and to identify which effects the chemical can cause.

For noncancer toxicity, the process includes an evaluation of the target organ or "critical" effects (i.e., the first adverse effect or its known precursor that occurs as the dose rate increases). In some cases, one needs to determine whether an effect is adverse or not. The choice of critical effect in the hazard identification process for noncancer toxicity is used as a basis for the dose-response assessment.

For cancer toxicity, hazard identification depends on professional judgment as to the overall weight-of-evidence of carcinogenicity, including epidemiological information, chronic animal bioassays, mechanistic data, mutagenicity tests, other short-term tests, structure-activity relationships, metabolic and pharmacokinetic properties, toxicological effects, and physical and chemical properties. The outcome of this judgment is the placement of the chemical into one of several categories, such as the system developed by the International Agency for Research on Cancer (IARC) in 1978:

Group 1:   Carcinogenic to humans

Group 2:   Probably carcinogenic to humans (including subgroups 2A for chemicals having limited evidence of carcinogenicity in humans, and Group 2B for chemicals having sufficient evidence of carcinogenicity in laboratory animals, and inadequate evidence in humans).

Group 3:   Cannot be classified as to its carcinogenicity to humans

U.S. EPA has also published general guidelines in developing and evaluating risk assessments for carcinogens (U.S. EPA 1986, 1996, 1999, 2003). The most recent guidelines advocate the development of a more comprehensive characterization of carcinogenic hazard in the form of a narrative. Within this context, a cancer hazard characterization should include all information relevant to the weight-of-evidence for carcinogenicity, not just tumor data in humans and animals. This means that mechanistic data can play an integral role in the hazard identification step for carcinogenicity, and may also influence the choice of a dose-response model. Moreover, the hazard characterization can provide specific information about the conditions under which a chemical is likely to be carcinogenic. For example, it may be "likely to be carcinogenic by the route of inhalation but not by ingestion."

2. Dose-response assessment follows the hazard identification in the risk assessment process. In dose response assessment, an adverse effect is presumed to either exhibit a threshold or not in the dose-response curve.

Depending on the nature of this curve, different approaches are employed to estimate the risk posed by the potential toxic agent.

For example, risk assessment for cancer toxicity generally assumes that no threshold exists below which no adverse effects could be expected. For these agents, the U.S. EPA and others assume that there are no exposures that have "zero risk", implying that even a very low exposure to a carcinogen can increase the risk of cancer. For these agents, the high dose in the experimental animal study is generally extrapolated to the low dose to which humans are generally exposed, or to a dose that is considered to be *de minimus*. Such extrapolation introduces significant uncertainties into the risk assessment process. These uncertainties are recognized in the presentation of the risk. For example, although risk is presented as the 95% upper confidence limit, the U.S. EPA and others note that the true risk could be as low as zero.

For non-cancer toxicity, it is generally assumed that a threshold exists at or below which no appreciable risk of deleterious effect is expected over a lifetime. Thus, the goal of the risk assessment is to establish a safe dose level for humans based on a no-observed-adverse-effect level (NOAEL) or lowest-observed-adverse-effect level (LOAEL) derived from well-conducted animal toxicity studies with application of uncertainty factors to compensate for (1) differences between experimental animals and humans, (2) differences between average humans and sensitive humans, (3) the lack of a NOAEL, (4) the lack of lifetime studies, and (5) the lack of bioassay that tests a variety of endpoints such as in young experimental animals. This safe dose is used by national and health agencies throughout the world and is variously referred to as reference dose or concentration (RfD or RfC), minimum risk level (MRL), acceptable daily intake (ADI), tolerable daily intake or concentration (TDI or TDC), or tolerable intake (TI) or tolerable concentration (TC) [Barnes and Dourson, 1988; Jarabek, 1994; U.S. EPA, 1994; Dourson, 1994; Pohl and Abadin, 1995; Lu, 1985, 1988; Meek et al.,

1994; International Programme on Chemical Safety (IPCS), 1994]. This threshold approach is sometimes used for cancer toxicity when indicated by mode of action data.

In the absence of human data (the most preferred data for risk assessment), the dose response assessment for either cancer or noncancer toxicity is determined from animal toxicity studies using an animal model that is relevant to humans or using a critical study and species that show an adverse effect at the lowest administered dose. The default assumption is that humans may be as sensitive as the most sensitive experimental species.

3. The third step in the risk assessment process is **exposure assessment**. In exposure assessment, the intake of a toxic agent from the environment is quantified using any combination of oral, inhalation, and dermal routes of exposure. This assessment may include a component for each route, such as when an assessor would investigate the potential impact of a point source of pollution. In this case, the magnitude of exposure depends on the amount of chemical used or released, chemical fate and transport, chemical concentration at the point of exposure, the routes and rates of uptake, the duration, the exposure setting (location and number of potential receptors, land use and human activities that could lead to exposure), and characteristics of receptors potentially exposed to the chemical.

In a quantitative risk assessment, these factors are typically combined to estimate a potential human dose rate (and concentrations to which organisms in the environment are exposed). Exposure can be quantified through direct measurement at the point of contact using personal monitoring devices. This method gives the most accurate exposure value for the period of time over which the measurement was taken. Exposure can also be measured indirectly through environmental fate and transport modeling. A number of models are available for

use in environmental modeling; many of these are describe in U.S. EPA's exposure assessment guidelines (U.S. EPA, 1992).

An exposure assessment may also be focused on one particular medium and one route of exposure, for example, the oral intake of a disinfectant byproduct from treating water to remove microbes. This type of exposure assessment is often used to determine whether sufficient human exposure to a chemical in a given medium is occurring to warrant regulation. The assessor must estimate the extent to which individuals may be exposed to the byproduct in drinking water, often using default values for these estimates, such as consumption of 2 L of water daily.

4. Risk characterization is the most important and final part of a risk assessment. It summarizes and interprets the information from hazard identification, dose-response and exposure steps, identifies the limitations and uncertainties in risk estimates, and communicates the actual likelihood of risk to exposed populations. The uncertainties identified in each step in the risk assessment process are analyzed and the overall impact on the risk estimate(s) is evaluated quantitatively and/or qualitatively.

Often protective levels or other criteria for various chemicals in environmental media are developed. This characterization includes an evaluation of the data quality, specific assumptions, and uncertainties associated with each step, and the level of confidence in the resulting criteria. Alternative risk characterizations are also discussed. Specific key qualities, or attributes, of risk characterizations have been identified [American Industrial Health Council (AIHC), 1992; U.S. EPA, 2000b). These attributes include transparency in decision making, clarity in communication, consistency, and reasonableness.

The ultimate goal of risk characterization is to provide the risk managers with enough information, presented in a comprehensible fashion, that they understand what is known about the risk from a specific situation. In order for risk assessors to meet this goal, they must understand the needs of the risk managers and should engage them in the process. This engagement often results in an iterative approach, which helps risk assessors meet a level of detail and analysis appropriate for the situation (e.g., initial screening versus national regulation). The iterative approach allows risk managers to better use limited resources and to develop environmental criteria that have a more firm basis in the science.

Can Science Effectively Predict Risks Through Quantitative Risk Assessments – A Policy Perspective
Over the years, scientists have gained a great deal of experience, through the conduct of risk assessments, in how to perform each step in the risk assessment more efficiently and accurately. Improvements to risk assessment have been identified, significantly advancing the usefulness of risk assessment.

Our ability to accurately assess risks is affected by the uncertainties inherent in the risk assessment process at each step. Some of the sources of uncertainties in the toxicity assessment include inadequate human or animal data, inappropriate dose-response models, lack of biological basis for the adverse effects, etc. The impact of these uncertainties is that the risk assessment tends to be conservative. For example, as described above, the U.S. EPA and others generally applies uncertainty factors to adjust the safe dose downwards when data are lacking as a matter of policy, despite the fact that some of these factors might actually adjust the safe dose upwards if sufficient data were available to characterize the uncertainties.

There are many parameters and factors that are components of an exposure assessment. Where there is lack of adequate information on any of these parameters and factors, default assumptions are used. However, some of

these parameters and factors (e.g., body weight, exposure frequency, and duration) can be represented by a range of values. If these uncertainties are not reduced, a highly conservative risk may result.

During the risk characterization step, most often risk for a hypothetical sensitive subgroup is reported; historically, no average or central tendency and population risks have been estimated, although recent work also includes such values. Furthermore, risk or hazard from individual chemicals is often added to produce aggregate risk or hazard. These biases provide potential sources of uncertainty during this phase of the risk assessment process. In part because of these biases, new methods for conducting dose response assessment have been developed, as discussed in the next section.

Developing Methods in Risk Assessment and the Impact on the Chemical Industry
In addition to the approaches described above to predict risk to chemicals, a number of recent research initiatives have led to improved methods for quantitative risk assessment and better incorporation of mechanistic data, both for noncancer and cancer assessments. Structure-Activity Relationships (SAR) can be used to predict chemical toxicity in the absence of adequate data on the chemical of interest. Methods to improve the use of available data include Chemical Specific Adjustment Factors (CSAFs) to replace default uncertainty factors, use of biomarkers to quantify internal dose and variations in host susceptibility, the use of dose-response modeling methods such as Benchmark Dose (BMD) and Categorical Regression, and Physiologically Based Pharmacokinetic (PBPK) and Biologically Based Dose-Response (BBDR) models to incorporate mechanistic data. These approaches are briefly described below. [1]

Structure-activity relationship (SAR) analysis is frequently employed as a first step in the analysis of a potentially hazardous toxic agent to predict and characterize its toxicity, particularly in screening assessments

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[1] A useful text to read in addition to this chapter is by Haber et al. (2001a), as well as other associated chapters found in the latest edition of Patty's Toxicology.

when no or very limited information on the chemical's toxicity is available. SAR is a computer-based modeling method that relates chemical structure to qualitative biological activity. The analysis involves comparing the molecular structure and the physical and chemical properties of the agent with unknown toxicity with those of other, similar chemicals with known toxic or carcinogenic effects. This is based on the assumption that the structure of a chemical determines its physical and chemical properties and reactivities. These properties will determine the biological or toxicological properties when the chemical interacts with a biological system. As a predictive tool, SARs can be used to reduce the need for costly and time-consuming animal and in vitro testing to support risk assessment and regulatory action. It is thus a useful tool in screening of chemicals for a wide range of toxicity endpoints.

Chemical Specific Adjustment Factors (CSAFs) provide a consistent approach for incorporating mechanistic data to replace the default uncertainty factors for interspecies extrapolation and intraspecies variability (IPCS, 2001). This framework is based on early work by Renwick (1993) and applied by IPCS (1994), in which the default uncertainty factor of 10 for interspecies differences is divided into two factors of 2.5 and 4.0 for toxicodynamics and toxicokinetics, respectively. The default factor of 10 for intraspecies variability is similarly divided into two equal factors for toxicodynamics and toxicokinetics. Any one or all of these four subfactors can be replaced by chemical-specific data. CSAFs have been used by the U.S. EPA in deriving an RfD for boron (U.S. EPA, 2004a) and by Health Canada in deriving a TC for 2-butoxyethanol (Health Canada, 2000).

Biomarkers are defined as any cellular or molecular indication of toxic exposure, adverse health outcome or susceptibility (NAS, 1987). From this definition, three distinct biomarkers are evident, that of exposure, effects of exposure and host susceptibility. As more extensively discussed by Maier et al. (2001), this field has

progressed to a point where application to risk assessment is possible. For example, biomarkers of effects,

exposure and host susceptibility can give insights into mode of chemical action. These insights are likely to

better inform the hazard identification and dose response assessment parts of risk assessment. Moreover,

advances in both genomics and proteomics will likely impact current biomarker research and thus may

ultimately change the way risk assessments are currently conducted.

Benchmark Dose (BMD) modeling is an alternative method to the NOAEL/LOAEL approach (Crump, 1984;

Dourson et al., 1985; Barnes et al., 1995; U.S. EPA, 2000a). The method fits flexible mathematical models to

the dose-response data and then determines the dose associated with a specified incidence of the adverse

effects. Once this dose is estimated, then a RfD is estimated with the use of one or more uncertainty factors or

Chemical Specific Adjustment Factors (CSAF) as described above. Advantages over the NOAEL/LOAEL

approach include (1) the BMD is not limited to the tested doses; (2) a BMD can be calculated even when the

study does not identify a NOAEL; and (3) unlike the NOAEL approach, the BMD approach accounts for the

statistical power of the study. Numerous examples of BMD use in the dose response assessment part of the

risk assessment process are available on the U.S. EPA's Integrated Risk Information System (IRIS) (2004b).

Categorical Regression is an analytical method by which a dose-response model may be fit to data where

only severity ratings are available (Hertzberg and Miller, 1985; Hertzberg, 1989; Guth et al., 1997; reviewed

by Haber et al., 2001b). For example, the only dose-response information available may be that there was mild

liver necrosis at 2 mg/kg/day, and moderate necrosis at 10 mg/kg/day. Thus, an advantage of categorical

regression is that it can be used to conduct dose-severity of response analyses in the absence of quantitative

data. Categorical regression can also be used for modeling dose-response information from disparate

endpoints, by using a common severity metric (in terms of severity categories), although care needs to be taken in how the data are combined (Stern et al., in press).

Categorical regression can be used to describe the dose-response relationship of a single (e.g., histopathology) endpoint observed in a single study (e.g., Piersma et al. 2000) or as a meta-analytical technique to simultaneously analyze the results from multiple studies (Guth et al., 1997; Dourson et al., 1997). In this latter application, it can be used to develop an overall concentration-duration–response analysis (Guth et al., 1997), providing information of particular interest for evaluation of acute inhalation exposures. Categorical regression has also been used to estimate the risk above the RfD (Dourson et al., 1997; Teuschler et al., 1999), one of the few approaches available for estimating noncancer risk. Such estimation is well-founded when the data are in close proximity to the RfD, but greater caution would be needed to estimate risks further from doses at which data exist. The ability to estimate risks above the RfD might be useful, for example, in the case of a chemical with unique usefulness where projected human exposures slightly exceed the RfD, or where it is desirable to set priorities for regulation within a group of chemicals based on the chemical with the greatest likelihood of harm.

Physiologically Based Pharmacokinetic (PBPK) models and Biologically Based Dose-Response (BBDR) models are finding increasing use in risk assessment applications. (See the U.S. EPA's IRIS, 2004b, for several examples.) PBPK models describe the flow and transformation of the chemical by the body (toxicokinetics) using species-relevant organ and tissue volumes, blood flows, and kinetic transformation parameters (reviewed by Clewell, 1995). This allows the estimation of the biologically important dose delivered to the target organ(s). PBPK modeling can be used to calculate tissue dose, to improve interspecies extrapolation, allow route-to-route extrapolation, and evaluate mechanistic questions. While PBPK models

only describe a chemical's kinetics, BBDR models also include descriptions of a chemical's interactions with the body (toxicodynamics), including a mathematical description of how the toxic agent interacts with its molecular target and damages the cell. While a number of PBPK models have been developed and used in risk assessments, the number of BBDR models is much lower, due to the very high data demands. Perhaps two of the most famous are the model of formaldehyde (Conolly et al., 2004) and the Moolgavkar-Venzon-Knudson (MVK) model of multistage carcinogenesis (Moolgavkar and Knudson, 1981), a general toxicodynamic model that can be combined with a specific chemical kinetic model for a full BBDR. BBDR models can be used to estimate dose-response at low doses not amenable to experimental evaluation.

Sensitivity analysis is a type of uncertainty analysis that is used to consider the impacts of uncertainty. In such analyses, one input is changed at a time to determine how the results of a model will change over the range of possible values of that single input. Multiple inputs can be varied simultaneously, using a sampling technique called Monte Carlo analysis, to obtain an overall distribution of the result.

Use of Screening Methods to Support Sustainability
While the evaluation of detailed mechanistic data on a chemical is the ideal approach to develop a scientifically rigorous assessment of a chemical, decisions often need to be made based on much less data. For example, a systematic science-based approach for evaluation of a chemical early in its development can help companies evaluate alternatives, identify potential toxicological concerns early in product development, apply science-based strategies for priority setting in their inventory of existing substances, and identify the most sustainable approach. In such cases, often only limited data are available. In these cases, toxicological information is supplemented by information on related chemicals (analogs), as well as professional judgement. Screening and ranking methods are also a major component of large national and international efforts for determining when a more detailed assessment is needed.

In the United States, companies are required to submit premanufacture notice to the U.S. EPA prior to introducing new chemicals to commerce. To encourage the application of pollution prevention principles and the development of inherently low hazard new chemicals, the U.S. EPA has instituted a pollution prevention (P2) framework under as part of its Sustainable Futures program (U.S. EPA, 2004c). As part of the program, training and support are provided to companies in the evaluation of new chemicals, with limited available information, using the U.S. EPA's hazard and risk characterization models and protocols. Quantitative Structure Activity Relationship (QSAR) models are used to supplement available data, and used to calculate physical/chemical properties, persistence, bioaccumulation, aquatic toxicity, and potential carcinogenicity. Similarly, when data on the chemical are not available, human health hazards from both noncancer and cancer effects are evaluated based on available data on the chemical and using SARs to extrapolate from analogs, focussing on key reactive structural groups that are likely to determine toxicity.

Broader comparisons of multiple chemicals use chemical hazard and risk ranking methods, of which more than 100 published versions exist, varying in level of sophistication and scope of coverage (reviewed in Pittinger et al., 2003; Swanson and Socha, 1997). Relative hazards could be evaluated based on human toxicity, ecological hazards, physical safety hazards, risk perception issues, regulatory alerts, or a combination of these factors. Interest in reliable screening and ranking methods has increased in recent years, partially due to a variety of new regulatory initiatives. For example, the Canadian Environmental Protection Act (CEPA) of 1999 requires categorization of all of the approximately 23,000 substances on the Domestic Substances List (DSL), a task that will require a variety of simple and complex tools for evaluating toxicity and exposure (Health Canada, 2004). Other programs that are likely to include large-scale screening and hazard identification tools include the European Union's Registration, Evaluation and Authorization of Chemicals

(REACH) program, which would require companies to register chemicals in a central database and provide safety information (EU, 2004), and programs evaluating High Production Volume (HPV) chemicals in the United States and Europe.

Another screening approach is to focus on exposure, based on "thresholds of concern." This approach is used to identify exposure levels that, with reasonable certainty based on informed judgment and evaluation of data for existing regulated chemicals, are unlikely to produce adverse health effects under specific conditions of exposure. Building on work by Munro (1990) and Rulis (1986), this concept is used by the FDA to establish "thresholds of regulation" for food additives [U.S. Food and Drug Administration (FDA), 1995]. Similar analyses have been conducted for noncarcinogens by Munro et al. (1996).

References

AIHC (1992) 'Improving Risk Characterization. Summary of Workshop Held September 26 and 27, 1991', American Industrial Health Council.

Barnes, D.G. and M.L. Dourson (1988) 'Reference Dose (Rfd): Description and Use in Health Risk Assessments', Regulatory Toxicology and Pharmacology 8: 471-486.

Barnes, D.G., G.P. Daston, J.S. Evans, A.M. Jarabek, R.J. Kavlock, C.A. Kimmel, C. Park, and H.L. Spitzer (1995) 'Benchmark Dose Workshop: Criteria for Use of a Benchmark Dose to Estimate a Reference Dose', Regulatory Toxicology and Pharmacology 21.2: 296-306.

Clewell, H.J. (1995) The Application of Physiologically Based Pharmacokinetic Modeling in Human Health Risk Assessment of Hazardous Substances', Toxicological Letters 79.1-3: 207-17.

Conolly, R.B., J.S. Kimbell, D. Janszen, P.M. Schlosser, D. Kalisak, J. Preston, and F.J. Miller (2004) 'Human Respiratory Tract Cancer Risks of Inhaled Formaldehyde: Dose-Response Predictions Derived from Biologically-Motivated Computational Modeling of a Combined Rodent and Human Dataset', Toxicological Sciences. In press.

Crump, K.S. (1984) 'A New Method for Determining Allowable Daily Intakes', Fundamental and Applied Toxicology 4: 854-871.

Dourson, M.L., R.C. Hertzberg, R. Hartung, and K. Blackburn (1985) 'Novel Approaches for the Estimation of Acceptable Daily Intake', Toxicology and Industrial Health 1.4: 23-41.

Dourson, M.L. (1994) 'Methods for Establishing Oral Reference Doses (RfDs)' (eds W. Mertz, C.O. Abernathy, and S.S. Olin), Risk Assessment of Essential Elements 51 – 61.

Dourson, M.L., L.K. Teuschler, P.R. Durkin, and W.M. Stiteler (1997) 'Categorical Regression of Toxicity Data: A Case Study using Aldicarb', Regulatory Toxicology and Pharmacology 25: 121-129.

EU (European Union) (2004) 'The New EU Chemicals Legislation – Reach', http://europa.eu.int/comm/enterprise/reach/overview.htm (Accessed October, 2004)

Guth, D.J., R.J. Carroll, D.G. Simpson, and H. Zhou (1997) 'Categorical Regression Analysis of Acute Exposure to Tetrachloroethylene', Risk Analysis 17: 321

Haber, L.T., J.S. Dollarhide, A. Maier, M.L. Dourson (2001a) 'Noncancer Risk Assessment: Principles and Practice in Environmental and Occupational Settings', Patty's Toxicology 5.1: 169 – 232.

Haber, L., J. A. Strickland and D. J. Guth (2001b) 'Categorical Regression Analysis of Toxicity Data', Comments on Toxicology', 7.5-6: 437-452.

Health Canada (2000) 'Priority Substances List Assessment Report: 2-Butoxyethanol. Draft for Public Comments', Ottawa. Ministry of Public Works and Government Services. August. Available at http://www.hc-sc.gc.ca/hecs-sesc/exsd/psl2.htm (Accessed October, 2004).

Health Canada (2004) 'Categorization of Substances on the Domestic Substances List', Available at http://www.hc-sc.gc.ca/hecs-sesc/exsd/categorization_dsl.htm (Accessed October, 2004).

Hertzberg, R.C., and M. Miller (1985) 'A Statistical Model for Species Extrapolation Using Categorical Response Data', Toxicology and Industrial Health 1: 43-57.

Hertzberg, R.C. (1989) 'Fitting a Model to Categorical Response Data With Application to Species Extrapolation of Toxicity', Health Physics 57: 405-409.

IPCS (International Programme on Chemical Safety) (1994) 'Environmental Health Criteria No. 170: Assessing Human Health Risks of Chemicals: Derivation of Guidance Values for Health-Based Exposure Limits', World Health Organization, Geneva.

IPCS (International Programme on Chemical Safety) (2001) 'Guidance Document for the Use of Data in Development of Chemical-Specific Adjustment Factors (CSAF) for Interspecies Differences and Human Variability in Dose/Concentration Response Assessment', World Health Organization, Geneva. Available at: http://www.ipcsharmonize.org (Accessed October, 2004).

Jarabek, A.M. (1994) 'Inhalation Rfc Methodology: Dosimetric Adjustments and Dose-Response Estimation of Noncancer Toxicity in the Upper Respiratory Tract' Inhalation Toxicology 6.(Suppl.): 301 – 325.

Lu, F. (1985) 'Safety Assessments of Chemicals With Thresholded Effects', Regulatory Toxicology and Pharmacology 3: 121 – 132.

Lu, F. (1988) 'Acceptable Daily Intake: Inception, Evolution, and Application', Regulatory Toxicology and Pharmacology 8: 45 – 60.

Maier, A., D.G. Debord, and R. E. Savage (2001) 'Incorporating Biomarkers Into 21st Century Risk Assessments', Comments on Toxicology 7.5-6: 519-540.

Meek, M.E., R. Newhook, R.G. Liteplo, and V.C. Armstrong (1994) 'Approach to Assessment of Risk to Human Health For Priority Substances Under the Canadian Environmental Protection Act', Environmental Carcinogenesis and Ecotoxicology Reviews C12.2: 105 – 134.

Moolgavkar, S.H., and A.G. Knudson (1981) 'Mutation and Cancer: A Model for Human Carcinogenesis', Journal of National Cancer Institute 66: 1037-1052.

Munro, I. C. (1990) 'Safety Assessment Procedures for Indirect Food Additives: An Overview', Regulatory Toxicology and Pharmacology 12.1: 2-12.

Munro, I.C., R.A. Ford, E. Kennepohl, and J.G. Sprenger (1996) 'Correlation of Structural Class With No-Observed-Effect Levels: A Proposal for Establishing a Threshold of Concern', Food Chemistry and Toxicology 34.9: 829-867.

NAS (National Academy of Sciences) (1987) 'Committee on Biological Markers of the National Research Council', Environmental Health Perspectives 74: 3.

Piersma, A.H, A. Verhoef, J.D. te Biesebeek, M.N. Pieters, and W. Slob (2000) 'Developmental Toxicity of Butyl Benzyl Phtalate in the Rat Using a Multiple Dose Study Design' Reproductive Toxicology 14: 417-425.

Pittinger, C.A., T.H. Brennan, D. Badger, P.J. Hakkinen, and M.C. Fehrenbacher (2003) 'Aligning Chemical Assessment Tools Across the Hazard-Risk Continuum', Risk Analysis 23.3: 529-35.

Pohl, H.R. and H.G. Abadin (1995) 'Utilizing Uncertainty Factors in Minimal Risk Levels Derivation', Regulatory Toxicology and Pharmacology 22: 180 – 188.

Renwick, A.G. (1993) 'Data Derived Safety Factors for the Evaluation of Food Additives and Environmental Contaminants', Food Additives and Contaminants 10.3: 275 – 305.

Rulis, A.M. (1986) '*De Minimis* and the Threshold of Regulation', In C. W. Felix (Ed.), Food Protection Technology (pp. 29-37) (Chelsea, MI: Lewis Publishers, Inc).

Stern, B. R. M. Solioz, D. Krewski, P. Aggett, T.-C. Aw, S. Baker, K. Crump, M. Dourson, L. Haber, R. Hertzberg, C. Keen, B. Meek, L. Rudenko, R. Schoeny, W. Slob, and T. Starr 'Copper and Human Health: Biochemistry, Genetics, and Strategies for Modeling Dose-Response Relationships', Journal of Toxicology and Environmental Health. Part B. Critical Reviews. In Press.

Swanson, M.B., and A.C. Socha (1997) 'Chemical Ranking and Scoring: Guidelines for Relative Assessments of Chemicals', (Pensacola, FL: SETAC Press).

Teuschler, L.K., M.L. Dourson, W.M. Stiteler, P. Mcclure, and H. Tully (1999) 'Health Risk Above the Reference Dose for Multiple Chemicals', Regulatory Toxicology and Pharmacology 30: S19-S26.

U.S. EPA (U.S. Environmental Protection Agency) (1986) 'Guidelines for Carcinogen Risk Assessment', Federal Register 51.185: 33992 – 34003.

U.S. EPA (U.S. Environmental Protection Agency) (1992) 'Guidelines for Exposure Assessment', Federal Register 57: 22888 – 22938.

U.S. EPA (U.S. Environmental Protection Agency) (1994) 'Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry', Office of Health and Environmental Assessment, Washington, D.C. EPA 600-8-90-066F.

U.S. EPA (U.S. Environmental Protection Agency) (1996) 'Proposed Guidelines for Carcinogen Risk Assessment', Office of Research and Development, Washington, D.C. EPA 600-P-92-003C.

U.S. EPA (U.S. Environmental Protection Agency) (1999) 'Guidelines for Carcinogen Risk Assessment (SAB Review Copy, July 1999)', Washington, D.C. Available at http://www.epa.gov/ncea/raf/crasab.htm (Accessed October, 2004).

U.S. EPA (U.S. Environmental Protection Agency) (2000a) 'Benchmark Dose Technical Guidance Document (External Review Draft)', Risk Assessment Forum, Washington, D.C. EPA/630/R-00/001. Available at http://cfpub2.epa.gov/ncea/cfm/recordisplay.cfm?deid=20871 (Accessed October, 2004)

U.S. EPA (U.S. Environmental Protection Agency) (2000b) 'Science Policy Council Handbook', Office of Research and Development, Washington, D.C. EPA 100-B-00-002.

U.S. EPA (U.S. Environmental Protection Agency) (2003) 'Draft Final Guidelines for Carcinogen Risk Assessment External Review Draft', Office of Research and Development. Washington, D.C. Available at http://cfpub2.epa.gov/ncea/cfm. (Accessed October, 2004).

U.S. EPA (U.S. Environmental Protection Agency) (2004a) 'Boron and Compounds', Available at http://www.epa.gov/iris/subst/0410.htm. (Accessed October, 2004).

U.S. EPA. U.S. Environmental Protection Agency (2004b) 'Integrated Risk Information System (IRIS)', Available at http://www.epa.gov/iris/subst/0410.htm (Accessed October, 2004).

U.S. EPA (U.S. Environmental Protection Agency) (2004c) 'Pollution Prevention (P2) Framework', http://www.epa.gov/oppt/p2framework/ (Accessed October, 2004).

U.S. FDA (U.S. Food and Drug Administration) (1995) 'Food Additives; Threshold of Regulation for Substances Used in Food-Contact Articles. Final Rule', Federal Register 60: 36581-36596.