ITER Peer Review Meeting Summary
Final

University of Cincinnati, College of Medicine
Cincinnati, Ohio
USA

An independent panel of expert scientists and risk assessors met in Cincinnati Ohio to review a hazard identification and dose-response assessment on nickel soluble salts. This meeting was conducted by Toxicology Excellence for Risk Assessment (*TERA*); a non-profit organization dedicated to the best use of toxicity data in risk assessment. Expert peer reviewers donated their time and talents to provide an independent review of the assessment. A comprehensive overall review of the materials was provided by the combined experience of all the reviewers.

Dr. James Wilson of Resources for the Future, who is also a *TERA* Trustee, chaired the meeting. Dr. Wilson noted that this meeting was unusual in that *TERA* had prepared the document to be reviewed and also is the organization charged with conducting the peer review. The chair noted that the *TERA* peer review program is unique and not duplicated elsewhere. To control for *TERA* influence on the results of this peer review, the sponsors (U.S. EPA, the Metal Finishing Association of Southern California and Health Canada) asked *TERA* to keep separate the planning and administering of this review meeting from the document development. To achieve this, *TERA* assigned separate staff to the document development and meeting planning and recruited a small group of *TERA* trustees to make the selection of reviewers. Four trustees volunteered to assist. The group consisted of Dr. Steve Lewis, Exxon Biomedical Sciences; Dr. James Wilson, Resources for the Future; Dr. Eula Bingham, University of Cincinnati; and Mr. Michael Keller, private citizen.

On behalf of the trustee group, Mr. Keller described the process for selection of peer reviewers. The sponsors and other interested parties were asked to submit names and CVs for individuals that they thought would be appropriate peer reviewers. The trustees examined this list and CVs, along with the regular *ITER* pool of reviewers and sponsor suggestions for the types of scientific expertise that would be most useful to the review. *TERA* staff assisted by determining the interest and availability of these individuals. The trustees narrowed the list of candidates and reported this smaller list to the sponsors and interested parties for their comments. After consideration of these comments, the trustees selected a panel using their best judgement, including three individuals whom they wanted to participate in discussions but did not think should be polled for consensus due to conflict of interest or appearance of a potential conflict of interest. Details on this process and the selection can be found in Attachment A.

This was followed by a discussion of conflict of interest. Prior to the meeting each reviewer certified that he or she did not have a conflict (real or apparent) with the chemical under review or sponsor, or identified the potential for such conflicts. Possible conflicts were discussed with each reviewer to determine if measures were needed to manage a potential conflict (or appearance of conflict). Options include excluding the reviewer from a particular discussion and

consensus, or allowing the reviewer to participate in the discussion, but not be polled for consensus. Panel members each identified themselves, summarized their backgrounds, and noted any possible conflicts. The panel agreed to each participant's participation as documented in Attachment B.

These review meetings follow a standard format beginning with a close examination of the supporting documentation and important references by the panel in the several weeks prior to the meeting. At the meeting, after the conflict of interest discussion and decision by the panel is made, the authors of the assessment or documentation briefly present their work. For chemical assessment documents, the panel then systematically discusses the assessment, starting with a discussion of the qualitative weight of evidence and a determination of whether adequate data exist on which to base a risk value, followed by a discussion of the appropriate critical endpoints and studies. Next, the quantitative aspects of the assessment are discussed, including proposed cancer risk estimates and reference doses and concentrations.

Full discussion and participation are encouraged and agreement is reached by consensus. Consensus for the purpose of these meetings is defined as "an opinion held by all or most, or general agreement." The meeting was open to the public and observers from the Metal Finishing Association of Southern California, the South Coast Air Quality Management District (California), U.S. EPA Office of Water, the University of Cincinnati, ICF Kaiser, Nickel Producers Environmental Research Association (NiPERA), and others were in attendance.

Assessment for Nickel Soluble Salts

Sponsor: Metal Finishing Association of Southern California
U.S. Environmental Protection Agency, Office of Water
Health Canada

Presenters & Authors: Dr. Michael Dourson, Toxicology Excellence for Risk Assessment (*TERA*)
Dr. Gary Diamond, Syracuse Research Corporation
Dr. Linda Erdreich, Bailey Research Associates
Dr. Lynne Haber, Toxicology Excellence for Risk Assessment (*TERA*)
Dr. Ron Ratney, Mabbet and Associates, Inc.
Dr. Jay Zhao, Toxicology Excellence for Risk Assessment (*TERA*)

Chair: Dr. James Wilson, Resources for the Future and *TERA* trustee

Review Panel:

Dr. P. Michael Bolger, Food and Drug Administration
Dr. James J. Collins, Solutia, Inc.
*Dr. Joyce M. Donohue, U.S. Environmental Protection Agency
Dr. M. Joseph Fedoruk, University of California, Irvine
Dr. Ernest Foulkes, University of Cincinnati
Dr. Ernest Mastromatteo, University of Toronto
Dr. Ann G. Schwartz, Allegheny University of the Health Sciences
*Ms. Donna J. Sivulka, private consultant
Dr. Alan H. Stern, New Jersey Department of Environmental Protection
*Dr. John S. Wheeler, Agency for Toxic Substances and Disease Registry

*Discussants without a vote; see Attachment A.

Scientists from *TERA* presented information on the nickel soluble salts assessment in three short presentations, preceding discussions on the cancer assessment, and the non-cancer oral and inhalation assessments. Each presentation was followed by a short period during which reviewers asked clarifying questions, followed by discussion of that portion of the assessment document. The panel's recommendations are found at the end of the discussion.

PRESENTATIONS & CLARIFYING QUESTIONS – Cancer Assessment

Dr. Michael Dourson of *TERA* presented information on the carcinogenicity of soluble nickel salts in experimental animals and conclusions reached in the draft document. Dr. Linda Erdreich presented the epidemiology data relevant to nickel soluble salts. Nickel sulfate (a soluble salt of nickel) was not found to be carcinogenic by the inhalation route in two species of rodents (NTP, 1996) exposed for two years. However, there is a question whether NTP tested high enough

concentrations to induce a positive effect. Human studies of occupational exposures suggest a secondary role for soluble nickel in inducing carcinogenicity.

Soluble nickel was not found to be carcinogenic in experimental animals by the oral route, although these studies had deficiencies that precluded definitive conclusions. A limited oral human epidemiology study is also negative. Some soluble nickel forms show weak cancer activity after parenteral administration in some bioassays at high doses. Other parenteral studies are negative.

The genotoxicity of soluble nickel is generally negative in bacterial assays and weakly mutagenic in mammalian systems. Soluble nickel salts have also tested positive for chromosomal aberrations, and cause strand breaks and DNA-protein crosslinks in mammalian cells. Nickel has been shown to bind preferentially to protein over binding to DNA.

The authors presented a cancer mode of action for nickel as proposed by Oller et al. (1997). The model considers that the *in vivo* effects of soluble nickel are not due to direct DNA reactivity. Soluble nickel compounds, such as nickel sulfate, dissolve in the extracellular fluid in the lung. The resulting nickel ions are poorly transported across the membrane and into the nucleus. The effects of nickel sulfate are likely due to the cytotoxicity and inflammation induced by the reactivity of nickel. Nickel subsulfide generally undergoes endocytosis, dissolves in the cytosolic milieu, and is taken up by the nucleus where it may have effects on DNA. Finally, nickel oxide tumors may be related to particle overload.

Dr. Linda Erdreich continued the presentation with information on the epidemiological issues, including cancer of the nasal sinuses. There is an extensive group of studies on nickel refinery workers, showing a relationship between working in these industries and increased risk of lung cancer. However, co-exposure to soluble and insoluble nickel, along with lack of control of potential sources of confounding exposure, make it difficult to assess the risk of exposure to soluble nickel alone. Generally, the available studies have small sample sizes overall or within a subgroup, and involve confounding factors, primarily co-exposure to insoluble nickel. The exposure assessments are crude and exposures changed over time in the plants studied. As a rule, few atmospheric measurements of nickel were taken during the early days of exposure, and when taken, they were based on total nickel. In many cases, no attempt was made to characterize the form of nickel compounds present. The relative amounts of soluble and insoluble nickel compounds have been estimated based on process information. The studies frequently had data gaps or inconsistencies across time periods and cohorts. The role of smoking in the lung cancer of the cohorts is not accounted for in the analyses. The authors concluded that the epidemiological evidence for carcinogenicity of soluble nickel is tenuous. They concluded that the evidence shows an interaction with other forms of nickel for development of lung and nasal cancer; while the evidence that soluble nickel alone increases lung or nasal cancer is equivocal.

Using the U.S. EPA's 1996 draft cancer guidelines (U.S. EPA 1996), the authors proposed the following narrative statement: "Inhaled soluble nickel compounds should be classified as *unlikely to be carcinogenic* when exposure occurs at low concentrations, but may be carcinogenic at high concentrations. The evidence for this hypothesized tumor response in humans at high

concentrations falls at the low end for chemicals in this classification. The carcinogenicity of soluble nickel compounds following oral exposures *cannot be determined*. Several negative oral experimental animal studies exist, but each of them has a deficiency that makes conclusive statements difficult."

The authors did not recommend development of a cancer dose response estimate for soluble nickel for either the oral or inhalation routes. They noted, however, that if this should be pursued for the inhalation route, a bounding estimate based on the negative NTP bioassay would be the most promising approach, to be used with a margin of exposure (MOE) approach.

The authors also noted that all forms of nickel are not equally toxic. When direct comparisons are possible, water-soluble salts of nickel are unequivocally different from water-insoluble nickel compounds with respect to their carcinogenic potential (both parenteral and inhalation exposures) and their noncancer inhalation toxicity. Therefore, water insoluble nickel compounds should not be used to predict the carcinogenic potential or systemic toxicity of water soluble nickel salts.

The authors provided a number of questions for the panel to consider. Are the differences in mode of action and toxicity between soluble and insoluble nickel salts sufficient to consider their risk assessment (particularly the cancer risk assessment) separately? Have the epidemiology data and uncertainties in exposure been appropriately considered in the assessment? Has the assessment appropriately considered the implications of the (mixed, but primarily positive) genotoxicity assays, and the parenteral carcinogenicity data evaluating nickel compounds of varying solubilities? Should the assessment of soluble nickel carcinogenicity take into account the data on nickel subsulfide and nickel oxide carcinogenicity in the related NTP studies? Are the conclusions of the assessment regarding the carcinogenic potential of soluble nickel supported by the data? Is there a quantitative, as well as a qualitative difference in carcinogenic potential between soluble nickel and insoluble forms of nickel?

Clarifying Questions on the Presentation

The panel asked a few clarifying questions. One reviewer asked the authors to expand on the deficiencies in the oral studies. The authors noted that the Schroeder et al. (1974) study in rats included only one dose and there were no obvious signs of toxicity. In addition, in the chronic feeding study by Ambrose et al. (1976) there was 60-70% mortality in the control and exposed groups. Another reviewer asked whether soluble nickel reaches the sinuses in humans, as generally most human nasal cancers are cancers of the sinuses. A reviewer noted that the human occupational exposures were always mixed exposures of soluble and insoluble forms of nickel. The ICNCM (International Committee on Nickel Carcinogenesis in Man) (1990) report (also referred to as the Doll Report) states that soluble nickel enhances the carcinogenicity of insoluble nickel compounds. The authors expanded that this statement is based on the observations in electrolysis workers (since these were the workers exposed to soluble nickel) at Clydach and at Falconbridge (ICNCM, 1990). In that study, exposure to soluble nickel occurred in conjunction with large oxidic and sulfidic nickel exposures.

A reviewer asked about possible misclassification of exposures and the air sampling that had been done at the various plants. The reviewer asked whether there may have been ambient circulation exposure in the plants, whether the measurements of insoluble nickel might be a sampling artifact, and what reactions one might see. An author responded that soluble nickel generally does not convert back to the insoluble form and that these early measures of exposure were not made directly; rather, they were assessments of the processes in the work areas. When direct measurements were started, they found insoluble compounds in electroplating plants, but they could not determine their origin. For example, up to one-third insoluble nickel was measured in electroplating areas. A reviewer pointed out that at Port Colborne there was insoluble nickel in the slimes in tanks. Therefore, the process did not involve soluble nickel exclusively. In addition, job classifications were not identified the same way in the various studies. An observer noted that mixed exposures to different nickel species occur in the electroplating facilities. Furthermore, any polishing or buffing that is taking place in the factory may result in dusts and aerosols drifting to other parts of the plant causing co-exposure to several nickel species.

After the clarifying questions, an observer, Dr. Adriana Oller of the Nickel Producers Environmental Research Association (NiPERA) made brief technical comments. Soluble nickel differs from insoluble nickel compounds not just in potency, (i.e., the magnitude of the cancer risk or size of the slope factor), but in potential, (i.e., whether, or under what conditions, soluble nickel causes cancer). Because insoluble nickel forms (such as nickel subsulfide) are particles, cells can take them up via endocytosis, a relatively efficient process. Because the nickel particles are contained in vacuoles, surrounded by a membrane, the nickel is protected from binding to protein. Eventually the vacuoles containing the nickel particles interact with lysosomes and nickel ion is released from the subsulfide. Because the resulting nickel-containing lysosomes congregate near the nucleus, the nickel ion is released where it can react with chromatin and DNA, and not be completely bound to protein. By contrast, inhaled particles of soluble nickel compounds readily dissolve in the extracellular fluid. Because the nickel is no longer in the particulate form, the cell does not take up ionic nickel by endocytosis. Instead, cellular uptake occurs by passive diffusion or by the magnesium transport system. Binding of nickel to extracellular proteins would be expected to inhibit uptake by passive diffusion, and competition from magnesium (which is present in much higher concentrations) would be expected to lead to low uptake via the magnesium transport system. Furthermore, the relatively rapid clearance of the soluble nickel from the lung to the blood can remove the nickel from the lung before it is taken up intracellularly by these inefficient mechanisms. Once taken up by the cell, soluble nickel forms have a high affinity for intracellular proteins and thus are less likely to reach the nucleus and bind to DNA.

The panel discussed the clearance and uptake of nickel in cells and asked Dr. Oller a number of questions. One reviewer commented that nickel reacts with many substances, not just proteins, and can be presented to the cell in a number of different forms. Furthermore, not all cells will use the same type of ion transport mechanism. Another reviewer asked how the genotoxic effects would be characterized. Dr. Oller replied that genotoxic effects are seen predominantly

with insoluble forms of nickel. Genotoxicity studies generally show that nickel produces chromosomal effects, rather than point mutations, although the ultimate mechanism is not known.

Another reviewer asked what type of evidence there is for endocytosis of insoluble nickel forms and whether this is the mechanism by which nickel gets into the cell to exert its effect. Dr. Oller replied that the oxide form of nickel is very insoluble and will produce particle overload. Also, nickel subsulfide lung burdens are not nearly as high as those seen with nickel oxide. *In vitro* studies in different cell types show that cellular uptake of ionic nickel is inefficient. A different reviewer commented that he favors the three-mechanism approach as proposed in the document, namely, different mechanisms for soluble nickel, insoluble nickel oxide and insoluble nickel subsulfide.

DISCUSSION – Cancer

The panel discussed the laboratory animal data on soluble nickel. A reviewer raised several issues regarding the NTP (1996a) study. While there were two animal species tested in the NTP (1996a) inhalation study with nickel sulfate hexahydrate and both had negative results, a reviewer suggested that mice are not a good model for nickel carcinogenicity, as nickel subsulfide was not found to be carcinogenic in mice (NTP 1996c). The authors responded that both the rat and mouse models provide useful information, even if there are apparent negative results or equivocal evidence. It was also stated by the reviewer that it appears that a lot of weight is given to the rat study. The authors responded that soluble nickel sulfate was tested to adequately high levels in both species and the study meets the criteria for using both species in developing cancer risk assessments.

The panel also discussed whether the NTP study reached the maximum tolerated dose (MTD). The concentrations used in the 2-year bioassay were based on observations from the subchronic study where 100 percent of the animals had active lung inflammation at the 0.22 mg Ni/m^3 concentration. Therefore, NTP chose to use 0.11 mg Ni/m^3 as the highest concentration for the chronic bioassay. Chronic inflammation was observed in about 80% of the male rats at the high concentration in the chronic study but was of mild severity. A reviewer reported on the meeting of the NTP peer review panel that reviewed these studies and discussed this issue. At that meeting NTP stated that they would not use a higher concentration because the next higher concentration (0.22 mg Ni/m^3) would risk the study. NTP also noted differences in severity of effects between the nickel species, although reading the slides is a subjective judgement by the pathologists. The *TERA* document authors agreed with the NTP conclusion that sufficiently high concentrations were tested based on the range finding of the subchronic study. The panel accepted the rationale and comments put forth by the authors.

A reviewer asked why the maximum tolerated dose in rats (0.11 mg Ni/m^3) is lower than what humans have been exposed to. Humans have had much higher exposures historically (the Doll Report indicates that exposures in the 10 mg Ni/m^3 range are associated with carcinogenicity) and humans appear to tolerate higher exposures of nickel than do rats. The reviewer asked why

rats are more sensitive. An author replied that while the exposure concentrations of nickel are higher in the occupational studies, the pulmonary concentrations received are not necessarily greater than those that the laboratory animals received. There are two reasons for this difference. The first is that there is less deposition per unit surface area in humans than animals, due to differences in the structure of the respiratory tracts. The second is that the size particles that humans were occupationally exposed to are larger than those administered to experimental animals, since the NTP study was using particle sizes more relevant to ambient environmental exposures. Particle size is important because particles greater than 30 microns do not penetrate into the human lung. The second factor alone has a significant effect. The authors calculated that occupational exposure to 4 mg Ni/m^3 corresponds to approximately 0.1 mg Ni/m^3 for humans continuously exposed to environmentally relevant particle sizes, after adjustments are made for particle size differences and adjustments are made between occupational and environmental exposure scenarios.[1] A reviewer also noted the importance of particle size, in that early occupational exposures were to much larger particles and the ratio of larger to smaller particles changed over time. It was also noted that the particle size varies according to the process being used in the plant and that soluble nickel is found in all different sized particle groups. The panel recommended that the authors present in their document a comparison of the NTP animal data to human occupational exposures for soluble nickel for the cancer discussion. The panel recognized that there is a lack of comparable histology data in humans, making the animal to human comparisons difficult.

The panel discussed the human epidemiology data. One reviewer began the discussion by summarizing what is known from the human data and is discussed in the draft document. It was stated in the document that soluble nickel might be a co-carcinogen. This conclusion of co-carcinogenicity agrees with that of the Doll Report (ICNCM, 1990). The reviewer noted that there apparently is something in nickel refining that is a carcinogen, based on the occurrence of lung and nasal cancers; however, this appears to be limited to a specific time when exposure was high, in general, in the industry. The exposure assessments were very crude (not unusual for these types of studies) and the mixed exposure to different forms of nickel is highly correlated with cancer. However, the exposure was mixed to the point that the effect of exposure to different forms of nickel cannot be separated. Workers in these studies typically held multiple jobs in a plant and the different work areas were not clearly separated at times, making evaluating the effects of soluble nickel alone very difficult

The same reviewer agreed with the *TERA* report's summary on confounding exposures and factors that could have caused the observed effects. While it is clear that there is a potent carcinogenic effect highly correlated to exposure, there has been a history of misclassification at the plants and it is not clear if plant workers had been classified correctly for exposure, and

[1]Post-meeting analyses identified additional data relevant to the calculation of the particle size distribution in the Muir study. Based on the new data, estimates for the LOAEL(HEC) for the human study range from 0.018 to 0.2 mg Ni/m^3. This postmeeting analysis was not reviewed by the peer reviewers.

whether nickel oxide exposure was really low or high. The highest exposures were during the periods of greatest misclassification.

The reviewer also discussed other considerations, including internal and external consistency in these studies. At Clydach (ICNCM, 1990 and Easton et al., 1992), Port Colborne (ICNCM, 1990) and Kristiansand (Andersen et al., 1996), there was no internal consistency within each study. The first two studies showed no concentration-response, while the third study demonstrated only slight concentration-response. Therefore, this reviewer stated that soluble nickel might not be the carcinogen. The reviewer thought that the issue of internal consistency needs to be better addressed in the *TERA* report. There is also a lack of external consistency among studies, (i.e., similar results for soluble nickel). Results of the Finnish (ICNCM, 1990; Karjalainen et al., 1992; Antilla et al., 1998), Kristiansand (ICNCM, 1990; Andersen et al., 1996), and Clydach (ICNCM, 1990; Easton et al., 1992) studies are consistent, but the Port Colborne (ICNCM, 1990) and the Pang et al. (1996) studies do not provide similar results.

The same reviewer noted that while the *TERA* document discusses interaction conclusions, interaction in epidemiology studies is rare and requires a very detailed exposure assessment. Given the lack of detailed exposure assessment in these studies, it is not clear what is occurring at high soluble nickel exposures, and rather than interaction, the observations might more appropriately be labeled effect modification. This reviewer concluded that soluble nickel is not necessarily a carcinogen and that the effects observed are more due to confounding and misclassification than effects of soluble nickel forms. The reviewer suggested that *TERA* should structure the discussion of the epidemiological data to consider possibilities other than interaction effects. In addition, there is a need to confirm that the epidemiological data are consistent with the conclusions, in a sense to provide biological plausibility by weaving the animal study results into the epidemiological assessment. This reviewer stated that most cancers in the nasal/sinus in humans are sinus cancers and may be a result of something other than soluble nickel exposure since it is unlikely that nickel reaches the sinus cavity.

Another reviewer, while agreeing with much of what the first reviewer said, reached a slightly different conclusion. This reviewer noted that the Doll Report concluded that there was also evidence that soluble nickel exposure increased the risk of these cancers and it may enhance risk. The reviewer noted that the *TERA* document discusses the enhancement effects, but one cannot discount the role of soluble nickel in nickel carcinogenesis. This reviewer was not as concerned about internal consistency given the lack of external consistency in the studies and noted that the Pang study was not powerful enough to determine anything. Using effect modification would be applying a very sophisticated approach to very messy data. The *TERA* conclusion on promotion is beyond what this reviewer would conclude from the epidemiology evidence. While there is some evidence that soluble nickel may be a carcinogen, there are lots of problems with this conclusion. One cannot say that the increased risk is due to soluble nickel alone, but one also cannot say that it is not due to soluble nickel. The panel suggested, and the authors agreed, that *effect modification* would be a better term to describe the interaction type effects seen in these studies.

Another reviewer thought that both of these reviewers were correct and noted that while the Doll Report stated that there was an association of soluble nickel with cancer, it did not use causal language. There is a role for soluble nickel, but soluble nickel at high concentrations did not give much effect. However, the Kristiansand results are harder to interpret. The Doll Report had suggested the need to look at animal data to interpret the epidemiology results.

Another reviewer noted that epidemiological evidence demonstrates that the conclusions are consistent with several interpretations and are consistent both with soluble nickel being non-carcinogenic and with it being carcinogenic. The authors agreed that if there were no epidemiological studies, that based on the animal data soluble nickel would be classified as a clear non-carcinogen and that nickel subsulfide would be classified as a carcinogen. With the human studies, the data are equivocal. One reviewer expressed concern with the issue of biological plausibility of soluble nickel causing cancer in humans. The reviewer stated that epidemiological information is not consistent with the conclusion that soluble nickel causes cancer. Therefore, this reviewer suggested that the animal toxicological data drive the risk assessment with the epidemiological data used to support it. There are too many problems with using the human data to support the risk assessment on its own.

A reviewer noted that the epidemiology studies showed an increased risk of lung and nasal cancer with exposure to insoluble nickel, but insufficient attention has been paid to potential confounders, and these factors have not been adequately evaluated. However, one cannot dismiss confounders for one cancer site, but not the other. This reviewer was not comfortable with the conclusion that soluble nickel is "*unlikely*" to be a carcinogen and would prefer "*cannot be determined*."

The differing results in the two animal species tested by NTP (1996a) were again discussed. One reviewer noted that there is an indication of the lack of carcinogenicity for soluble nickel in one study in one rodent species (rats). However, there is a question whether the second species (mouse) is inappropriate and therefore should not be used. An author replied that an alternative explanation is that the mouse is a relevant species, but that it did not show an effect at the concentrations tested. Another author noted that the female mouse data for nickel oxide showed a tumor increase that was not statistically significant. The authors stated that, if there were no epidemiological data available for this assessment, then clearly, nickel subsulfide would be classified as carcinogenic and soluble nickel would not**.** Uncertainties in the assessment for soluble nickel result because the human data are equivocal with regard to soluble nickel.

The panel briefly discussed the parenteral data and its role in an oral or inhalation risk assessment. One reviewer cautioned that parenteral administration of various chemicals often produces local tumors and that one should be careful how much weight to give this data. Another reviewer commented that the parenteral data suggest a transport mechanism, but the relevance to environmental exposures is not clear. He thought the parenteral route is too different to make conclusions.

The panel summarized their conclusions on the animal and epidemiology evidence as follows:

- There is some evidence of an association between high soluble nickel exposure and cancer, but there are limitations to the studies, including mixed exposures, uncertainties in the exposure assessments and confounding exposures not taken into account.

- The *TERA* document should address the uncertainties in interpreting the epidemiological data. It should be noted that the evidence does not allow a clear choice of whether exposure to soluble nickel causes cancer or not. Both possibilities should be discussed.

- In rats there is a clear lack of evidence for carcinogenicity for soluble nickel compounds. In mice, data also failed to show carcinogenicity for soluble compounds. Concerns were raised about how informative the mouse data are, since nickel subsulfide was not carcinogenic in mice, and the panel recommended that the *TERA* document should address these concerns.

Mode of Action

The panel discussed the mode of action for soluble nickel toxicity. One reviewer questioned how cytosolic nickel concentrations relate to those in the nucleus. Specifically, the reviewer asked whether any measurements have been performed to detect differences in nuclear and cytosolic nickel concentrations for both the soluble and insoluble nickel forms and as a function of concentration. An author responded that those measurements have not been undertaken *in vivo* and that the intranuclear and intracytosolic distributions of soluble or insoluble nickel are not known from *in vivo* testing.[2] Dr. Oller added that there are data showing that, for a given *in vitro* concentration of nickel in cell culture medium, the intracellular concentration is higher with insoluble nickel compounds than with soluble nickel.

Another reviewer asked what evidence is available that insoluble nickel (subsulfide) is taken into cells in that form. The reviewer also asked how nickel subsulfide leads to cancer once it is inside the cell, if it is not due to dissolution of nickel or due to the subsulfide itself. An author responded that in cell culture it takes a large concentration of soluble nickel relative to nickel subsulfide to get the same response. Dr. Oller indicated that this is related to phagocytosis and that a succession of steps is needed for mutagenesis. The subsulfide particle is insoluble in water and will be easily phagocytized by epithelial cells. In the acid environment of the lysosomes, nickel ions are released. These lysosomes accumulate near the nucleus, leading to a high nuclear-to-cytoplasm ratio of nickel ions. The interaction of nickel ions with chromatin and DNA may lead to tumor induction by a number of proposed mechanisms. By contrast, nickel ions derived from nickel sulfate are present at the cell surface. Their rapid clearance, combined with binding to extracellular proteins and inefficient transport into the cell, results in a much lower intracellular uptake of nickel ions and a very low nuclear to cytoplasm ratio. Even if inhaled concentrations of soluble nickel compounds are very high, animals and humans are expected to experience serious toxic effects before a non-negligible nuclear concentration of

[2] Postmeeting comments from a reviewer provided a reference for a study comparing intracellular concentrations of nickel following *in vitro* dosing with soluble nickel compounds and with nickel subsulfide: Fletcher et al., 1994. Environ. Health Persp. 102: 69-79.

nickel ions could be achieved in the respiratory cells. The Chair recommended that document be modified to make clear the mechanisms involved and that the distinction between insoluble and soluble nickel species be differentiated.

The following weight of evidence narrative was proposed in the draft document. It follows the U.S. EPA proposed cancer guidelines (U.S. EPA, 1996):

> *Inhaled soluble nickel compounds should be classified as unlikely to be carcinogenic when exposure occurs at low concentrations, but may be carcinogenic at high concentrations. The evidence for this hypothesized tumor response in humans at high concentrations falls at the low end for chemicals in this classification. The carcinogenicity of soluble nickel compounds following <u>oral</u> exposures cannot be determined. Several negative oral experimental animal studies exist, but each of them has a deficiency that makes conclusive statements difficult.*

The authors clarified that the statement in the narrative about the evidence falling at the low end for chemicals in this classification means that the evidence for the hypothesized tumor response in humans exposed to high concentrations is weaker than for other chemicals placed in this category according to the EPA guidelines. In an initial discussion on the proposed narrative text, the panel discussed the appropriateness of including a distinction between high and low exposures. The panel discussed whether there was sufficient information to make the distinction. One reviewer noted that in regard to the occupational exposures today, there is much less nickel exposure than when the data for the epidemiological studies were compiled. One of the authors pointed out that when making the statement of potential confounders one must be careful about throwing out the dual classification of the risk statement, (i.e., different effects at the low and high exposures). Another reviewer noted that low exposure to soluble nickel does not increase the risk of cancer under any scenario. Therefore, high concentrations need to be distinguished from the low.

The authors indicated that the high concentration statement was put in to account for the parenteral data; without these data there are no positive carcinogenicity data on soluble nickel by itself. One of the reviewers noted that the relevance of parenteral data to environmental exposures is not clear and the route is too different to draw conclusions. Another of the authors added that the term "high" in this context refers to the amount relative to that particular mode of action. One reviewer added that if the document is moving more towards a mode of action approach, then the authors should provide data supporting that mode of action. It was suggested that if the document was proposing different effects at high and low concentrations, then the mode of action data supporting nonlinearity needs to be presented.

A statement was proposed that there is some evidence that soluble nickel is carcinogenic, but this observation occurs in the presence of other exposures. The panel agreed that there is a need to qualify any statement regarding the use of the epidemiological studies. There is evidence of an association between high soluble nickel exposure and cancer when exposure to insoluble nickel is also high, but it is difficult to separate the effects of soluble and insoluble nickel compounds. Exposure assessments are uncertain and the confounding exposures are not taken into account.

In rats there is a clear lack of evidence for carcinogenicity for soluble nickel compounds. In mice, the data also failed to show carcinogenicity for soluble nickel compounds.

A reviewer recommended that the document make reference to the ACGHI TLV for nickel compounds, noting that the recommendation of the TLV Committee for soluble nickel carcinogenicity was category A4, "not classifiable as a human carcinogen."

The panel recommended the cancer narrative be revised to indicate that the carcinogenic potential of inhalation exposure to soluble nickel cannot be determined because the existing evidence is composed of conflicting data and the mode of action statement does not have sufficient concentration-response information to be useful in risk assessment. The panel decided that low and high exposure distinctions were not necessary with a conclusion of *cannot be determined*. The panel asked the authors to draft new text and forward a revised narrative and discussion of the evidence that supports that narrative to the panel for their concurrence.

The following narrative was sent to the panel after the meeting and was approved by the panel. The panel also reviewed additional text discussing the evidence that supports the narrative and their comments will be incorporated into the revised document.

> The carcinogenicity of soluble nickel via the inhalation route *cannot be determined*. According to EPA's 1996 draft cancer guidelines, the following subdescriptor applies. The carcinogenic potential of inhalation exposure to soluble nickel "*cannot be determined* because the existing evidence is composed of *conflicting* data (e.g., some evidence is suggestive of carcinogenic effects, but other equally pertinent evidence does not confirm any concern)." Epidemiology studies have demonstrated an association with increased cancer only when co-exposure or prior exposure to insoluble forms of nickel was likely. Thus, data from epidemiology studies are insufficient to determine whether exposure to soluble nickel *alone* causes cancer. In animal studies, response to exposure to soluble nickel is negative in well-conducted 2-year bioassays in both male and female rats, and male and female mice. Several parenteral studies have been conducted with soluble nickel and results from these studies are either negative or weakly positive. Results from parenteral studies make definitive statements regarding inhalation difficult.
>
> The carcinogenicity of soluble nickel compounds for oral exposures *cannot be determined* at this time. According to EPA's 1996 draft cancer guidelines, the following subdescriptor applies: The carcinogenic potential of oral exposure to soluble nickel "*cannot be determined* because there are *inadequate data* to perform an assessment." Several negative oral experimental animal studies exist, but each of them has a deficiency that makes conclusive statements difficult. Moreover, the available parenteral and initiation and promotion studies, which have indirect relevance to tumor formation after oral (or inhalation) exposure, suggest some tumorigenic activity for some soluble nickel compounds in some assays.

At the meeting, the authors presented the panel with additional language regarding whether all forms of nickel are equally toxic. The proffered language stated: "When direct comparisons are

possible, water-soluble salts of nickel are unequivocally different from water insoluble nickel compounds with respect to carcinogenic potential (both parenteral and inhalation exposures), and noncancer toxicity (inhalation exposure). Therefore, assays for carcinogenic activity or systemic toxicity of water-insoluble nickel compounds should not be used to predict the carcinogenic potential or systemic toxicity of water-soluble nickel salts."

The panel discussed this briefly and reviewers voiced several objections, including that direct comparisons did not yield unequivocal differences in the noncancer toxicity of soluble and insoluble nickel, especially in light of the 2-year results of the NTP studies. The panel agreed that the concluding statement was not needed because the classification of soluble nickel was unanimously approved as "cannot be determined" and discussion on this area was not continued.

Concentration Response Assessment

The authors of the assessment document recommended that no dose- or concentration-response estimates could be calculated because there were no tumor data. The panel agreed that a concentration-response assessment should not be done because there is no evidence of carcinogenicity in the animal studies and the carcinogenicity of soluble nickel *cannot be determined.*

PRESENTATION AND CLARIFYING QUESTIONS – Inhalation Non-cancer

Dr. Lynne Haber of *TERA* presented information on the derivation of a reference concentration (RfC) for inhalation exposure to soluble nickel. She noted that there are very little human data for noncancer effects and these are mostly mortality studies. An exception is the study by Muir et al. (1993) which was a radiographic investigation of fibrosis in nickel sinter plant workers at Copper Cliff, Sudbury, England. NTP has performed inhalation bioassays on nickel sulfate, nickel oxide, and nickel subsulfide in rats and mice (NTP, 1996a, 1996b, 1996c).

The draft document derived a RfC of 6E-5 mgNi/m^3 (0.00006), based on lung fibrosis seen in male rats in the NTP (1996a) study. A NOAEL of 0.027 mg Ni/m^3 was identified. Duration and dosimetric adjustments for particle deposition were made according to the U.S. EPA's RfC methodology to calculate human equivalent concentrations (HECs). The proposed RfC was based on a benchmark concentration [BMC(HEC)] of 0.0017 mg Ni/m^3 and an uncertainty factor (UF)of 30. The NOAEL(HEC) was 0.0021, mg Ni/m^3, similar to the BMC(HEC). In response to comments on an earlier draft of the document, *TERA* also calculated a RfC based on the Muir et al. (1993) occupational study where slightly increased prevalence of irregular opacities was seen with increasing exposure duration. Based on a LOAEL of 4 mg Ni/m^3 [LOAEL(HEC) of 0.11 mg Ni/m^3] and an uncertainty factor of 100, a RfC of 1E-3 or 0.001 mg Ni/m^3 results.

Dr. Haber presented a number of questions that the panel had been asked to consider. These included whether the choices of principal study, critical effect, BMC and UFs are appropriate; whether human data would be a better basis for the RfC; whether the BMC is appropriate given the issues of model fit; whether the conclusions regarding alveolar macrophage hyperplasia being

non-adverse are appropriate; and whether the assessment should consider background human exposure levels in the determination of the RfC.

Clarifying Questions on the Presentation

The panel had a few clarifying questions and comments, mostly on the Muir et al. (1993) study. One reviewer noted that regarding the Muir study, lung function might be a more pertinent endpoint than opacities. Another reviewer noted however, that this study only looked at X-ray films and did not consider other effects. A reviewer asked about the exposure analysis in the Muir study and whether roof top monitors were used. The authors noted that there were several rooftop monitors and one monitor on the floor. The assumption was that the rooftop results are a sample of what one would expect on the floor. However, because larger particles weigh more, they may stay lower to the floor, and therefore the rooftop concentrations may be lower than concentrations of nickel in the breathing zone near the floor. The result of using the rooftop data would be conservative (health protective), in that the effects observed may have been due to higher concentrations than those measured. An observer noted that roof top monitors are used to determine how much nickel is being lost to the atmosphere from the processes, and not to estimate occupational exposure or environmental releases.

A reviewer asked the authors to clarify whether the animal reproductive studies had a complete developmental evaluation including examination for teratogenic effects. An author noted that no standard developmental studies with soluble nickel species via either the oral or inhalation routes were located. However, one oral multigeneration reproduction study (Research Triangle Institute, 1988) included teratological evaluation of the F2 generation rats. There is an inhalation developmental toxicity study in rats exposed to nickel oxide (Weischer et al., 1980) but there was only minimal evaluation of the pups. Although nickel oxide is an insoluble form of nickel, any observed systemic effects would be attributable to absorbed nickel, which presumably would be in a soluble form.

DISCUSSION – Inhalation Noncancer

Choice of Study and Choice of Critical Effect

The panel discussed alveolar macrophage hyperplasia, whether this effect is adverse or not and whether it is a more appropriate endpoint for basis of the RfC based on the NTP (1996a) study. Reviewers questioned the causes of hyperplasia, whether there is a relationship between alveolar macrophage hyperplasia and fibrosis, and whether hyperplasia is an adaptive response. Several reviewers thought macrophage hyperplasia is an adaptive response to injury and not an adverse response. Others felt that it leads to inflammation, which then leads to fibrosis. One reviewer noted that ATSDR debated this and their *Toxicological Profile* (ATSDR, 1997) on nickel concluded that there is a continuum of effects, which are concentration and duration dependent, with macrophage hyperplasia leading to fibrosis. One reviewer was not sure that this is clear-cut and noted that with benign pneumoconiosis, damage to the macrophages is the cause of irritation in the lung. One reviewer noted that the text of the NTP study did not use the term macrophage

hyperplasia (although the tables did use that term). The reviewer noted that the origin of the macrophages is unclear, whether they derive from the lung (and thus truly represent hyperplasia), or whether they represent macrophage migration to the lung in response to damage.

The authors noted that they discussed macrophage hyperplasia in the draft document and judged this response to be non-adverse. However, they calculated a benchmark concentration (BMC) for macrophage hyperplasia results from the NTP (1996a) study for comparison purposes and the resulting RfC was within a factor of two of the proposed RfC based on lung fibrosis. The panel agreed that the authors should attempt to improve the discussion of alveolar macrophage hyperplasia in the document and note that these endpoints may exist on a continuum leading to fibrosis, but that they should not be labeled non-adverse. One observer added parenthetically that in humans a noted small opacity is not proof of fibrosis, but is just an observation from the X-ray films. The small opacities cannot be correlated to fibrosis in animals.

The panel discussed the Muir et al. (1993) study. Various reviewers highlighted a number of problems with this study and its use. They noted that the study did not include an unexposed control group and there is uncertainty in the exposure measurements, and there was co-exposure to insoluble nickel compounds. Another difficulty with the study is the lack of a lower bound on the LOAEL, as exposure to soluble nickel is estimated only as less than 4 mg Ni/m^3, and the actual exposure is unknown. One reviewer was not certain that the effect of irregular opacities is an appropriate endpoint for toxicity, because nickel may exert other effects and other acute inflammatory responses. This reviewer also noted that the LOAEL from this study is forty times greater than the TLV for nickel. The authors pointed out that after dosimetric adjustments and application of uncertainty factors there is just a 10-fold difference between the RfCs derived from the animal and human data. A reviewer noted that there are large differences among the scores assigned by the five readers on the percent prevalence of irregular opacities. Another reviewer pointed out that the majority of readings that were not zero were 0/1 or 1/0 which means they may be considered abnormal or they may also be normal. Another reviewer questioned the groups for which radiographs were evaluated; noting that people who died earlier were not included. An observer pointed out that the age distribution indicates an age effect, and age could be a confounding factor. The panel recommended that the text be added to the document outlining these limitations of the Muir et al. (1993) study.

The panel agreed with the choice of the NTP (1996a) study and the critical effect of lung fibrosis, but recommended that the authors present the RfC based on Muir et al. (1993) for comparison purposes only. The panel recommended revising the discussion on alveolar macrophage hyperplasia as discussed above and adding a discussion on the limitations of the Muir study results.

One reviewer noted that there are unique neurological symptoms of anosmia that have been found in nickel workers likely exposed to high levels of both soluble and insoluble forms of nickel during the earlier years of nickel refining. Evidence of degenerative changes in the olfactory epithelium were reported in the NTP studies of mice and rats. Norwegian researchers have also carried out a number of studies indicating that nickel refinery workers showed

increased levels of nickel in nasal biopsy material (Torjussen and Andersen, 1979). The authors agreed to add this information to the document.

Duration Adjustment, Dosimetric Conversions and Benchmark Concentration

TERA adjusted the experimental concentrations to account for the discontinuous exposure by multiplying by 6 hours/ 24 hours and 5 days/ 7 days. The critical study reported lesions in the extrathoracic (nose) and pulmonary (lesions such as inflammation and fibrosis) regions of the rat. A human equivalent concentration (HEC) for particulates was calculated by multiplying the duration adjusted exposure concentration by the Regional Deposited Dose Ratios (RDDR) using the U.S. EPA methods (U.S. EPA, 1994).

One observer pointed out that the RDDR adjustment used was for insoluble particles and that this specific RfC was for soluble salts. The authors responded that the lack of a separate RDDR approach for soluble particles is a shortcoming of the current EPA RfC methodology (U.S. EPA, 1994) and the insoluble adjustment was used, in the absence of a better choice. The panel agreed that the duration adjustment and dosimetric conversions were consistent with the EPA methodology.

TERA calculated the RfC based on a human equivalent benchmark concentration [BMC(HEC)] of 0.0017 mg Ni/m^3. The panel agreed with the BMC calculations, although one reviewer noted that the two models produced similar results but questioned how the two models were chosen. An observer stated if two models have good fits, additional models usually have similar goodness of fit, and it is superfluous to run BMC models beyond what is needed to show consistency of response. The panel agreed that the calculation of the BMC was consistent with normal practices.

Uncertainty Factors

TERA proposed a composite uncertainty factor of 30. This was based on the application of a factor of 10 for intrahuman variability, given the absence of sufficient data on sensitive human subpopulations. A factor of 3 was also used to account for the potential interspecies differences in toxicodynamics. Because the RfC dosimetric adjustments were used, a factor of 1 is appropriate for the toxicokinetic aspects of interspecies extrapolation (resulting in a UF of 3 for interspecies variability).

The panel discussed the choice of uncertainty factors. The panel agreed that the UF of 10 for intrahuman variability is appropriate. However, because extensive occupational exposure experience shows that rats are more sensitive than humans, the panel decided that a factor of one should be used for interspecies extrapolation, rather than a factor of three. This results in a composite uncertainty factor of 10 for use with the human equivalent benchmark concentration of 0.0017 mg Ni/m^3. The panel agreed on the resulting RfC of 2E-4 mg Ni/m^3.

An alternative RfC developed with data from a human epidemiology study by Muir et al. (1993) was considered. However, in light of numerous uncertainties in the study, the panel thought the

NTP study preferable but asked the authors to include in the document the RfC based on the Muir study, for comparison purposes. The panel discussed whether the cascade of events leading up to lung fibrosis is a continuum. Members of the panel suggested that if a sensitive endpoint of anosmia was observed, that this would be a full LOAEL with a factor of 10 needed to adjust from LOAEL to NOAEL. With a full factor of 10 for anosmia, the RfC would decrease by 3-fold from that proposed in the document.

The panel briefly discussed the question presented to it regarding whether the assessment should consider background human exposure levels in the determination of the RfC. They agreed that this is not a question for risk assessment, rather it is a risk management issue that should not be discussed in a risk assessment document.

PRESENTATION AND CLARIFYING QUESTIONS – Oral Non-cancer

Dr. Lynne Haber of *TERA* presented information on the oral reference dose (RfD) originally calculated in the draft document and on a proposed new RfD the authors calculated in response to comments on the draft document. In the draft document *TERA* had selected the 6-month drinking water study in rats by Vyskocil et al. (1994b) as the principal study. A LOAEL of 6.9 mg Ni/kg-day in male rats (for increased urinary albumin) was divided by a composite uncertainty factor of 1000 (10 each for interspecies and intraspecies extrapolation, and three 3-fold factors for subchronic to chronic extrapolation, a minimal LOAEL and database inadequacies). The resulting RfD was 7E-3 mg Ni/kg-day. *TERA* reconsidered this RfD after comments on the draft and subsequently proposed to the panel a different RfD based on the chronic dietary rat study by Ambrose et al. (1976). In the Ambrose study, the critical effect was decreased body and organ weights with a NOAEL of 100 ppm diet (8 mg Ni/kg-day). Applying a composite uncertainty factor of 300 (10 each for interspecies and intraspecies extrapolation and 3 for database inadequacies) results in a RfD of 3E-2 mg Ni/kg-day.

There are strengths and weaknesses in each study. The authors asked the panel to consider the basis for each and to also consider whether the assessment appropriately addressed the issue of nickel-related contact dermatitis.

Clarifying Questions on the Presentation

One reviewer asked whether there are any occupational measurements of albuminuria. Another reviewer noted that increased albuminuria was reported anecdotally in a short-term, single exposure study (Sunderman et al., 1988), but not in long term studies. The reviewer also asked whether Vyskocil observed increases in urinary β-2 microglobulin, a measure of tubular proteinuria. The authors confirmed that this parameter was measured in the urine of the rats, but no statistically significant increases were observed.

DISCUSSION – Oral Non-cancer

Choice of Study and Choice of Critical Effect

A reviewer asked the authors how the authors weighted the Vyskocil and Ambrose studies. One of the authors responded that reasonable scientists can argue either way, but her preference is for the Vyskocil study. This choice was based on the fact that kidney toxicity is observed at higher doses in short-term studies, that there is a minimal effect on kidney function in occupational studies at relatively high exposures, that there was minimal reporting of data in the Ambrose study, and that the Ambrose study had high mortality in the control animals. One reviewer stated that the body weight deficits in the Ambrose study may reflect deficits related to nutrient transport. A reviewer noted that the arguments made in the oral presentation were better than in the draft document, which should be revised to include these points. The authors agreed that the human response of albuminuria (Sunderman et al., 1988) should also be included in the text.

Another reviewer noted that Vyskocil is a good study, but would caution against using the male rat for assessing albuminuria. While the results were statistically significant, this effect in male rats is tremendously variable and is not typically a measurable response. It therefore should not be used to assess glomerular function. Metals may cause different kinds of damage at different levels of exposure. A classic example is cadmium, which causes glucosuria before aminoaciduria. The reviewer also noted that nickel absorption differs based on whether the nickel is administered in food or water and under fasting or non-fasting conditions. This reviewer suggested that any future recommendations for research should include using the hamster as an appropriate model to measure kidney effects from nickel.

The panel expressed concern about the wide variability in albuminuria levels in the Vyskocil study. It was requested that the authors attempt to obtain individual animal data for that study, in order to determine whether individual animals exhibited increases in albumin levels, or whether the apparent increases were artifacts of the high variability.

The results of Schroeder and Mitchener (1971) were discussed. A reviewer noted that the problem with this study is that the animals may have been nutritionally deficient, lacking in trace elements. The panel agreed that it is not appropriate to use this study because of the inadequacy of the diet. The Sunderman et al. (1989) study was mentioned, in which there is a LOAEL for acute toxicity in humans. Another reviewer noted that Sunderman himself discounted the toxic endpoint in this kinetics study. The panel asked that the authors improve the text on the reasons for discounting this effect.

Another reviewer noted that the Metals Subcommittee of the EPA Science Advisory Board met in 1991 to advise EPA on the best study to use in setting a RfD for nickel. The committee reviewed the dermal and reproductive information on nickel, and recommended that the existing dermatological studies not be used to set the RfD, due to experimental design problems (i.e., lack of both control subjects and appropriate double blinding within these studies). The committee also concluded that the "most cogent" data from the reproductive studies "failed to yield an RfD that was substantially different" from that derived from the Ambrose et al. study.

The majority of the panel preferred the Vyskocil study to Ambrose, but acknowledged the limitations of the former study. The panel agreed to derive the RfD based on albuminuria (indicating renal glomerular dysfunction) in male and female rats exposed to nickel in drinking water for 6 months at the only dose tested of 6.9 mg Ni/kg/day. The panel indicated that this should be considered a minimal or equivocal LOAEL.

The panel requested that the document better discuss the issue of nickel-related contact dermatitis and sensitization. The document should also clearly state that the RfD is not necessarily protective for those individuals who may be sensitized.

Uncertainty Factors

A composite of uncertainty factor of 1000 was proposed for use with the Vyskocil study. The default uncertainty factor for intraspecies variability of 10 was accepted by the panel. It was suggested that individuals with kidney dysfunction might be more sensitive to ingested nickel. This would include groups with decreased kidney function such as dialysis patients and diabetics. A default uncertainty factor for interspecies variability of 10 was also accepted, as there are insufficient data to replace the default.

A partial uncertainty factor of 3 was accepted for the extrapolation of subchronic to chronic data. The 6-month exposure in the Vyskocil study and the 2-year exposure in the NTP inhalation study provide some insight into the accumulation of nickel in the kidney over time. However, there was evidence of progression between the 3-month and 6-month sacrifices in the Vyskocil study. The oral database does not provide sufficient reproductive data to meet the completeness of database criteria and a UF of 3 for database was approved. Finally, for a LOAEL to NOAEL extrapolation, an uncertainty factor of 3 was selected for the minimally adverse critical effect. The authors explained how these final three factors of 3 are generally considered equivalent to one factor of 10 in EPA practice. A proposal was offered that one uncertainty factor of 10 be used for subchronic to chronic extrapolation, LOAEL to NOAEL extrapolation, and incomplete database. The composite uncertainty factor would be 1000. There was tacit agreement by the review panel to this proposal. The panel agreed to a resulting RfD of 7E-3 mg Ni/kg-day. However, the panel recommended that low confidence be assigned to the RfD.

The panel requested that the authors investigate the amount of nickel in the experimental diets and either include the dietary amount and express the RfD for total nickel or state that the RfD is for the amount in addition to the background in the diet. In addition, they want to encourage risk managers to consider the bioavailability of nickel when using this RfD.

RECOMMENDATIONS FOR REVISION

Carcinogenicity Assessment

- The panel recommended that the authors present a comparison of the NTP animal data to human occupational exposures for soluble nickel for the cancer discussion, but recognized that there is a lack of comparable histology data in humans, making the animal to human comparisons difficult.

- The document should address the uncertainties in interpreting the epidemiological data. It should be noted that the evidence does not allow a clear choice of whether exposure to soluble nickel causes cancer or not. Both possibilities should be discussed.

- The panel suggested that *effect modification* would be a better term to describe the interaction type effects seen in the epidemiology studies.

- The Chair recommended that document be modified to make clear the mechanisms involved and that the distinction between insoluble and soluble nickel species be made.

- The panel asked the authors to draft a revised cancer narrative to indicate that the carcinogenic potential of inhalation exposure to soluble nickel *cannot be determined*. This revised narrative and discussion of the evidence that supports that narrative should be sent to the panel for their review and concurrence.

Inhalation Non-cancer

- The panel agreed to base the RfC on NTP (1996a) but asked the authors to include a RfC based on the human data (Muir et al., 1993) for comparison purposes. Limitations of the Muir study should be fully discussed.

- The panel recommended revising the discussion on alveolar macrophage hyperplasia and note that these endpoints may exist on a continuum leading to fibrosis and that this hyperplasia should not be labeled nonadverse.

- The authors agreed to add information on anosmia to the document.

- The panel recommended that the composite uncertainty factor for the inhalation RfC be lowered from 30 to 10, in light of evidence from occupational studies that humans are less sensitive than rats to noncancer respiratory effects of nickel.

Oral Non-cancer

- The panel suggested improving the discussion of the Vyskocil and Ambrose studies to include additional arguments presented by the authors in their presentation of the oral RfD.

- The authors also agreed that the anecdotal human response of albuminuria, reported by Sunderman (1988), should be included in the document.

- The panel requested that the authors attempt to obtain individual animal data for the Vyskocil study, in order to determine whether individual animals exhibited increases in urine albumin levels, or whether the apparent increases were artifacts of the high variability.

- The panel requested that the authors investigate the amount of nickel in the experimental diets for the Vyskocil and Ambrose studies and either include the dietary amount and express the RfD for total nickel, or state that the RfD is for the amount in addition to the background nickel in the diet.

- The panel requested that the document better discuss the issue of nickel-related contact dermatitis and sensitization. It should also clearly state that the RfD is not necessarily protective for those individuals who may be sensitized.

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Attachment B
Managing Potential Conflicts of Interest
ITER Peer Review Meeting
(approved by panel)

ITER peer reviewers donate their time and talents to this effort. They are selected based upon their expertise and qualifications and are employed by many types of organizations. *TERA* strives to create a balance of expertise and affiliations for each meeting. However, individual peer reviewers are representing their own expertise and views, not those of their employer. The *TERA* Board of Trustees approves *ITER* peer reviewers for inclusion in this program. A complete list of potential reviewers and more information on the *ITER* peer review program are available at http://www/tera/org/peer. Additional, *ad hoc* reviewers are selected to participate for their special expertise that may be needed for a particular chemical or discussion. For this meeting, a subgroup of *TERA* trustees selected the peer review panel from the scientists in the larger *ITER* peer reviewer pool and from those nominated by interested parties. The trustee group invited several scientists to participate as discussants, without a vote, to contribute their knowledge and expertise. A summary of the process of selection is found in Attachment A.

TERA requested that each peer reviewer identify potential conflicts of interest related to the review of the health risk assessment of nickel soluble salts, and/or the sponsor of these discussions. Each reviewer has signed a statement indicating that he or she does not have a conflict of interest concerning this assessment.

A summary of the reviewers' statements was presented to the panel and each panel member spoke of their expertise and any potential conflicts. The panel approved the following.

P. Michael Bolger – Dr. Bolger is Chief of the Contaminants Branch of the Center for Food Safety and Applied Nutrition of the Food and Drug Administration. Dr. Bolger's office has developed a Safety/Hazard Assessment of Nickel in diets, which has been provided to states for reference in setting fish advisories. Dr. Bolger has no conflicts and will participate fully in all discussions and polling for consensus.

James J. Collins – Dr. Collins is an epidemiologist with Solutia, Inc. and has been asked to participate as an *ad hoc* reviewer for this meeting. He has no conflicts and will participate fully in all discussions and polling for consensus.

Joyce M. Donohue – Dr. Donohue is a biochemist and registered dietician with the U.S. Environmental Protection Agency's Office of Water. The Office of Water is one of the sponsors of the Nickel assessment, but Dr. Donohue is not the chemical manager for nickel. The Trustees have asked Dr. Donohue to participate as a full discussant without being polled for consensus.

M. J. Fedoruk – Dr. Fedoruk is an occupational medicine physician and Medical Director of the University of California Irvine, Center for Occupational and Environmental Health. He has been asked to participate as an *ad hoc* reviewer for this meeting. Dr. Fedoruk has previously reviewed this assessment document for the South Coast Air Quality Management District, along with other

nickel assessments. He wrote a brief report for that organization summarizing different groups conclusions regarding nickel toxicity. This included a risk management/policy recommendation that from a regulatory point of view the AQMD might want to consider all forms of nickel together and potentially carcinogenic. However, he has indicated to the AQMD that there are ongoing deliberations in the form of this peer review and he brings an open mind to this peer review meeting. He has no conflicts and will participate fully in all discussions and polling for consensus**.**

Ernest Foulkes – Dr. Foulkes is a heavy metals toxicologist and Professor Emeritus at the University of Cincinnati, Department of Environmental Health. He has no conflicts and will participate fully in all discussions and polling for consensus**.**

Ernest Mastromatteo -- Dr. Mastromatteo is Professor Emeritus at the University of Toronto in occupational medicine and environmental health and has been asked to participate as an *ad hoc* reviewer for this meeting. He has been employed by the International Labour Organization and was employed by Inco Limited, a major producer of nickel and nickel compounds. He retired from Inco in 1985 to return to the University of Toronto. He does not own stock or do any consulting for Inco. Dr. Mastromatteo is also on the TLV Committee which recommends TLVs for chemicals, including nickel. He does not consider these conflicts of interest, nor would they prevent him from sharing his personal opinions on the nickel assessment. Dr. Mastromatteo will participate fully in all discussions and polling for consensus.

Ann G. Schwartz – Dr. Schwartz is a cancer epidemiologist, specializing in lung cancer genetics with the Allegheny University of the Health Sciences. She has been asked to participate as an *ad hoc* reviewer for this meeting. She has no conflicts and will participate fully in all discussions and polling for consensus.

Donna J. Sivulka – Ms. Sivulka is a private consultant who has been asked to participate as an *ad hoc* reviewer for this meeting. She worked for the U.S. EPA from 1977 to 1988 and in that capacity co-authored and served as Project Manager on assessment documents, including the Health Assessment Document for Nickel and Nickel Compounds. She also served as the EPA representative to the International Committee on Nickel Carcinogenesis in Man. From 1988 to 1995 she served as Executive Director of the Nickel Producers Environmental Research Organization (NiPERA) and left in 1995 to pursue an independent consulting career. While Ms. Sivulka no longer works directly for NiPERA she provides occasional consulting services to that organization. Because of the potential for a perceived conflict of interest, the Trustees have asked Ms. Sivulka to participate as a full discussant without being polled for consensus.

Alan H. Stern—Dr. Stern is the Chief of the Bureau of Risk Analysis for the New Jersey Department of Environmental Protection (NJ DEP). While a copy of the nickel assessment was made available to his department, Dr. Stern did not see the assessment before this review, nor has he discussed it with anyone in NJ DEP. He has no conflicts and will participate fully in all discussions and polling for consensus.

John S. Wheeler - Dr. Wheeler is a toxicologist with the Agency for Toxic Substances and Disease Registry of the Centers for Disease Control. He has been asked to participate as an *ad hoc* reviewer for this meeting. Dr. Wheeler was the Profile Manager for the ATSDR Toxicological Profile for Nickel. Because of the potential for an appearance of conflict as the Profile Manager for a recently published assessment, the Trustees have asked Dr. Wheeler to participate as a full discussant without being polled for consensus.

James D. Wilson – Dr. Wilson is a Trustee of *TERA* and will chair the meeting. He will not offer substantive comments. Dr. Wilson has no conflicts.