

Response to Comments on the Scientific Review Panel Draft of the

***Air Toxics Hot Spots Risk Assessment Guidelines Part I:
Determination of Acute Reference Exposure Levels
for Airborne Toxicants***

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Comments on the chloropicrin acute REL submitted by the Chloropicrin Manufacturers' Task Force (CMTF) in a letter from Stephen Wilhelm dated November 30, 1998

Comment 1: In regard to physical and chemical properties, a more complete description of the metabolites would be that chloropicrin photodegrades into phosgene, which is hydrolyzed to CO₂, HCl, NO_x, and monatomic chlorine.

Response: Comment noted. OEHHA did not attempt a complete description of all the fates of the chemicals studied, but appreciates the commentator's extension of our description.

Comment 2: In regard to major user or source, the draft document does not make clear that chloropicrin's primary use is as a preplant soil fumigant by itself or in formulations with other products. In addition it is no longer used for grain fumigation

Response: OEHHA will revise the draft to incorporate the comment.

Comment 3: A substantial body of recently completed chloropicrin studies was not included in the draft summary. Many are inhalation studies and should be considered in evaluations of chloropicrin inhalation toxicity. These studies are cited in the references to this document and include those by Chun and Kintigh, 1993; Yoshida, 1987; Schardein, 1994; Schardein 1993a and 1993b; Burleigh-Flayer, 1994; NCI, 1978; Wisler, 1995; Ulrich, 1995.

Response: The comment lists several studies to consider. Only Yoshida, 1987 is a study reported in the peer-reviewed literature and is a subchronic study. The others are a 1978 NTP carcinogenicity bioassay and unpublished studies (both inhalation and oral) from the Bushy Run Research Center (BRRC) and the International Research and Development Corporation (IRDC). None appear to be acute studies, but data in the Schardein developmental studies may be usable to develop an acute REL protective against a severe effect. OEHHA conducts a literature search before developing an REL. OEHHA prefers to use studies from the peer-reviewed literature, such as the Kane *et al.* paper used as the key study. In the interests of space and time, we only describe key studies used in deliberating the REL. Both J.L. Schardein of IRDC (64 papers listed on Medline in December 1998) and H. Burleigh-Flayer of BRRC (11 papers), who are listed as authors of the unpublished reports, publish in the peer-reviewed literature. Neither has published their work on chloropicrin. In fact Medline lists only 25 papers with the key word chloropicrin published since 1965. Publication of these recent studies would be a valuable addition to the toxicologic literature on chloropicrin and might be useful in protecting the public.

Comment 4: The Task Force believes that in developing the acute REL, OEHHA has inappropriately applied uncertainty factors to chloropicrin toxicity data. The draft acute REL for chloropicrin is derived with the use of a 10-fold dose reduction factor for interspecies uncertainty and an additional 10-fold dose reduction for intraspecies uncertainty. The 10-fold interspecies UF proposed for the acute REL is inconsistent with the 3-fold UF proposed by OEHHA for the chloropicrin chronic REL.

Response: The 10-fold interspecies UF proposed for the acute REL should not be directly compared with the 3-fold UF proposed by OEHHA for the chloropicrin chronic REL. The latter 3-fold factor was used instead of 10 because a correction had been made in the chronic REL derivation for the differences between human and animal respiratory tracts, a correction developed by USEPA for Reference Concentrations (RfCs). No such correction was made in the acute REL development. Therefore, the full 10-fold uncertainty factor is applied.

Comment 5: The most appropriate model for the use of uncertainty factors with chloropicrin is presented on page 43 of the draft. OEHHA explains situations where UFs of less than 10 can be used in the development of the REL. The example cited by OEHHA is acrolein, an acute respiratory irritant like chloropicrin. No UF was used for interspecies extrapolation because human data were cited, and a factor of 3 was used for the uncertainty of extrapolating from a LOAEL to a NOAEL. The CMTF believes that because the critical effects supporting the derivation of the chloropicrin OEHHA REL are limited to sensory and respiratory irritation and are not progressive, there is no need for an interspecies uncertainty factor. Nonspecific irritation effects seen at the portal of entry and target organ following exposure to chloropicrin are equivalent across all species tested (cites above). Nonspecific irritation at the site of contact was seen in all species evaluated, including dogs, rabbits, rats and two strains of mice. There is no basis to conclude that humans will respond differently from these mammalian species. Likewise, there is no basis to conclude that human respiratory tissue will be differentially susceptible to chloropicrin irritation.

Response: The UF of 3 used for acrolein cited in the comment was for LOAEL to NOAEL extrapolation. In the key study used for developing the chloropicrin REL, an animal NOAEL was available. In the case of acrolein, no interspecies extrapolation was necessary because the study was conducted in humans. The use of 1 as an interspecies UF when the study is conducted in animals contradicts most experience in toxicology and would have to be done on a case by case basis. While there is merit to the argument that nonspecific irritation at the site of contact might occur at similar concentrations across mammalian species, more data are needed before assuming that is the case in evaluating public health impacts. It would be useful (1) to sponsor studies of people exposed to varying airborne concentrations of chloropicrin for time periods up to 1 hour, so that the human and animal data could be directly compared or at least (2) to summarize the available data supporting the commentator's contention that an interspecies factor of 1 is adequate to protect public health.

Comment 6: Although the draft suggests that acute exposures to airborne toxicants follow a graded response (OEHHA, 1998), exceptions are known and acknowledged by OEHHA. Airborne exposures to chloropicrin stimulate the trigeminal nerve in the nose. This system is protective and responds on an all-or-none basis to chemicals such as CO₂, acetic acid, and H₂S in addition to chloropicrin. Human data for chloropicrin exposure are cited by OEHHA and support the position that an UF for interspecies differences in chloropicrin responsiveness is not justified. Likewise a 10-fold factor for intraspecies variability is not justified.

Response: It is not clear from the comment why human data cited in the OEHHA document support the position that an UF for interspecies differences in chloropicrin responsiveness is not justified. The human data are relatively limited. Grant (1986) reports that exposure to 1 ppm (6.7 mg/m³) causes immediate lacrimation and eye irritation. Eye irritation and lacrimation were observed in humans exposed to 0.3 ppm for 10 minutes (Prentiss, 1937). In the report cited by the commentator, Krieger (1996) indicates that Flury and Zernick (1931) report intensive irritation for 3-30 second exposures to 0.3-0.37 ppm chloropicrin. These levels bracket the observed NOAEL for decreased respiratory rate in mice in Kane *et al.*, 1979. The data suggests that eye irritation in humans is a more sensitive measure than respiratory decrease in mice based on the NOAEL in mice of 0.6 ppm.

OEHHA uses a 10-fold intraspecies uncertainty factor to account for variability in human response. The commentator provides no information why an uncertainty factor for variability in human response is not appropriate.

Comment 7: Because the respiratory effects of chloropicrin are concentration and not dose dependent, duration of exposure is not a factor in producing effects or in preventing effects. RELs are intended to protect against mild adverse effects, severe adverse effects and life threatening adverse effects. By definition, the duration of exposure for these effects is one hour. Chloropicrin is well-known for its exposure warning properties and the likelihood of a one-hour exposure at a level that would cause any degree of adverse effect is quite low. According to the document, An Assessment of Implied Worker Exposure and Risk Associated with Chloropicrin Loading, Application, and Field Tarping Activities Following Application, and Implied Exposure and Risk of Off-Field Concentrations Resulting From Soil Fumigation (Kreiger, 1996), “the inherent human and animal warning response to chloropicrin occurs at low levels (0.15-0.3 ppm) of exposure in air. Adverse effects of higher levels (1 ppm or more) of chloropicrin have revealed remarkably similar patterns of pulmonary injury in humans and test animals. Protective reflex responses and adverse effects represent two distinct responses of humans and animals to chloropicrin inhalation.” The protective warning properties of chloropicrin occur at airborne concentrations of 0.15ppm. Adverse effects as defined by OEHHA, “any effects resulting in functional impairment and/or pathological lesions that may affect the performance of the whole organism, or that reduce an organisms’ ability to respond to an additional challenge” will not occur at the chloropicrin concentrations that provoke the common chemical sense, i.e., the warning property. Exposure to chloropicrin below this concentration has no effect and an application of safety, or uncertainty, factors is without rationale. The California acute REL should therefore be established at 0.1 ppm.

Response: OEHHA considers irritancy an adverse health effect. The chloropicrin REL is based on measures of irritancy in an animal model that may not be a particularly sensitive measure of irritant effects. There are not adequate data in humans to characterize chloropicrin irritant effects well. As such, for the purposes of protecting sensitive members of the population, we use uncertainty factors. No data are provided that would substantiate that an individual will not be irritated at the “warning level” of 0.15 ppm. In fact, Flury and Zernick, 1931 report intensive eye irritation and lacrimation upon very short-term (3 to 30 second) exposures to 0.3 – 0.37 ppm

chloropicrin. In addition, the qualitative observation of similar “patterns” of toxicity cited in the comment are not helpful for quantitative evaluation of the REL.

OEHHA plans to update the guidance periodically. If human (or more animal) data become available which indicate that the proposed REL should be reassessed, OEHHA can reevaluate the REL in a future update.

Comment 8: OEHHA relies on an application of Haber’s Law to establish a time-concentration relationship for exposure to chloropicrin and effects of that exposure. Despite the statement on page 51 of the draft OEHHA document acknowledging the National Academy of Sciences position that Haber’s Law does not apply to some irritants, discussion is presented about the application of various “chemical-specific parameters” (n) in the Haber’s Law equation. The discussion suggests that the value for n be greater than 1 for chemicals in which the toxicity is determined more by exposure concentration than by duration of exposure. That is, n should be greater than 1 for chemicals like chloropicrin. The example for this case in the draft OEHHA document is ammonia and the range of values for n given in the draft document is 0.8-4.6. Table 1 presents a series of calculations of Haber’s Law for chloropicrin using several values for n and values for exposure time that are realistic. “Normalizing the time of exposure to 60 minutes and employing a value for n that is not greater than 1 can inflate the REL calculation by a factor of 60 to nearly 16,000.” The value for n used by OEHHA for the development of the chloropicrin REL was 1. Additional uncertainty factors for species extrapolation are not needed. [The comment also contains a Table 1 in which no UFs were applied.]

Response: OEHHA has suggested a modified Haber’s Law for use in time extrapolation. This modification allows for an exponent, n , to be applied to concentration other than one. As the exponent increases in value, the implication is that concentration is more important than time. Values greater than 3 or so reflect almost complete concentration dependence. There are a number of values of “ n ” that have been derived by ten Berge *et al.* (1986), OEHHA, and USEPA listed in Table 12. The values vary even for the same chemical using different datasets. While it is theorized that the value of “ n ” for chemical irritants should be greater than one, the data don’t always reflect that. For example, for the irritant chemical, chlorine, analysis of different datasets have produced values of “ n ” ranging from 1 to 3.5 (see Table 12, p. 52).

The comment supplies a table of extrapolated one-hour concentrations using assumptions of $n=1$, 2, or 3. Unfortunately, the extrapolations shown are for 10 second or 1 minute exposures extrapolated to one-hour exposures. We would not recommend using a modified Haber’s Law for extrapolating such short duration exposures as 10 seconds or even one minute. Thus, the comment that the extrapolation varies tremendously when using different values of “ n ” is not really appropriate for the extrapolation conducted by OEHHA, which was from ten minutes to one hour. When using an exponent of 2, the value of the OEHHA REL changes from 1 to 2.5 ppb. When using a value of n of 3, the REL would be 3.3 ppb. Thus, while there is definitely a difference in evaluating the REL using different values of n , the difference is not orders of magnitude as implied by the comment.

**Comments from the Ethylene Glycol Ethers Panel
submitted by Courtney Price of the CMA**

Comment 1: EGBE is not a primary reproductive or developmental toxicant. The comprehensive EGBE toxicology data base (including the Tyl 1984 rabbit developmental study relied on by OEHHA) has been reviewed by many expert groups. None have found the compound likely to be a human reproductive or developmental hazard. The National Institute of Occupational Safety and Health's (NIOSH) 1990 Criteria Document, for example, after noting (at p. 45) that maternal toxicity occurred at 200 ppm in the Tyl study on which OEHHA relies for its proposed REL, concludes (at p. 65): "Data obtained from animal studies indicate that EGBE and EGBEA do not cause adverse reproductive or developmental effects." Government agencies have not set guidelines based on reproductive/developmental effects. EGBE is not listed as a reproductive or developmental toxicant under Proposition 65.

OEHHA presents a contradictory assessment of EGBE developmental studies. Its assessment interprets the Tyl (1984) rat study as have other reviewers including NIOSH; it finds (at p. C-109) that it is not clear whether the high dose reproductive findings (delayed skeletal ossification) are direct effects of EGBE or secondary effects of concurrent maternal toxicity. On the other hand, OEHHA's assessment (at p. C-109) of the concurrent Tyl rabbit study notes the maternal toxicity at 200 ppm, but ignores that finding in determining that the acute REL will be based on "developmental effects" found at the same dose. The proper assessment of both Tyl studies (rat and rabbit), as NIOSH and others have found, is that EGBE is not a direct reproductive nor a developmental toxicant in rodents. Therefore, acute human exposure level guidelines for EGBE should not be based on such effects. OEHHA reaches a second unjustified conclusion about the Tyl rabbit study.

Response: OEHHA agrees with the comments. We have revised the proposed REL based on reproductive/developmental effects and have instead used the human data described in Carpenter *et al.* (1956) and Johansen *et al.* (1991).

Comment 2: The draft (at p. 110) acknowledges, as have other reviewers, that hematological effects contributed to the high dose adverse developmental outcomes in rats. The draft, however, argues that the high dose reproductive and fetal toxicity in the rabbit study was not secondary to hematological effects and that rabbits do not appear to be susceptible to EGBE-induced susceptibility (at p. C-110). To the contrary, although Tyl (1984) took no blood measurements during exposure that could have detected hemolysis (blood was only analyzed 11 days after the cessation of exposure), she reports red urine in the cages (57 Env. Health Perspect. at p. 60). Rabbits, like rats and mice, have been found susceptible to EGBE-induced hemolysis. Indeed, OEHHA itself notes on the previous page (C-109) that "rabbit erythrocytes resemble rat erythrocytes and are therefore also sensitive to the hemolytic effects of EGBE (Ghanayem *et al.*, 1992)." See also: Carpenter 1956; Tyler, 1984; Truhaut, 1979 (EGBE acetate); and Allen 1993a and 1993b, all reporting hematologic effects in rabbits by inhalation, oral or dermal exposures. Particularly pertinent to interpretation of the Tyl blood results 11 days after cessation of exposure

are the findings reported in Tyler, 1984 of hemoglobinuria in rabbits during exposure, but with recovery after 14 days of non-exposure, indicating that recovery occurs and thus explains why the Tyl study did not detect hemolysis 11 days after exposure.

Response: OEHHA agrees with the comment and has revised this proposed REL based on the conclusion that hemolysis did occur in the rabbits as pointed out in the comment. We have instead used human data on irritation as the basis for the REL.

Comment 3: The acute REL should be based on human data. The draft determines (at p. C-111) an acute REL of 3.8 ppm (19 mg/m³) based on a LOAEL for mucous membrane irritation of 113 ppm in Carpenter (1956) and uncertainty factors of 10 for intra-species and 3 for the LOAEL (to NOAEL extrapolation). The acute REL to be derived from the Carpenter data should be increased at least three-fold. A ten-fold uncertainty factor for intra-human variability is unwarranted. The OSHA PEL has been 50 ppm for many years (although OSHA proposed reducing it to 25 ppm to conform to the ACGIH TLV) and the European Union Occupational Exposure Limit is 20 ppm. No reports of irritation have occurred at these limits. For irritation effects of EGBE, an uncertainty factor of 3 should be fully adequate. Thus, the REL should be 11.4 ppm (55 mg/m³).

Response: In the Carpenter *et al.* (1956) report the study subjects were 2 male volunteers, one 34 years old, the other 44, who were presumably in good health. Subjects were exposed to 113 ppm for 4 hours. Subjects reported irritation of the eyes and nose. No NOAEL was noted in this study at this exposure level and time. In Johansen *et al.* (1991), 7 healthy males were exposed to 20 ppm for 2 hours, with no apparent effect. The absence of reports of irritation at the various occupational exposure limits in the working population is encouraging. However, the intraspecies factor is designed to address the variability in the general human population. Since the sample sizes are so small (n = 2 and n= 7), a factor of at least 10 is needed to protect women, infants, children, the elderly, those less “healthy”, those too infirm to work, etc.

Comments from Elizabeth Margosches, Ph.D.,

Comment 1: P. 13 The level protective against severe adverse effects is the REL when the most sensitive endpoint found is a severe adverse effect. The REL then might not be protective against mild effects.

Response: The REL is protective against essentially all effects even when the endpoint is derived for a severe effect. The reason is that the most sensitive endpoint is used, that is, the endpoint that occurs at the lowest experimental concentration is used as the basis of the REL, and that effect might be classified as severe (e.g., teratogenic effects) rather than mild (e.g., mild irritant effects).

Comment 2: p. 14 of the document states that “It is OEHHA’s intent that, to the maximal extent possible, the levels will protect nearly all individuals.” This is so vague as to suggest you cannot succeed.

Response: We have tried to convey the idea that we would like to protect as many people as is feasible. However, there are individuals who may exhibit idiosyncratic responses to chemicals which would not show up in typical animal or human studies. In addition, it is difficult at best to quantify what percentile of the population one is protecting at a specified concentration since there are too many uncertainties in human response to accurately ascertain that value. Hence we cannot be confident in stating what percentile of the population we believe are being protected from a given REL.

Comment 3: p. 14 Section 1.6 I would include some language indicating that some kind of manipulation of the exposures observed or administered in the basis studies is needed to be able to make inferences about one-hour exposures and whether these will be elaborated elsewhere in the document.

Response: We will indicate that time-extrapolation is needed when the exposure duration is not one-hour, and that this is described later in Section 3.4.

Comment 4: If 35 of 51 RELs are based on human data, why write in Section 1.6.1 that your choices are driven by what you get from animal toxicology? More elaboration is needed.

Response: Section 1.6.1 deals with the issue of how people are exposed in real time and contrasts this with how animals are exposed in laboratory settings. The same could be said of chamber exposures of humans. We will add that into the paragraph that describes the differences between experimental exposures and real-life exposure patterns.

Comment 5: Section 2.4.1.1.1 shouldn't refer to negative epidemiological studies unless you wish to denote ones that may indicate protective effects. Even then, you can see the ambiguity of your terminology.

Response: Section 2.4.1.1.1 states "Negative epidemiological studies present an additional difficulty in interpretation. Estimating the power of the study to detect an effect can be useful in providing an indication of the maximum incidence consistent with the failure to show that the exposed group was statistically different from the control group." It is not clear why the commentator objects to this or why the terminology is ambiguous.

**Comments of Ernest V. Falke, Ph.D.,
U.S.EPA, Office of Pollution Prevention and Toxics**

Comment 1: You have put together a good document. I hope you leave the door open for frequent revisions as you gain experience. The biggest impedance to any progress is the adherence to established procedures after they become obsolete. I also note that you have not used dosimetry corrections and believe that is a good decision.

Response: Comment is noted and appreciated.

Comment 2: I work on the National Advisory Committee for Acute Exposure Guideline Levels so many of my comments are related to that effort. As an overall comment I suggest you include the following statement which is in the AEGL SOP. "NAC/AEGL Committee reasonableness test: The committee generally evaluates the resultant AEGL values within the context of other supporting data to determine the reasonableness of the extrapolated values. A consensus of the committee favors the use of uncertainty factors that result in an AEGL value that best fits the supporting data." The reasonableness test is also referred to as the laugh test. Look at the bottom line. Do the numbers make sense? If they don't, then adjust the uncertainty factors. Do not rigidly adhere to rules which give a nonsensible number.

Response: Comment noted. We have attempted to be flexible in the use of UFs where the data indicate that such flexibility is appropriate. Where it is most difficult to know if the numbers make sense are in those cases where there is the least information available - where there is little to compare the number against. Comparisons with occupational standards are generally not helpful unless the underlying basis of the standard is known and relevant; unfortunately, that is generally not the case.

Comment 3: Regarding your definition of mild adverse effects. Will the person experience 'slight' irritation at or below the level? How does odor detection enter into this equation? Can odor be perceived below the mild effects level? What if the odor is objectionable? How does this enter into the equation?

Response: Very few (those with an idiosyncratic reaction) should experience any irritation below the level protective against mild adverse effects. Depending on the chemical, odor may be detected below the level protective against mild adverse effects. The odor may even be objectionable but by itself an odor is a nuisance but not an adverse health effect. Many people find normal odors objectionable, such as those from garlic and other foodstuffs, but the perception of the odor is not usually considered an adverse health effect. However, when the perception of odor is accompanied by physiological responses such as headache and nausea, OEHHA considers such an effect an adverse health effect.

Comment 4: On page 12, you include reproductive/developmental effects in the 'severe' level. Should developmental effects be in the 'life-threatening' level since many times the consequence of chemical exposure can be fetal death?

Response: Developmental effects such as fetal death could be considered life-threatening whereas malformations are generally severe adverse health effects. This needs to be addressed on a case by case basis. We have not used fetal death as an endpoint to extrapolate from in deriving RELs.

Comment 5: You present values in terms of mg/m^3 . You should also express them in ppm. Most publications use ppm and having the REL level presented in both units will facilitate REL comparisons to published literature toxicity values.

Response: In the chemical summaries (appendix C) both are presented. Some materials (metals) cannot be expressed as ppm. In the Hot Spots program the RELs are compared to ground level concentrations expressed as mg/m^3 or $\mu\text{g}/\text{m}^3$ in a hazard index approach. Thus these units are much more useful than ppm or ppb for our program.

Comment 6: On page 28 (table 7), you mention specific decrements in pulmonary function tests as severe. What is the basis for this? What is the normal variability seen in humans? In the latest SAB review of the EPA ARE guidelines there was criticism of the use of a RAW decrement which was considered within normal variation.

Response: A severe effect based on pulmonary function tests would have a clinically significant change in specific airway resistance (100% increase) or airway conductance (50% decrease) plus a $\geq 20\%$ drop in FEV1 or other symptoms consistent with bronchoconstriction. This combination is consistent with reactive airways disease/asthma which is a serious, occasionally life-threatening condition. This is described more fully on the following page of the TSD.

Comment 7: In the text, you refer to Appendix D for Categorical Regression as a methodology. This method came under extensive criticism at the recent Scientific Advisory Board review of the ARE guidelines. It has a number of problems which preclude its use at this time. What is extremely useful is assigning effects to categories and plotting them. This allows one to visualize the entire data set in one chart. It provides a very useful tool to identify data trends, outliers, and how well the REL levels chosen fit against the entire spectrum of toxicity data on a chemical. With all of the emphasis on mathematical models people tend to overlook the incredible capacity of the human brain to intuitively make associations from patterns that no statistical model can approach.

Response: The Categorical Regression Methodology is included in an appendix for completeness. We have not used it to derive any values.

Comment 8: On page 31, in the discussion of BD, you cite the work on developmental toxicity in arriving at conclusions. This is not valid to extrapolate to acute outcomes. The developmental toxicity analysis has very complex algorithms to account for litter effects among other things.

Response: The discussion is included for completeness. We acknowledge that the algorithms are complex. Staff recognizes that there are differences in how well the benchmark dose (BD) (or benchmark concentration, BC, in our case) approach works for different endpoints. We did not arrive at conclusions for other endpoints from the developmental toxicity work cited in the document.

Comment 9: In the discussion of BD, you cite Fowles and Alexeeff (1996) as support for the choice of the 5% incidence level. This is an abstract. Your choice of the response level and 'model' is the most important conclusion you draw with respect to the use of the BD. How broad is the spectrum of chemicals used in drawing this conclusion? What were the endpoints? LC50?

Response: The study examined 18 chemicals from 29 studies. The endpoints included lethality in animals, eye irritation in animals and people, respiratory irritation in animals and people, and CNS effects in people. The most acutely lethal compounds included phosgene and methyl isocyanate while the least acutely lethal included vinyl chloride.

Comment 10: On page 33, in comparing the log-normal probit with the Weibull model you talk of the statistical fit. The 'fit' applies only to the data region. The model is used to extrapolate outside the data region where the validity of the 'model' is questionable. The EPA Benchmark software (beta version) has about 5 different models which seem to fit the data reasonably well in the data range and even make similar predictions at the 10% level but diverge wildly at the 1% response level. It would be interesting to compare the divergence at the 5% response level. The 5% level may indeed be a good compromise. You mention that the log-normal probit works the best for steep dose response curves. If you have a steep dose response curve, why not use a ruler? What will you do with a shallow dose response curve? The 5% response level is disturbingly close to a probable biological response. You should compare your predicted 5% response with actual observed NOAELs to give the reader a better feel for how well your methodology fits the data and the confidence one can have in using the model.

Response: The problem of extrapolating beyond the observed range has been a long-term criticism of cancer and noncancer risk assessment. Unfortunately we have no choice but to extrapolate in order to protect public health. In regard to comparing the 5% response rate predictions (BC_{05}) and the NOAEL, Fowles and Alexeeff (1996) examined studies of 16 chemicals in animals and people for 4 acute endpoints and found that both the 1% and the 5% BCs were within a factor of 2 of the NOAEL. Thus the NOAEL was generally between the 1% and 5% BC which is one reason to place the BC below the NOAEL in Figure 6. The BC_{05} is not always below an identified NOAEL. The BC_{05} is a more accurate estimate based on linear regression of at least one dose-response curve (sometimes more) than the NOAEL which is constrained by the investigator's choice of dose levels. Thus, the comparison to the NOAEL is compromised by the imprecision of the NOAEL estimate and should not necessarily be used to engender confidence in the BC_{05} . If anything, it should be the other way around – the BC_{05} should engender confidence in the NOAEL. Fowles and Alexeeff (1996) also evaluated two models, the probit and the Weibull models. The results from the two models were not substantially different at the BC_{05} level.

Comment 11: Ideally if one were going to use statistical models one would fit an infinite number of curves ('models') against the data and choose the one with the best fit for each chemical. Pragmatically if one is going to do statistical modeling the log-normal and 5% response is probably a reasonable fit. However, consideration may in the future be given to using something like the EPA benchmark dose software to model a number of different curves and picking the one with the best fit in the data range to extrapolate to the response of interest. Just because Hattis effectively modeled some human data in the data range with a specific model does not mean it is the best model available. The choice of the best model to use to predict in the non-data range is almost a leap of faith. Also why is the log-normal biologically plausible - what are you getting at here?

Response: Comment noted. The log-normal is biologically plausible when several factors work together to produce the toxic response. In addition, many biological parameters are lognormally distributed probably because multiple factors influence the end result. Finally, our analysis and Crump's original analysis indicated that the results do not substantially differ at the response level we are using.

Comment 12: The best, most valid use of the benchmark dose is to predict a NOAEL from a LOAEL. However, the MLE should be used as the estimate of dose response and the statistical variability around that estimate used in the consideration of the selection of uncertainty factors - along with the entire body of supporting evidence.

Response: Comment noted. We disagree with the use of the MLE in the benchmark analysis because it does not utilize all of the available information. OEHHA has used the entire body of evidence to decide on what uncertainty factors we propose applying.

Comment 13: On page 34 Table 8, I disagree with the blind lowering of uncertainty factors (UF) because a benchmark dose analysis was performed. Conversely the blind use of an UF of 10 for intraspecies variability when animal studies are used is not productive. The benchmark dose is a tool to aid the evaluator. Once you extrapolate outside the data range you go beyond science - its use is not necessary more accurate since 'more accuracy' is a hypothesis you have proposed but not proven with data. Statistics is a 'precise methodology' within the data range of a specific experiment. Once you go outside that range or consider the entire body of evidence then other factors become important. The entire body of supporting evidence, including mechanism of action, should be considered when setting UFs with the benchmark concentration being only one component of the equation. The blind application of UFs in a rigid paradigm cuts out the powerful capacity of the human brain to interpret information and draw conclusions.

Response: The problem of extrapolating beyond the observed range has been a long-term criticism of both cancer and noncancer risk assessment. Unfortunately in risk assessment we have no choice but to extrapolate given the practical limits on the number of animals that can be tested and the ethical wrong of exposing people to harmful levels of chemicals. At some point we resort to scientific judgment (the human brain) and risk management. The lowering of the UF because a BC approach has been used is not entirely blind since one must first have better data than one

would have in, for example, the worst case of a free-standing NOAEL. In addition, more of the data (e.g., the entire dose-response curve and in some cases multiple dose-response curves) is being used to determine the BC thus addressing the uncertainty of using only a NOAEL (free-standing or otherwise). OEHHA has used judgment and data in assigning the uncertainty factors. There is support in the scientific literature for a 10-fold UF for intraspecies uncertainty (see Section 3.3.4.2). Where we felt there were sufficient information on sensitive subpopulations we reduced the intraspecies uncertainty factor of 10.

Comment 14: On page 36, Figure 6, you place the BC below the NOAEL. This is not necessarily so and fails to take into account the different spectrum of data one gets on different chemicals. With steep dose-response curves one could easily have a BC above the NOAEL. The more shallow the dose-response curve the more uncertain the extrapolation of the BC into a non-data range where mechanisms may differ. If you are going to propose this relationship (BC < NOAEL) and use it as a cornerstone to your methodology you should at least demonstrate that the relationship holds for most chemicals - including chemicals with steep dose-response curves and shallow dose-response curves - and across a number of chemical classes.

Response: We agree with the commentator that the BC could occur below the NOAEL, at the NOAEL or above the NOAEL. We selected the first possibility for illustrative purposes. The figure was not meant to be exhaustive.

Comment 15: On page 37, you justify lowering the UF in humans to 3 if a BC analysis is performed on data on human subjects. This should not be done in a rote manner. The mechanism of action of the chemical should be considered along with the body of data. A higher UF may be called for. Conversely, the use of NOAELs should not automatically entail the use of an UF of 10. The entire body of supporting data should be used when selecting UFs.

Response: Comment noted. As stated above, the lowering of the UF because a BC approach has been used is not entirely blind since to use the BC approach one must first have better data than one would have in the worst case of a free-standing NOAEL or LOAEL, and more of the data is being used in the BC approach thus addressing the uncertainty of using only a NOAEL or LOAEL (free-standing or otherwise). OEHHA has considered the body of evidence for each chemical before deciding on which UF to use. Staff agree that there could be cases in which the UF used with the BC₀₅ might be greater than 3, but it seems less likely when enough subjects have been exposed such that the BC approach can be used. Of course there is always the possibility that there are people with severe idiosyncratic reactions at low levels in the population.

Comment 16: On page 37, the formaldehyde example, you state 'vinyl chloride for 3 hours'. Do you mean hydrogen chloride? As for time scaling, the use of n=2 is based on lethality data but you are modeling a mild irritation endpoint. Irritation tends to be more concentration dependent. In this case the response occurs at a threshold concentration regardless of time of exposure. With irritants the body should be able to handle a specific level of chemical exposure at a steady state with no discomfort.

Response: The document should say “formaldehyde for 3 hours.” We have made the appropriate change to the text of the document. The best way to deal with the time and concentration aspects of irritant effects is a topic of ongoing discussion and research.

Comment 17: Page 39 contains an excellent example of addressing all of the supporting evidence and relying on a rigid paradigm.

Response: Comment noted.

Comment 18: On page 40, Alexeeff *et al.*, 1997 is not in the references.

Response: Staff will add the reference to the revised TSD.

Comment 19: In Table 9, unless the data base is so poor as to be useless, composite UFs of 1000 should not be used. If the data base is that bad it should not be used to set levels. Multiplying worst case by worst case by worst case to get 1000 is unrealistic and will lead to numbers too low to have any relevant meaning.

Response: Staff agree that the use of high composite UFs is troubling. For chronic RELs USEPA limits the maximum composite UF to 3,000. If a chemical is known to be acutely toxic, protection of public health indicates that an attempt be made to attempt to determine health guidance values. Additional experimental data may later lead to revision of the REL.

Comment 20: On page 48, a sentence implies children are ALWAYS more sensitive than adults. This is not necessarily so.

Response: Comment noted. However, the word always does not appear in the statement.

Comment 21: On page 45, the reference Gillis *et al.*, 1997 is not in the references.

Response: Staff will include the reference in its final revision of the TSD.

Comment 22: These are useful guidelines on page 46 (table 10) but should be viewed as such. Rigorous, unthinking application of these uncertainty factors without considering all of the supporting information can lead to numbers too conservative or not conservative enough.

Response: Comment noted. Staff agree that rigorous, unthinking application of such UFs without considering all of the supporting information can lead to numbers too conservative or not conservative enough. We have internally debated the application of the UF in developing each REL in this document.

Comment 23: On page 52 (Table 13), state why you use n=2 one way and n=1 the other way. Currently the AEGL Committee is using an experimentally derived n where available and n=2 where it is not available but is beginning to consider using n=1 or n=2 according to the direction of extrapolation.

Response: The value of 2 is explained in the last sentence on page 49. The value of 1 was chosen as a value protective of public health since adequate experimental data to justify any other value were not available. Staff is revising the text to provide better explanation of why we chose $n=1$ in Haber's Law when extrapolating from less than one hour to one-hour exposures.

Comment 24: On page 53, Item 6, you may want to start listing international planning levels also. We are becoming more and more involved with the international community.

Response: Comment noted.

Comments from Chemical Manufacturer's Association Isopropanol Panel

Comment 1. Isopropanol (IPA) should not be regulated as an air toxic. An extensive toxicological database exists on the toxicity of IPA and demonstrates that this chemical is of low toxicological concern. It is not regulated at the federal level based on toxicity concerns and the OSHA PEL of 400 ppm confirms that it is relatively nontoxic. IPA has relatively low photoreactivity and has been approved as a substitute for ozone-depleting substances. Thus, the removal of IPA from California's air toxics list would facilitate pollution prevention efforts. The panel has submitted a petition to CARB requesting that IPA be removed from the air toxics list.

Response: Isopropanol is a listed substance under the Air Toxics Hot Spots Act and is emitted in fairly large amounts in California. The REL is based on toxicity information and IPA is judged to be sufficiently toxic to justify the development of the REL by OEHHA.

Comment 2: OEHHA should not finalize an acute REL for IPA until the panel has an opportunity to complete additional studies. The proposed acute REL is based on Nelson *et al.*, 1943 where ten human volunteers exposed for three to five minutes were asked to report subjective symptoms of irritation. IPA at 400 ppm produced mild eye, nose and throat irritation in an unspecified number of subjects. The use of naïve subjects, short duration of exposure, and reliance on subjective responses do not provide a sufficient basis for distinguishing between odor perception and sensory irritation. The Panel is sponsoring a new study with human volunteers to identify the sensory irritation thresholds for IPA. The study will be completed in 1999. CMA encourages OEHHA not to finalize the REL until the results of this research can be considered.

Response: OEHHA has used the best current human data available to develop the REL. The process of REL development is an iterative process. As new data become available, OEHHA can update these guidelines. OEHHA intends to conduct approximately annual updates. OEHHA welcomes the additional study and will carefully consider the data when it becomes available.

Comment 3. Although improved, the revised REL for isopropanol remains inappropriately low. OEHHA took into account the 1995 comments of the CMA isopropanol panel in choosing a NOAEL of 200 ppm from the Nelson study, rather than starting with 400 ppm as a LOAEL. Also, OEHHA now uses 4 minutes rather than 3 minutes as the exposure duration from which to start the time extrapolation. While the Panel appreciates these changes, we continue to believe that the proposed value is not scientifically appropriate. The revised REL is more than 300 times lower than the ACGIH 8-hour TLV and OSHA PEL (400 ppm). It is more than 380 fold lower than the ACGIH and OSHA 15-minute STEL of 500 ppm. The revised REL is more than 10 times lower than the odor threshold.

An uncertainty factor of 15.4 is unnecessary to account for the short duration of exposure of the Nelson study. The use of Haber's Law for time extrapolation is not appropriate for chemicals such as isopropanol whose effects are based primarily on concentration. Where the physiologic effect is primarily concentration-dependent, use of Haber's Law will produce incorrect values

because it assumes that the triggering of the physiologic effect is based on both concentration and time. OEHHA should therefore not use Haber's Law for these substances. The comment goes on to compare IPA with acetone and MEK that, it is stated, do not produce irritation in a time-dependent but only concentration-dependent fashion. No correction factor is needed because time is not relevant to triggering the effect. The Panel's study is "expected to include assessments of both brief and occupationally-relevant exposure durations, and therefore should provide definitive data on this issue".

Response: Comparison of occupational standards with the REL developed for the general public is problematic because of the greater sensitivity of members of the general public relative to healthy workers. The general public includes infants and children, the elderly, pregnant women, the infirm, and other sensitive subpopulations. Frank health effects are also known to occur at the TLV in some instances. Thus, comparison of the TLV or STEL to the REL does not provide much information.

Use of time extrapolation does have associated uncertainties. It is true that some effects are primarily concentration-dependent and less dependent on time. As such, we are using a modification of Haber's Law, which reflects the dependency on concentration where data are available. The exponent, n , in the equation $C^n \times T = K$ goes to infinity as the effect becomes entirely concentration dependent and not time dependent. For example, ammonia has an exponent " n " of 4.6 in the equation $C^n \times T = K$, which indicates that the irritancy is largely concentration dependent and only a little time-dependent. However, empirical information is not available to develop a data-derived value for the exponent, n , for isopropanol. Hence, we used a default value of 1 to extrapolate from less-than one hour to one-hour exposures. When the Panel completes its study, and if it shows that time extrapolation should be using a larger exponent if appropriate for irritancy from isopropanol exposure, OEHHA can use this information in an update of the REL for isopropanol.

Comment 4. The revised REL inappropriately includes eye, nose, and throat irritation with pulmonary irritation under the category of respiratory irritation. OEHHA continues to use a hazard index approach for risk characterization. The comment is concerned that adding the other irritants will in effect decrease the REL for IPA. OEHHA improperly groups chemicals whose effects are probably not additive. Numerous airborne chemicals stimulate different nerve endings in the respiratory tract. The mechanism of action and severity of effect may differ significantly. The comment supplies a table from Alarie that refines the types of irritant effects on the respiratory tract. The comment is concerned that the lumping of IPA as a respiratory irritant might lead the public to believe that IPA causes pulmonary irritation when it only causes eye, nose, and throat irritation. The hazard index should group only those chemicals which effect the same portion of the respiratory tract or have the same mechanism of action.

Response: OEHHA has indeed grouped chemicals which may act with different mechanisms on different portions of the respiratory tract. Since chemicals usually act on more than one cell type in the respiratory tree while perhaps one region is more affected than another, we are suggesting designating the entire respiratory system as one target organ. This simplistic grouping is health protective in that it is unknown whether irritation of the upper and lower airway simultaneously

by two different chemicals is additive or synergistic or less than additive. Overall, we assume that the effect on the whole organism would be at a minimum additive. There is no reason to assume the actions of an irritant acting on the upper airway primarily would be antagonistic to an irritant acting mostly on the lower airway. If there were data to the contrary, we would be interested in seeing the data and including it in our risk assessment approach.

Comment 5. The proposed Level II REL for isopropanol is not consistent with other established values and is not scientifically appropriate. OEHHA proposes a level II REL of 12 ppm. It is not justifiable to say that concentrations above 12 ppm are likely to be disabling or produce long-lasting effects. The level II REL is based on effects in the rat. OEHHA identifies a LOAEL based on slight but statistically significant decreases in motor activity observed in male but not female rats at 1500 ppm and similar effects observed in a chronic study. These mild effects in rats do not provide a defensible basis for setting a level II value for humans. OEHHA should return to its original proposal of 400 ppm based on the Nelson *et al* study.

Response: OEHHA has utilized information from two studies in rats, Gill *et al.* (1995) and Burleigh-Flayer *et al.* 1994, which examined effects on motor activity of exposure to up to 10,000 ppm isopropanol. The Gill *et al* study identified a NOAEL of 500 ppm for CNS effects (as decreased motor activity). An uncertainty factor of 10 was applied for interspecies extrapolation and another factor of 10 was applied for intraspecies extrapolation. A time adjustment based on modified Haber's Law with $n=2$ brings the REL to 12 ppm (about 31 mg/m³). Effects on the CNS are considered serious effects.

The ACGIH and the NRC did not have these studies available to them at the time the TLV and EEGL were established. In addition, in developing the EEGL, NAS did not extrapolate from the 3-5 minute exposure of the Nelson study out to one hour. If this were done, then they would have derived an EEGL of 20 ppm. This number is consistent with the 12 ppm we have derived from the animal data.

**Comments on the Methyl Bromide Acute REL Submitted By
Courtney Price of the CMA CHEMSTAR Panel.**

Comment 1: OEHHA proposes a REL of 1 ppm (3.9 mg/m³) for methyl bromide. If accepted, this REL would be based on a NOAEL of 103 ppm from a study in beagle dogs exposed to methyl bromide for 23-24 days (Pharmaco-LSR, 1994). Dogs exposed to 103 ppm showed minimal evidence of neurotoxicity, primarily characterized by decreased activity on Day 9 of the study. OEHHA declines to use the standard lognormal time extrapolation because the limited number and size of the distinct dose groups in the study was deemed insufficient for analysis using this model. Rather than using the NOAEL derived from the acute exposure study, OEHHA inappropriately proposes to apply a 100-fold safety factor to the NOAEL observed after a 7-hour/day exposure for 8 days. This approach is inconsistent with OEHHA's standard procedure.

The acute neurotoxicity study in rats (Driscoll and Hurley, 1993) is the appropriate acute toxicity endpoint study for calculation of a 1-hour REL for methyl bromide. The selection of this study is consistent with procedures currently used by USEPA for acute toxicity hazard assessment.

Response: The acute REL is based on the Pharmaco LSR (1994) unpublished study submitted to the Department of Pesticide Regulation (DPR) and reviewed by DPR and OEHHA scientists. Groups of dogs were exposed for 7 hours to between 103 and 394 ppm methyl bromide for varying numbers of days. The critical endpoints were CNS and pulmonary effects, and lacrimation. The REL is based on effects observed after the first day of exposure. The 103 ppm exposure level was identified as a NOAEL for the one-day exposure. The statement in the comment that OEHHA based the NOAEL on an 8-day exposure is incorrect.

After much discussion with Department of Pesticide Regulation staff and outside experts at University of California, Davis, it was decided not to extrapolate to a one-hour concentration due to the limited nature of the database for evaluating time-concentration relationships, as well as the complicated acute toxicity of methyl bromide when exposures occur close together. The concentration required to induce adverse effects decreases with repeated exposures. This complicates application of a one-hour REL to the real world where the REL is compared to a "maximum" modeled one-hour concentration that might be experienced in consecutive hours or days. An uncertainty factor of 100 was used for interspecies and intraspecies extrapolation, yielding an REL of 1 ppm.

The 1993 study by C.D. Driscoll and J.M. Hurley entitled "Methyl bromide: single exposure vapor inhalation neurotoxicity study in rats" is an unpublished report from the Bushy Run Research Center. The commentator did not submit a copy of the unpublished report with the comments. If the commentator wishes to submit the report, the study can be considered in future updates.

Comment 2: The (Driscoll and Hurley) study also meets the requirements for numbers of animals and dose groups necessary for using the standard log-normal model with extrapolation for exposure time.

Response: Without the study in hand staff cannot evaluate whether the data are adequate.

Comment 3: The NOAEL in the Driscoll and Hurley study for a six-hour exposure was 100 ppm for neurobehavioral effects. Since effects produced by methyl bromide are both time and concentration dependent, the 100 ppm 6 hour NOAEL was extrapolated (by the commentator) to a one-hour NOAEL. "In other words, the 100 ppm/6-hour exposure is equivalent to a 600 ppm/1-hour exposure". Based on the following calculations:

Concentration x MW conversion (ppm to mg/m³) x inhalation volume/hour x hours = Total Dose to animal

Animal total dose x MW conversion (mg/m³ to ppm) x 1/human inhalation volume/hour = human equivalent ppm

a 6-hour exposure in rats is equivalent to a human 1-hour exposure of 2182 ppm. Application of a 100X Margin of Safety to this value yields a 1-hour REL of 21.82 ppm. This value is supported by the results shown in several methyl bromide acute endpoint toxicity studies in rats, mice, rabbits and dogs. (The commentator supplied a table of RELs calculated in the same manner from different studies.)

Response: Unless OEHHA is provided a copy of the study, we cannot evaluate the study. However, if the study by Driscoll and Hurley is well-conducted, the following analysis could be considered. According to p. 6 of the comment letter, Driscoll and Hurley obtained a NOAEL of 100 ppm for a 6 hour exposure of rats to methyl bromide. If time extrapolation is not done, the NOAEL can be divided by a UF of 100 (10 each for inter- and intraspecies uncertainty) to yield an acute REL of 1 ppm, the same value proposed by OEHHA based on the dog study. If time extrapolation is done using Haber's equation with the default value of n=2, we obtain an equivalent 1 hour NOAEL of 245 ppm, and an acute REL of 2.45 ppm which is rounded to 2 ppm, again very close to the OEHHA proposed value.

The commentator obtained a value of 21.82 ppm by using a combination of 2 methods - (1) a log-normal time extrapolation model and (2) an inhalation exposure calculation for methyl bromide used to convert a one-hour animal exposure to a one-hour human exposure as described in the comment. (1) The text of the letter indicates that the time extrapolation used is the modified Haber's Equation using n=1. We discuss this in the response to comment 1 above. (2) For animal to human extrapolation, the USEPA Human Equivalent Concentration (HEC) methodology results in a human HEC equal to or lower than the animal exposure concentration. The methodology submitted by the commentator results in a human equivalent concentration at least 10 times greater than the animal concentration for all the datasets presented in the comment (Table 2 in the comment letter), an unusual result. While these methods may have merit, the commentator would need to present much more information to show that they are scientifically

preferable to those used by USEPA for calculating the human equivalent concentration and by OEHHA for calculating the one-hour REL.

**Comments on the Acute Reference Exposure level for Nickel and Nickel Compounds by
Neil J. King of Wilmer, Cutler & Pickering on behalf of NiPERA, NiDI, and Inco**

Comment 1: OEHHA calculated the acute REL for Ni and Ni compounds on the basis of Cirla *et al.* (1985) in which a sensitive population of metal platers with occupational asthma were exposed to nickel sulfate hexahydrate, a soluble nickel compound, and evaluated for atopy and pulmonary function challenge. The critical effect was an FEV₁ decrement > 15%, a mild adverse effect that is reversible following removal from exposure. Because the Cirla *et al.* (1985) study involved a sensitive human population, there was no need to apply an interspecies or an intraspecies uncertainty factor. However, since the critical endpoint was a LOAEL (33 µg as extrapolated to a one-hour concentration), OEHHA's calculation reflects application of a LOAEL uncertainty factor of 3, which produced a 1-hour acute REL of 11 µg Ni/m³.

We believe OEHHA correctly selected this human study to derive the acute REL for nickel sulfate and other soluble nickel compounds which may release nickel ions that bind to cellular proteins to produce an inflammatory response in the respiratory tract. It probably is not appropriate, however, to apply a REL derived from a study of soluble nickel sulfate to metallic (elemental) nickel, which undoubtedly would have a much higher acute inhalation REL (assuming it could be acutely toxic at all). An acute REL associated with exposure to soluble nickel also would be lower than an acute REL derived from studies where exposure to insoluble nickel compounds, since they are far less likely to produce an inflammatory response. Thus the Acute REL that OEHHA has derived from the Cirla *et al.* study of nickel sulfate-exposed asthmatics can be viewed as a "worst-case" value -- to the extent it is applied to nickel compounds generally.

Response: The commentator's statements are plausible, but unfortunately are not backed by available data. For this reason, we would not consider the REL a worst-case value. Furthermore, without data on more nickel species we are only theorizing about relative acute toxicity. We derive RELs with the data available. Data were available in the Cirla *et al.* study for nickel sulfate. It may be possible in the future to speciate nickel compounds for the purposes of developing more than one REL. However, it would then require facilities in the Hot Spots program to speciate their nickel emissions, a potentially costly prospect for most. Facilities currently just report their total nickel emissions. However, risk managers may weigh such statements about toxicity and the type of processes occurring at a facility when dealing with a hazard index exceeding 1.

Comment 2: We also agree with OEHHA's application of a LOAEL uncertainty factor of 3 rather than 10, since the adverse effect in the study by Cirla *et al.* -- a small reversible decrement in airway function as evidenced by FEV₁ measurements -- is caused by mild irritation of the respiratory tract. Accordingly, we support the Acute 1-hour REL of 11 µg Ni/m³ that OEHHA has calculated for soluble nickel sulfate. We believe, however, that its application should be limited to nickel compounds and that it should be identified as a "worst-case" value when applied to insoluble or sparingly soluble nickel species.

Response: As indicated above, we are not aware of sufficient data to draw the distinction between soluble and insoluble compounds as suggested by the comment. Further while we have classified the effects as mild, it is on the borderline of severe and mild. The study documents FEV₁ changes >15%. We generally categorized effects < 20% as mild. Thus, some of the subjects may have responded in the severe range. Further as suggested by the Scientific Review Panel, the UF for mild effects was changed to 6 from 3 based on available data and analyses of the LOAEL to NOAEL ratios. Consequently, the REL has decreased by 50%.

Comment 3: Accordingly, OEHHA should modify the heading of the Acute Toxicity Summary for “Nickel and Nickel Compounds” by limiting it to nickel compounds.

Response: Until we see specific data documenting that elemental nickel is not acutely toxic, we will retain the current heading. Staff note that metallic mercury has toxic effects and that elemental lead was included with lead compounds when the California ARB identified lead as a toxic air contaminant.

Comment 4: In addition, OEHHA should correct one confusing entry in the Acute Toxicity Summary. Section I of that Summary shows the Acute REL to be 11 µg Ni/m³, as does the derivation calculation in Section VII of the Summary. But the initial line in Section VII shows the REL to be 3.3 µg Ni/m³. That entry should be corrected.

Response: The value of 3.3 µg Ni/m³ was incorrectly listed on the initial line of Section VII. The value of 11 µg Ni/m³ was based on the use of 3 for the LOAEL to NOAEL uncertainty factor when the effect is mild irritation. Based on a comment by the Scientific Review Panel at the December 2, 1998 meeting we are changing the LOAEL to NOAEL uncertainty factor to 6 and the nickel REL to 6 µg Ni/m³.

Comment from Dr. Kathy Norlein, Minnesota Department of Health

Comment: California must be commended on the work completed to date on the acute values. The commentator expressed the concern that when a study was available that tested asthmatics no additional uncertainty factors were used to account for sensitive subpopulations. While it is reasonable to assume that asthmatics are a potentially sensitive subpopulation, the group of asthmatics that would be accepted for study is a “healthy” subpopulation of all asthmatics. To ethically be able to test asthmatics, they need to be adults who are in good health. Subjects with other health ailments are generally rejected for study (smokers, drug/alcohol users, very young, very old. Etc.) A factor of 10 would not be necessary because a somewhat sensitive subpopulation was tested. Rather than using a factor of “1” assuming that a sensitive subpopulation has been tested, a factor of 3 or 2 would be more prudent.

Response: The comment is an interesting one. When we chose an intraspecies uncertainty factor of 1 for chemicals tested in asthmatics, it is because we know asthmatics in particular are more sensitive to the chemical in question. There may be cases where a different group represents a sensitive subpopulation (lead and children for example). Then, a test in asthmatics would not be a test in sensitive subjects. The other point of the comment is a bit harder to argue, namely that because most asthmatics in a study are relatively healthy, there should be an additional uncertainty factor of 2 or 3 to protect less healthy individuals. We believe that there may be situations where it would be appropriate to use an intraspecies uncertainty factor of 2 or 3 when tests were conducted on a sensitive subpopulation. Determination of the most appropriate additional factor is problematic due to a lack of data on which to base such a factor. However, we think we have covered the most important groups fairly well in our analyses and REL derivations to date. We thank the commentator for the suggestion and will make use of it in future deliberations.

Comments from Mr. Ted Holcombe, Pacific Gas and Electric

Comment 1: The commentator is concerned with RELs which have large uncertainty factors, and notes that in Table 9 five compounds have UF of 1000, and fifteen compounds have a UF between 100 and 300. The comment also states that “OEHHA reduces LOAEL data by time factor multiplication and then by uncertainty factor multiplication”. The commentator suggests that the time adjustment factor should be included as an uncertainty factor. The comment also notes that “successive multiplication of these time and uncertainty adjustments factors leads to large differentials between LOAELS and proposed RELs”.

Response: The uncertainty factors are designed to provide a factor for interspecies extrapolation, intraspecies variability, and use of a Lowest-Observed-Adverse-Effect Level rather than a NOAEL. There are a number of studies indicating that humans are more sensitive than laboratory animals to a number of toxicants on a mg/kg-day basis. This is due to toxicokinetic differences (generally faster metabolism and clearance of the toxicant in the smaller lab animals) and can also be due to toxicodynamic differences (differences in how the toxicant interacts at the receptor). When data are available to define these differences, they are used in REL development. However, for the most part, these data are unavailable. There are also a number of papers that evaluate the range of human sensitivity to different toxicants. It can be several-fold to orders of magnitude. A ten-fold factor is adequate for most compounds and is thus the default. If data are available to refine this, then these data are utilized in the REL calculations (e.g., when sensitive subgroups are the study population). Use of large uncertainty factors reflects a relatively poor database for that chemical and endpoint.

Time adjustment does not always result in a “lowering of the LOAEL” as indicated in the comment. The purpose is to adjust from varied exposure durations to a one-hour exposure. It is not an uncertainty factor per se. Instead, it is the best scientific method we are aware of for adjusting for the toxicologic relationship between concentration and time.

Comment 2: The proposed acrolein REL is 41 times below the level of detection of the best available source test technique used in the 1996 risk assessment for the Kettleman Compressor Station.

Response: While this information is interesting, it does not necessarily mean that the proposed REL for acrolein is not valid. It might indicate that source test methods may be inadequate to evaluate the public health impacts of acrolein. Also, it appears that the test method limit of detection is above the concentrations evaluated in human subjects.

Comment 3: Citing a 1988 paper, the comment states that the proposed arsenic REL of 0.39 $\mu\text{g}/\text{m}^3$ is 25-times lower than the suggested arsenic intake level of 16 to 50 $\mu\text{g}/\text{day}$ as an essential nutrient.

Response: An element is considered essential if a diet deficient in the element leads to adverse health effects. Uthus and co-workers (1983) and the EPA (1984) have summarized studies demonstrating adverse effects of arsenic-deficient diets in goats, mini-pigs, chicks, and rats, where arsenic-deficiency affected manganese metabolism. However, further study is needed to resolve whether an arsenic-deficient diet is adverse to humans. No one has claimed that inhalation of arsenic is necessary to maintain good health. A trace element may also be classified as essential if the amount of the element in the body is maintained by biological processes. By this criterion, arsenic is nonessential (Liebscher and Smith, 1968). Neither a specific receptor nor a physiological role has been identified in humans.

It should also be noted that for many metals toxicity by the inhalation route is greater than toxicity by the oral route. Thus, it may not be appropriate to compare dietary exposures or even essentiality with inhalation exposures to the same element.

Comment 4: “Arsine gas is generally recognized as one of the more hazardous arsenic compounds, while pentavalent arsenic is generally recognized as less hazardous. Yet OEHHA’s methodology leads it to propose an REL for trivalent arsine gas of $160 \mu\text{g}/\text{m}^3$, while all other arsenic compounds are assigned a REL of $0.39 \mu\text{g}/\text{m}^3$,” which is based upon trivalent arsenic. “Pentavalent arsenic is more deserving than arsine of being assigned a separate REL.”

Response: Arsine gas has its own peculiar toxicity, lysis of red blood cells, and data are available to evaluate an REL for this compound. While we may be able to evaluate specific pentavalent arsenic compounds in future updates to this document, at the present time, we chose to use trivalent arsenic compounds as the basis for the REL. As a practical matter, most facilities report emissions of arsenic without speciating into trivalent or pentavalent. Thus, it is more health protective to have an REL based on trivalent compounds, since in general they are more toxic than pentavalent arsenic compounds.

Comment 5: PG&E appreciates the effort OEHHA has put into uncertainty estimation and does not dispute that each individual step OEHHA contemplates has a plausible justification. OEHHA does not adequately explain why it multiplies these uncertainty factors by one-another rather than adding them first. Adding the factors would yield far more believable RELs. The comment goes on to give examples of acrolein REL determined by dividing by the sum of the uncertainty factors rather than the product and noting that such a REL would unlikely to be exceeded for most combustion sources.

Response: The uncertainty factors are designed to account for specific uncertainties. We do not have data that indicates accounting for one also accounts for another, for example we do not know if a 10-fold uncertainty factor for interspecies differences also accounts for some or all of the intrahuman variability. Therefore, it is most prudent to treat the factors separately, which is what one does in using a multiplicative scheme.

Comment 6: The commentator disagrees with only providing one REL for a chemical to use in risk assessment. The comment suggests developing RELs by dividing a known effect level by uncertainty factors that have been added together rather than multiplied. The comment suggests

retaining our current approach but renaming that REL an “Uncertainty Elimination Level”, and suggests that the risk assessment guidelines include hazard indices that use both a “known effect level” and an “uncertainty elimination level” as the reference points to divide into the modeled ground level concentration. These three points (“uncertainty elimination level”, “reference exposure level” using additive Ufs, rather than multiplicative, “known effect level”) would provide the public with more information than just using an REL.

Response: The commentator’s suggestion to provide more information to the public and risk managers by having three levels to compare the ground level concentration to is an interesting one. In fact, we have attempted to provide the risk manager with information on not only the REL which is designed to protect against all adverse effects, but also with information on levels that would protect against severe adverse effects and life-threatening effects. The purpose of this is to allow the risk managers to see what adverse effects occur above the REL, and to judge the seriousness of that exceedance. As noted in the above response, we do not agree that the REL should be based on a method which adds the uncertainty factors before dividing the LOAEL by those factors, rather than multiplying the uncertainty factors. This would not be likely to protect sensitive subpopulations. In addition, an interested party can go into our documents (they are on the Internet on our Webpage) to learn how the REL was developed and see what the LOAEL is from the key study used in the calculations.

References used in the response:

Uthus, EO *et al.* (1983) Consequences of arsenic deprivation in laboratory animals. In: *Arsenic: Industrial, Biomedical, Environmental Perspectives*, Lederer WH and Fensterheim RJ eds. New York: Van Nostrand and Reinhold Company, pp. 173-189.

U.S EPA (1984) Health assessment document for inorganic arsenic: Final report. Office of Research and Development. Research Triangle Park, NC 27711 (EPA-600/8-83-021F).

Liebscher K and Smith H (1968) Essential and nonessential trace elements: A method of determining whether an element is essential or nonessential in human tissue. *Arch Environ Health* 17:881-890.

**Comments from Courtney Price, Phenol Regulatory Task Force,
Chemical Manufacturers Association**

Comment 1: The task group agrees with OEHHA's decision to withdraw and revise its original proposed REL of 0.38 ppm for phenol. As the Task Group pointed out in its prior comments, the originally proposed REL was based on a animal study and the application of highly conservative uncertainty factors. The Task Group agrees with the OEHHA decision to rely on human data, but believes that the proposed REL for phenol of 1.5 ppm still is unduly conservative and does not accurately reflect phenol's acute inhalation risks. The proposed value is inconsistent with standards established by other regulatory bodies.

OEHHA based its proposed REL for phenol on a study designed to evaluate absorption of phenol across the lung and through the skin, not to evaluate phenol's toxicity. Since no adverse affects were noted in the study, OEHHA took the highest concentration tested and called that a NOAEL. The Task Group does not believe that the NOAEL should be without reference to other data. The most direct and relevant measure of phenol's potential irritating effects can be found in Ruth (1986) in which the human irritancy threshold for phenol was determined to be 47 ppm. Therefore, the true human NOAEL for irritancy should be higher than 5.2 ppm but not higher than 47 ppm.

Animal data also support a higher REL for phenol's respiratory effects. The comment cites a study in which no phenol was detected in blood of rats exposed to phenol at 25 ppm. The comment states that these data indicate that inhaled phenol is readily conjugated and detoxified. The comment cites another ongoing study sponsored by CMA which does not show toxic effects at exposures of 25 ppm for up to two weeks.

OEHHA is urged in the comment to consider the rat data and revise the REL upward.

Response: The comment is correct in noting that the REL is based on a "free-standing" NOAEL from Piotrowski, 1971. However, the REL was developed after looking at the Ruth (1986) review. A measured irritancy threshold of 47 ppm is not inconsistent with an REL of 1.5 ppm after including time extrapolation and uncertainty factors. The time extrapolation was conducted because the exposure in the Piotrowski study was for 8 hours. Thus the 1-hour equivalent concentration was 15 ppm. Application of an uncertainty factor of 10 to account for sensitive subpopulations leads to a proposed REL of 1.5 ppm.

The information cited by the commentator that there were no adverse effects in rats at 25 ppm or that phenol could not be detected in rat blood at 25 ppm is not compelling. The phenomenon of irritancy would not be tested by measuring phenol concentrations in the blood. In addition, there is no indication given that objective measures of irritancy were taken in the ongoing study in rats cited in the comment. It is difficult to know when a laboratory animal is experiencing irritation until it is rather pronounced.

Comment 2: OEHHA should not apply an uncertainty factor of 10 to account for potential variability in human response to phenol's mild irritating properties. The Task Group believes that, in light of the endpoint at issue (mild irritancy effects) and the entire toxicological database, OEHHA's use of an uncertainty factor of 10 is overly conservative and yields an artificially low REL for phenol. The RAAC recommended that OEHHA delineate situations where uncertainty factors less than 10 could be used in the REL development process. The RAAC also recommended that OEHHA consider the appropriateness of the existing data and severity of the effect in establishing the uncertainty factors. The NOAEL used for the REL already represents a conservative estimate of the human threshold for irritation effects by phenol. OEHHA did not use an uncertainty factor of 10 for ammonia, formaldehyde, hydrochloric acid, hydrogen sulfide, nitric acid, nitrogen dioxide, sulfates, and sulfur dioxide.

Response: OEHHA has consistently used an uncertainty factor of 10 for intraspecies variability when the test subjects did not include sensitive individuals. There is no evidence that the human variability in response to mild irritancy is less than that associated with other toxicological endpoints. There is therefore no a priori reason to use an uncertainty factor less than 10 for intraspecies variability in response. The examples cited by the commentator were either examples where a benchmark dose calculation was involved (thus decreasing the need for a 10-fold UF) or where sensitive subpopulations were included in the studies upon which the REL is based.

Comment 3: The Task Group urges OEHHA to consider other existing standards for phenol. Existing standards are significantly higher than the level OEHHA seeks to establish. The OSHA PEL for phenol is 5 ppm. NIOSH recommends an 8-hour exposure limit of 5 ppm. Most relevant here is the ERPG-1 value of 10 ppm for phenol. The ERPG-1 level is similar in concept to the OEHHA REL. The ERPG-1 level is the maximum airborne concentration below which it is believed that nearly all individuals could be exposed for up to one hour without experiencing other than mild transient adverse health effects or without perceiving a clearly defined objectionable odor.

Response: OEHHA evaluated all available existing standards in developing the RELs. The occupational standards lack a consistent basis for derivation, are not designed for or recommended for protection of the general public, and in many cases may not prevent adverse health effects among workers. The ERPG-1 level is designed for emergency response, not routine predictable releases. The ERPG-1 level definition indicates that mild transient effects may occur at this level. For the Air Toxics Hot Spots program, OEHHA is interested in protecting against all effects including mild transient effects in a residential setting due to routine and predictable releases, not emergency situations. Thus the ERPG-1 is not directly applicable to the Air Toxics Hot Spots program.

**Comments from Robert Reynolds, Air Pollution Control Officer,
Lake County Air Pollution Control District in a letter to Dr. John Froines**

Comment 1: There is an ambient air quality standard for H₂S that was adopted which has been reviewed formally and informally on several occasions over nearly thirty years of existence. The latest formal review that I am aware of occurred in 1984. The standard is presently set at 0.03 ppm which is utilized by all air districts. This standard is considerably lower than the proposed REL forwarded to you by OEHHA staff for your consideration of adoption. CAPCOA guidelines set the original acute REL and AAQS at 42 µg/m³. OEHHA staff proposes a value of 142 µg/m³, but in Table A-1 of the referenced report a value of 100 µg/m³ is indicated.

Field observations and review of public complaints historically received by the Air Districts would indicate a “no observed effects level” (NOEL) at or below the AAQS. The public has complaints on record to the air districts of both nausea and headaches at or below the AAQS of 35 µg/m³. These are the same symptoms reported in the laboratory study utilized to adjust a reported “lowest observed effects level” (LOEL) to the proposed 142 µg/m³ REL. There is no scientific data to refute the argument of a NOEL that is lower than that proposed and there is valid data in the AAQS H₂S review record to indicate a lower value.

Response: OEHHA is revisiting the H₂S REL and has obtained records of complaint and air concentration from the Air District. OEHHA intends to revise the REL back to the AAQS based on the physiological responses of headache and nausea at levels substantially above the detection of H₂S odor.

Comment: The referenced human exposure studies were for 30 minute exposures and adjusted for a one-hour exposure by dividing the identified LOEL by two. There is no scientific evidence to indicate a linear time exposure relationship, or that a one-hour averaged exposure that allows markedly higher peaks than the hourly REL value is appropriate. From field responses and other exposure studies it appears that H₂S is unique in that a few minutes of exposure may induce a noted effect such as nausea. In the 1984 review of the AAQS it was noted that some districts had adopted a shorter term standard (i.e., 3 minutes) in addition to the state AAQS. A shorter than one-hour AAQS was recommended by our District. It was further noted that ambient air monitoring documented peak values as high as 22.5 times the hourly value, and peaks several fold the hourly average were common.

Response: Comments noted. OEHHA agrees with the commentator and is revising the proposed REL for H₂S to base it on the AAQS.

Comment: The OEHHA utilized study was performed on a sensitive population and no safety factor for a more sensitive population was used for this reason. There is no indication that the noted effect is the most sensitive health effect, nor that other sub-populations found in the general population such as asthmatic children, pregnant women, infants, or the respiratory impaired are not more sensitive to H₂S. I would suggest that the frequently noted effects judged from public

complaints are in fact odor annoyance with the corresponding physiological effects of nausea and headache. Likely the most sensitive sub-populations are pregnant women or respiratory impaired children.

Response: Comment noted. OEHHA's REL was to be based on respiratory irritation. This was in part because we were using the REL in a hazard index approach with respiratory irritation as an endpoint. The revised REL will be the AAQS. However, it will not be used in a hazard index approach for respiratory irritation, but rather will be used in a hazard index approach with odor-induced headache and nausea as the endpoint. As such, it will likely be in a class of its own.

Comment: In the case of the acute REL OEHHA should at a minimum confer with the California Air Districts and assess the complaints received from the public over the years to determine a NOEL prior to reaching a conclusion and making a final recommendation not based on direct scientific evidence.

The acute REL should remain at the AAQS value until such time as a NOEL with a direct scientific basis different than the AAQS is conclusively established.

Response: The commentator's concerns have been taken into consideration and OEHHA is now proposing to go back to the original proposed acute REL, namely the AAQS.

**Comments from Dr. Judy Strickland, U.S.EPA,
National Center for Environmental Assessment, Research Triangle Park**

Comment 1: In general, I found the Technical Support Document to be thorough in explaining definitions of adversity, level of severity, populations of concern, identification of key studies, weight of evidence, and strength of evidence. These concepts are difficult to convey to the reader, but the TSD provides the best concise treatment I've seen.

Response: The comment is noted and much appreciated.

Comment 2: Page 1, paragraph 3, line 1: The recommendation from the NAS should be supported with a citation from the reference.

Response: We will add the citation.

Comment 3: Page 3, Figure 1 – This is the only place in the whole document where dosimetric adjustments and HEC are mentioned. The document should provide some discussion of dosimetric adjustments and guidance on how they are to be made. An appropriate section for this discussion would be 3.3.4.1 which discusses uncertainties for animal to human extrapolations. If dosimetric adjustments will not be used to extrapolate from animals to humans, “dosimetric adjustments” and “HEC” should be removed from the figure.

Response: OEHHA agrees this is a bit confusing. We did not use dosimetric adjustments and HEC calculations in this set of compounds presented in the document. However, we may want to use it in the future and that is why we put it into the figure. We will indicate in the text in Section 3.3.4.1 that while we did not do any HEC adjustments in deriving the RELs in Appendix C, we may use dosimetric adjustments in the future.

Comment 4: Page 13, Section 1.5 – This is a good discussion on sensitive subpopulations. Some of our internal reviewers requested a discussion like this in our acute methodology (U.S.EPA, 1998).

Response: Comment noted and appreciated.

Comment 5: Page 24, paragraph 5, lines 5-6 – this is the only mention of an inadequate toxicology database. The document should explain the type of data required for a chemical-specific database to be adequate in terms of the types of toxicological endpoints studies during acute exposures. For example, is a database complete if no reproductive or developmental data are available for short-term exposures? The answer may be yes for a chemical that acts at the point of contact (an irritant), or no for a chemical which acts systemically. We have not made a decision (at EPA) regarding what types of endpoints are the minimum requirements for developing an acute RfC. We do have such requirements for RfC development (USEPA, 1994a).

Response: This is an interesting point, and one we have not completely addressed. We have not set out what exactly is required for an acute database to be considered complete. Rather, on a case-by-case basis, we have evaluated the literature and set RELs based on available data if the studies were adequate to do so. We have not, for example, included an additional uncertainty factor for missing reproductive/developmental studies. However, for the most part, the chemicals we have evaluated have enough information to know what the key toxic effects of that chemical are.

Comment 6: Page 29, paragraph 3, line 7 – I’m having trouble matching up the criteria for mild effects in this text with those in Table 7. Does “inhalation challenge” here refer to methacholine challenge in the table or does it refer to challenge with the chemical of interest? Please clarify.

Response: In this context (paragraph 2, page 28 in the hard copy version), the inhalation challenge is with the chemical of interest. We will clarify that in the text.

Comment 7: Page 31, paragraph 4, line 5-7 – Table 7 indicates that these criteria correspond to severe effects in a methacholine challenge test, not as a response to inhalation of an airborne chemical. Please clarify. Would the criteria in Table 7 for a methacholine challenge apply to a histamine challenge as well?

The criterion for the FEV₁/FVC ratio should be added to Table 7 also.

Response: Table 7 categorizes the adverse effects on pulmonary function into severity categories using methacholine challenge as the example in row 2. When evaluating the effects of a chemical, for instance SO₂, it is the effects of the inhalation challenge with the chemical that we are rating in comparison to Table 7 using methacholine challenge results. We would have to research the histamine challenge question, but the point of the table is really how much of an effect on the various pulmonary function measures is mild, severe, or life-threatening.

Comment 8: Page 35, paragraph 1, lines 8-9 – the USEPA, 1997, reference needs to be listed in the reference section.

Response: We have added it to the reference section.

Comment 9: We will be posting our own benchmark dose software on our web page. This software includes seven models for dichotomous data, several models for continuous data and a few nested models for developmental data. During the Science Advisory Board’s review of the acute reference exposure methodology, the Board was divided on whether to recommend the use of one default benchmark model or the use of several models to determine the best fit to the data.

Response: Comment noted.

Comment 10: page 53, Table 12 – All these chemicals have at least two effects listed in the table. One is in parentheses and one is not. A note in the table or text should explain the significance of the effects in parentheses and denote which effect was used to calculate the n.

Response: The parenthetical refers to whether the chemical is a locally acting irritant or whether it acts systemically. The endpoint is given first, and then the general statement on the mechanism (local v. systemic) is given in parentheses. We will clarify that in the table.

Comment 11: Hydrogen sulfide REL - I had also characterized the >30% decreased airway resistance in the two subjects as an adverse effect but was admonished for doing so during the SAB review of the acute exposure methodology. Dr. Mark Utell insisted that this magnitude of decrease in airway resistance is within the range of normal variation.

Response: We would disagree with the SAB member in that regard. We characterized the effect as a mild adverse effect in the two individuals.

Comments from Western Independent Refiners Association

Comment 1: OEHHA has not considered the ACGIH Threshold Limit Values. TLVs are limits that refer to airborne concentrations of substances and represent conditions under which it is believed that nearly all workers may be repeatedly exposed day after day without adverse effect (ACGIH, 1997). It does not appear that OEHHA ever considered the TLVs in deriving their RELs. We believe that the draft OEHHA RELs should be compared to the TLV and any major differences reconciled.

Response: As noted in the methodology section of the document, pp. 15-18, OEHHA evaluated existing guidelines including TLVs as sources of information during the REL development process. However, TLV values lack a consistent basis for derivation, are not designed for use with the general public and in fact are not recommended for use for the general public by ACGIH. In addition, in many cases, they do not prevent adverse health effects among workers (Roach and Rappoport, 1990).

Comment 2: The RELs do not consider sensory irritation effects associated with background, or ambient, exposure level. Sensory irritation studies are difficult to interpret because they are based on subjective human responses. Many studies report that subjects exposed to clean air have reported eye, nose, and throat irritation in up to 22% of the volunteers. We recommend that OEHHA begin the analysis of the dose-response relationship for sensory irritation at concentrations that effect at least 20% of the experimental subjects to avoid incorporating data that represents background or variable irritant effects due to factors unrelated to the test chemical.

Response: Although no reference was supplied by the commentator, the comment is apparently referring to a review by Paustenbach *et al.* (1997) which points out that many studies of irritancy of formaldehyde report greater than 0% response rate in the clean air exposed controls. The effect noted in the comment (controls feeling sensory irritation) may be real. However, it would be inappropriate to assume that in each human study of irritation, 20% of the people would have been irritated by clean air anyway and only response levels above 20% should be considered. Of the 7 studies of formaldehyde eye irritancy described in Paustenbach *et al.* (1997) which indicated a percent response for eye irritation in controls (0 ppm formaldehyde group), 3 had 0% response, one had 5% response and the others reported 22, 27, and 39 % response. OEHHA is striving to use the best available information and emphasizing human studies. The chemicals that irritate the eye and respiratory tract are known to be irritating from a number of reports, not just the reports we used as the basis of the REL. The basis of the commentator's statement that only those responses above 20% should be considered is not substantiated in the comment or in the paper by Paustenbach *et al.* (1997).

Comment 3: Uncertainty factors used to derive sensory irritants concentrations should be smaller than those used to establish safe exposure levels for systemic toxicity. Most irritant gases act directly on the mucous membranes or on the lungs and the intensity of effect is usually primarily dependent on the maximum concentration in air. This is unlike other adverse health

endpoints. We recommend that OEHHA consider the available data on susceptible populations for each chemical and use safety factors appropriate to the mechanism of toxic action. Further the size of the safety factor should vary according to the severity of the most sensitive adverse effect and the anticipated diversity of susceptibility. A safety factor of 2 is adequate for reversible eye and upper respiratory irritants. Higher safety factors should be used when the effect is not reversible.

Response: The uncertainty factor of 10 for intraspecies variability is not meant to reflect the severity of a response. Rather, it is meant to protect sensitive subpopulations by encompassing the wide variability in response of humans to toxicants. In fact, a 10 fold uncertainty factor might not be adequate for some compounds (Calabrese, 1990). The commentator does not provide data to substantiate the statement that a safety factor of 2 is appropriate for irritants or that a smaller uncertainty factor is justified based on mechanism of action.

Comment 4: OEHHA improperly used animal data to set RELs when human data were available. OEHHA selected critical endpoints using animal data when human data was available. WIRA believes that OEHHA should set RELs on human studies when they are available.

Response: As stated in our document, OEHHA prefers the use of human data when it is available and adequate. The comment provides no specific instances in referring to use of animal data when there were human data available.

Comment 5: In setting many RELs, OEHHA used studies in which repeated daily exposures to the chemical under study was for 4 to 8 hours per day over an extended time period. When setting short-term limits, studies with an exposure duration of about one-hour should be used and in no cases should studies where exposure durations exceed 8-hours be used.

Response: OEHHA has largely used studies with exposure durations less than 8 hours and down to ten minutes to generate one-hour RELs. OEHHA did use repeated dose studies of reproductive/developmental toxicity for several chemicals. Developmental and reproductive toxicants produce their effects during critical developmental periods that can be quite short (on the order of hours). Toxicity studies of necessity expose the dams throughout pregnancy since it is not known necessarily which time point is the most critical. To expose sets of dams for a given one-hour period or even 8 hour period throughout the pregnancy would not be logistically feasible, and would be very costly. Thus, for these types of toxicants, we only have repeated exposures studies available to us. OEHHA makes the assumption that a one-hour exposure sometime during development could produce a developmental or reproductive effect. We extrapolate from the daily exposure, which is generally 6 to 8 hours/day, to a one-hour exposure using a modified Haber's Law to derive the REL. This is justifiable given the mechanism of action of many reproductive/developmental toxicants.

December 10, 1998

Comments from ChemRisk on behalf of the Western States Petroleum Association

Comment 1: OEHHA should use the dose-response literature to develop one-hour RELs rather than rely upon a single study. The comment goes on to recommend using the method described in Guth *et al* (1992) to develop a dose-response curve based on an aggregate of all various high quality studies. This method was recently performed for formaldehyde (Paustenbach *et al.*, 1997). The dose –response analysis for formaldehyde was then adopted as the basis for the TLV by ACGIH. Approaches using a single NOAEL neither integrate information across the entire exposure-duration range, nor allow for the use of all data at a particular duration. Also, the NOAEL method does not allow for consideration of the shape of the dose-response curve, the number of subjects in each group and the statistical variation in the response and its measurement.

Response: OEHHA is well-aware of the limitations of the NOAEL approach and they are discussed in our document. However, the approach used by Guth 1992, categorical regression, is very data intensive and is not useful for the vast majority of chemicals. We have acknowledged the method (see Appendix D), but have not applied it in this document. The analysis alluded to in the comment was not supplied and we do not know how uncertainty factors were applied to the analysis, or if they were applied. Also, the TLV is not useful for the general public and is not recommended for use by ACGIH for that purpose. In addition, U.S.EPA has been developing the categorical regression analysis and has yet to finalize their approach or develop reference levels using that approach.

Comment 2: Sensory irritation studies are difficult to interpret because they are based on subjective human responses. Subjects exposed to clean air have reported eye, nose, and throat irritation in up to 22% of the volunteers (Anderson *et al.*, 1974; Sauder *et al.*, 1986; Kulle *et al.*, 1987; Green *et al.*, 1987; Kulle, 1993). These studies clearly show that symptoms of sensory irritation are often due to factors unrelated to exposure to the chemical. We recommend that OEHHA begin the analysis of the dose-response relationship for sensory irritation at concentrations that effect at least 20% of the experimental subjects to avoid incorporating data that represents background or variable irritant effects due to factors unrelated to the test chemical.

Response: OEHHA staff recognize that there is uncertainty in any experimental design. The effect noted in the comment (controls feeling sensory irritation) may be real. However, it would be inappropriate to assume that in each human study of irritation, 20% of the people would have been irritated by clean air anyway and only response levels above 20% should be considered. It should also be noted that of the 7 studies described in Paustenbach *et al.*, 1997 that indicated a percent response for eye irritation in controls (0 ppm formaldehyde group), 3 had 0% response, one had 5% response and the others reported 22, 17, and 39 % response. OEHHA is striving to use the best available information and emphasizing human studies. The chemicals that irritate the eye and respiratory tract are known to be irritating from a number of reports, not just the reports we used as the basis of the REL. The basis of the commentator's statement that only those responses above 20% should be considered is not substantiated in the comment or in the paper by Paustenbach *et al.* (1997) referred to later in these comments.

Comment 3: Uncertainty factors used to derive sensory irritants concentrations should be smaller than those used to establish safe exposure levels for systemic toxicity. Most irritant gases act directly on the mucous membranes or on the lungs and the intensity of effect is usually primarily dependent on the maximum concentration in air. Most other adverse health endpoints, such as developmental or neurotoxic effects, are primarily determined by the pharmacokinetics of the chemical. When attempting to prevent systemic toxicity from occurring in an exposed population, the type, number and size of uncertainty factors should be different than that used to predict an acceptable level of exposure to a sensory irritant (Paustenbach, 1997). We recommend that OEHHA consider the available data on susceptible populations for each chemical and use safety factors appropriate to the mechanism of toxic action. Further the size of the safety factor should vary according to the severity of the most sensitive adverse effect and the anticipated diversity of susceptibility. A safety factor of 2 to 5 should be adequate for reversible eye and upper respiratory irritants. Higher safety factors should be used when the effect is not reversible.

Response: The uncertainty factor of 10 for intraspecies variability is not meant to reflect the severity of a response. Rather, it is meant to protect sensitive subpopulations by encompassing the wide variability in response of humans to toxicants. In fact, a 10 fold uncertainty factor might not be adequate for some compounds (Calabrese, 1990). The commentator does not provide data to substantiate that a safety factor of 2 is appropriate for irritants.

Comment 4: At times, OEHHA selected a critical endpoint in animals when other quality human data were available that reported a dose-response relationship for the most sensitive adverse effect. We suggest that OEHHA set RELs primarily on appropriate human studies. Otherwise, RELs will quite often be overly stringent due to the repeated, and unnecessary application of uncertainty factors. For example, OEHHA selected a decrease in fetal body weight as the critical adverse effect for developing a one-hour limit for toluene to protect against severe adverse effects. Human data were available that demonstrate neurological impairment following acute exposure to toluene. While our recommended NOAEL of 1,875 mg/m³ toluene is the same as OEHHA's selected NOAEL based on animal weights, OEHHA's ultimate "severe adverse effects level" represents an overly conservative estimate because an additional uncertainty factor of 10 for animal to human extrapolation is incorporated. We have reviewed the published papers regarding developmental effects and find that toluene is only a developmental risk at doses that produce frank toxicity. These doses are much greater than those recommended here, and they also illustrate the inappropriateness of using studies that use repeated daily exposures for setting acute exposure limits.

Response: The chemical toluene is a reproductive and developmental toxicant under Proposition 65. Animals studies show clear evidence of developmental and reproductive toxicity. We used human studies of the CNS effects of toluene to develop the REL and have used reproductive/developmental effects as the basis of the level protective against severe adverse effects. The REL is used in risk assessments. The level protective against severe adverse effects is provided for the risk manager to help in deciding what steps need to be taken when the REL is

exceeded. The commentator does make an important point that when available and adequate, human data should be used. We have attempted to follow that guideline in developing our RELs. Studies of reproductive/developmental toxicity in humans are quite rare and usually derive from occupational exposures. As such, appropriate data on this endpoint necessarily come from animal studies. To ignore this effect of toluene because human studies are not available for developmental/reproductive toxicity would not be protective of public health. At the same time, OEHHA acknowledges the uncertainty of extrapolating from the repeated exposures studies to a one-hour exposure.

Comment 5: OEHHA should use appropriate exposure studies with relevant durations of exposure as the basis for determining RELs based on sensory irritation. In setting many RELs, OEHHA used studies in which repeated daily exposures to the chemical under study was for 4 to 8 hours per day over an extended time period. When setting short-term limits, studies with an exposure duration of at least 15 minutes but no greater than 4 to 8 hours should be used for setting exposure limits, particularly for the sensory irritants.

Response: OEHHA has largely used studies with exposure durations less than 8 hours and down to ten minutes to generate one-hour RELs, particularly for irritants. The comment apparently is referring to the use of reproductive/developmental toxicity studies that are always longer than one day. Developmental toxicants produce their effects during critical developmental periods that can be quite short. Toxicity studies of necessity expose the dams throughout pregnancy since it is generally not known which time point is the most critical. To expose sets of dams for a given one-hour period or even 8 hour period throughout the pregnancy would be logistically difficult to impossible, and would be very costly. Thus, for these types of toxicants, we only have repeated exposures available to us. OEHHA makes the assumption that a one-hour exposure sometime during development could produce a developmental effect, and thus extrapolate from a 6 or 8 hour exposure in each day of gestation. This is justifiable given the mechanism of action of many developmental toxicants. To ignore developmental toxicity from short-term exposures is imprudent.

Comment 6: OEHHA should appropriately consider information for setting ambient and emergency air limits from the ACGIH TLV and Ceiling values. During the past 15 years, whenever community ambient air limits have been developed for both acute and chronic exposure, most regulatory agencies have at least consulted the ACGIH TLVs to determine whether they contained information that might be helpful. Often, some fraction of the 8 hr TLV or the STEL or Ceiling Value was adopted as the chronic or acute ambient air limit (Paustenbach, 1997). By definition, TLVs are limits that refer to airborne concentrations of substances and represent conditions under which it is believed that nearly all workers may be repeatedly exposed day after day without adverse effect (ACGIH, 1997). It does not appear that OEHHA reviewed the Documentation for the TLV. The purpose of the short-term exposure values is virtually identical to the objectives OEHHA wishes to achieve. We believe the draft RELs should be compared to the STELs or CV and any major differences reconciled.

Response: OEHHA evaluated TLVs in our examination of existing guidelines during the REL development process. However, these values lack a consistent basis for derivation, are not

designed for use with the general public and in fact are not recommended for use for the general public by ACGIH. In addition, in many cases, they do not prevent adverse health effects among workers (Roach and Rappoport, 1990). ACGIH documentation has been consulted to identify potentially relevant studies.

In addition, the purpose of the short-term exposure values set for occupational settings is not identical to OEHHA's objectives as stated in the comment. OEHHA is attempting to protect nearly all people in a population including sensitive individuals. The occupational standards are set for healthy largely male workers, not the general population.

Specific comments on individual chemicals from ChemRisk on behalf of WSPA:

Comment on Acrolein: We recommend a one-hour REL of 0.046 mg/m^3 (0.02 ppm) for acrolein to protect against mild irritant effects in the community. This is based on the eye irritation threshold of 0.46 mg/m^3 (0.2 ppm) (NRC, 1981) and a safety factor of 10 to account for variability in susceptibility to acrolein.

Response: OEHHA based the REL on a study in 36 healthy humans that examined eye irritation by acrolein (Darley *et al.*, 1960). The study reported a LOAEL of 0.06 ppm, lower than the NRC estimate of the threshold used by the commentator. The basis for the designation of an eye irritant threshold by NRC is unclear. The NRC document is a secondary source of information. OEHHA applied an uncertainty factor of 3 for the LOAEL to NOAEL extrapolation and an additional uncertainty factor of 10 for intraspecies variability, for a cumulative uncertainty factor of 30. The resultant REL was 0.17 ppb. At the SRP meeting, we were given direction that for mild effects, we should be using an uncertainty factor of 6 for the LOAEL to NOAEL extrapolation. Therefore, the REL may change to 0.08 ppb ($0.17 \text{ } \mu\text{g/m}^3$).

Comment on Ammonia: As delineated in our 1995 comments, WSPA still believes that datasets from individual studies should not be combined and modeled simultaneously for developing a one-hour REL for ammonia. Normally, the benchmark concentration approach (BMC) involves modeling studies individually and selecting the best dataset most relevant to human exposure effects. In addition, no clean air controls were evaluated in the studies incorporated in OEHHA's BMC approach. As a result, the background effects of ammonia for irritation are assumed to be zero. We recommend that OEHHA consider modeling the BMC approach on the individual studies and selecting the most appropriate dataset relevant to one-hour exposure to the community.

Response: It is unclear why the commentator recommends against combining individual datasets in the benchmark concentration approach. One of the advantages of the benchmark approach is that you can use information from multiple appropriate studies available on that endpoint. This same commentator in comment number one suggests using the methodology of Guth *et al.*, 1992, which develops a dose-response curve based on an aggregate of all of the various high quality studies. The categorical regression analysis recommended in comment # 1 combines datasets and conducts a regression analysis on the combined data points.

Comment on Arsenic: OEHHA used the Nagymajtenyi *et al.*, 1985, study on developmental toxicity of arsenic oxide in mice as the basis for their REL. The ATSDR (1997) interpreted the Nagymajtenyi study to show that high levels of arsenic can cause developmental effects, but does not provide a clear basis for estimating a level of concern in humans. In addition, Ide and Bullough (1988) and Perry *et al.* (1948) show that no respiratory tract irritation is observed in occupational workers exposed to inorganic arsenic at a concentration of 0.11 mg/m³ for two months. ATSDR identified 0.11 mg/m³ as a NOAEL for respiratory irritation, which is the most sensitive adverse endpoint in humans.

The acute toxicity of organic, inorganic and metallic forms of arsenic is significantly different and is primarily attributed to the extent of absorption in the lungs. For example, arsenic sulfide and lead arsenate are cleared from the lungs slowly, indicating the rate of absorption may be lower if the inhaled arsenic is a highly insoluble form (Marafonte and Vahter, 1987). Therefore, a one-hour REL for total arsenic compounds will overestimate the amount of biologically available arsenic and will result in an overly conservative REL for anticipated exposures of the general population. We recommend that OEHHA consider developing one-hour RELs for the different forms of organic, inorganic, and metallic arsenic compounds. The one-hour REL to protect against severe adverse effects of developmental toxicity should not be considered when there is insufficient data available to support fetotoxic effects at low concentrations of exposure anticipated in the community. As a result, OEHHA has developed a one-hour REL based on an inappropriate critical endpoint when other more sensitive toxicity data endpoints are available in humans.

Response: OEHHA does not agree with ignoring the developmental effects of arsenic because there are insufficient data in humans. Arsenic compounds are fetotoxic and teratogenic in several laboratory animals. Epidemiological studies in Sweden (Nordstrom, 1978a,b; Beckman, 1978, Nordstrom *et al.*, 1979) indicate an increase in congenital malformations and adverse pregnancy outcome in smelter workers exposed to arsenic and other toxic substances. It is quite difficult to conduct epidemiological studies, particularly studies of people exposed to lower environmental levels. The suggestion by the commentator to wait until data are available in humans would be imprudent from a scientific and public health standpoint. The lack of adequate data in humans regarding reproductive endpoints is not a reason to ignore the reproductive and developmental toxicity of arsenic.

The arsenic REL is not intended to be used with organic arsenicals. The toxicity summary heading is "Arsenic and Inorganic Arsenic Compounds". We also recognize that there are differences in the potency of the arsenic compounds as indicated on page C-22. We have based the REL on a trivalent arsenic compound, arsenic trioxide. Trivalent arsenic compounds tend to be more potent toxicants than pentavalent compounds. Arsenic oxide is not necessarily the most potent trivalent arsenic compound, though. We used a LOAEL from a reproductive/developmental study in mice as the point of extrapolation, and as such do apply an uncertainty factor of 1000. While this creates a higher degree of uncertainty than using human data on respiratory irritation as suggested in the comment, we do not think it appropriate to ignore the fact that arsenic compounds are developmental toxicants.

It may be possible to research separate arsenic compounds and develop some compound-specific RELs. However, as a practical matter, facilities in the Air Toxics Hot Spots program report their emissions as total arsenic and do not speciate. If facilities were to speciate, it would provide incentive to develop compound-specific RELs. At this point, OEHHA does not plan to do so.

Comment on Benzene: OEHHA based the one-hour REL of 0.24 ppm for benzene on decreased inflammatory cell numbers in the spleen of mice following repeated daily exposures (Rosenthal and Snyder, 1985) (NOAEL of 10 ppm). Two dosing schedules were followed and it was only under the second regimen involving exposure 6 h/d for 5 days, pathogen challenge, and an additional exposure for 7 days that the animals exhibited decreased immunocompetence. We do not think it is appropriate to base a NOAEL on a regimen that uses a pre-exposure and continuing exposure. The commentator argues for a NOAEL of 100 ppm based on increased bacterial counts on day 4 post-infection. Since there was no overall functional impairment by Day 7 after infection in any exposure group, the commentator argues for a NOAEL of 300 ppm with no observed LOAEL. It appears that OEHHA believes that any delay in the immune response, however slight, should be taken as an indicator of a toxic effect. Due to the transient nature of the effect and since the effect was seen only after sub-chronic exposure, the combined inter- and intraspecies modifying factors of 100 on the NOAEL should be decreased by a factor of at least 3 to 10 to account for these departures from a true single exposure study.

We also recommend that OEHHA consider other available studies that involve acute single exposures.

The OEHHA level protective against severe adverse effects for benzene of 3.25 mg/m³ is based on decreased mean fetal birth weights following repeat exposures. There is insufficient evidence to indicate that benzene is teratogenic or embryotoxic in animals or humans at concentrations of 10 ppm for 8 hr/day (Schwetz, 1983). Instead, we recommend that OEHHA consider more appropriate human data available in the literature involving the health effects of benzene following acute or intermittent exposure. We suggest a one-hour REL of 7.1 ppm, which is below the average odor threshold of 61 ppm to protect against mild transient effects. This is based on a NOAEL of 25 ppm from a human study showing no effects following a single 8-hour exposure (NRC, 1986; Gerarde, 1960). The NOAEL is adjusted with a time extrapolation based on a modified Haber's Law with $n = 2$ and divided by an uncertainty factor of 10.

We recommend a one-hour "severe adverse effect level" of 71 ppm and believe that such a limit would be adequate to protect against irreversible or severe adverse effects. The recommended level is based on a 250 ppm NOAEL for hematopoietic effects in human workers (Paustenbach *et al.*, 1992). The NOAEL is adjusted using a modified Haber's Law with $n = 2$ and then divided by an uncertainty factor of 10 for human variability. We suggest OEHHA consider studies reporting acute human effects of benzene following a single, short-term exposure, rather than effects associated with repeated-dose subchronic exposure in a developmental toxicity study conducted in experimental animals.

Response: The commentator points out an important issue in developing acute one-hour reference exposure levels. When a sensitive endpoint is studied using repeated exposures, how

does one use that data to develop a one-hour REL? We have already discussed our position with respect to developmental/reproductive toxicity in response to earlier comments. Since all developmental/reproductive toxicity studies use repeated exposures, it is only possible to use those repeat exposure regimens to address this important and sensitive toxicological endpoint. Since we do not know at which point in time the developmental effect is exerted, we use the daily exposure as a starting point for time extrapolation.

In the case of benzene immunotoxicity, we again are faced with a study that used repeat exposures over 5 days. OEHHA used the Rosenthal and Snyder (1985) study in mice which evaluated the immune response to *Listeria monocytogenes* infection following exposure to benzene at 0, 10, 30, 100, and 300 ppm 6 h/d for 5 days, with or without continuing exposure for 7 days post-infection. The commentator indicated that effects (decreased immunocompetence) were only observed in the animals continually exposed after the infection. This is not the case. Lymphocyte proliferation in response to the infection was suppressed in all groups exposed to 30 ppm or higher benzene for 6 hours/day for 5 days pre-infection, as well as in all groups who were benzene-exposed for 7 days after the infection. We identified a NOAEL of 10 ppm based on the numbers of lymphocytes in the spleen as well as on the number of *L. monocytogenes* in the spleen at 4 days post-infection, in both the groups exposed to benzene prior to infection only and those exposed both prior to and for 7 days after infection. Hence the argument that the NOAEL should be 100 ppm for those not continuing exposure post-infection based on increased bacterial counts in the spleen ignores the effects on the hosts' immune system cells. Rosenthal and Snyder conclude that their study suggests a suppressive effect of benzene on T-cell function and/or number. The study authors also state that the observation of no significant changes at Day 1 of infection suggests that benzene exposure does not affect the ability of non-T-cell activated macrophages to eradicate *Listeria* cells during the early phase of the immune response.

The commentator makes the point that the effect was transient, and that the uncertainty factors should be decreased due to the transient nature of the effect and because the exposures were repeated over 5 days. The authors of the paper note that neither exposure regimen (5 days pre-infection or continued for 7 days post-infection) suppressed the immune response enough to enable the bacteria to persist through to Day 7. The increased numbers of *L. monocytogenes* at Day 4 of infection suggests a delay in the immune response to this infection. Rosenthal and Snyder state that the reason for the apparent recovery is not known but may be related to the mechanism of resistance in *L. monocytogenes*-resistant C57Bl/10 mice used in the study. After sublethal challenge, *L. monocytogenes*-resistant mice show an increase in the number of monocytes during infection and a progressive influx of macrophages into infective foci, whereas this chemotactic and inflammatory response is absent in *L. monocytogenes*-susceptible mice. It is not clear where humans would stand on the *L. monocytogenes* susceptibility scale. The extrapolation of multiple 6 hour/day exposures to a one-hour exposure is more uncertain than if the exposure were for only one 6 hour period. OEHHA agrees that this is an uncertainty. Unlike reproductive/developmental studies, where it is largely agreed that a short exposure at a key time in gestation will produce a developmental/reproductive adverse effect, we are unsure if a one-hour exposure prior to infection in the mouse model would produce the same effect as the 6 hour/day for 5 day exposures. We acknowledge that there are several studies showing adverse impacts on the hematopoietic system in animals after relatively short-term exposures. However,

because of the uncertainty in extrapolating for this endpoint from repeated exposures to a one-hour exposure, we are revising the REL and basing it on the studies of Kuna and Kapp (1981), and Coates *et al.* (1984) on reproductive/developmental toxicity in rats. The resultant REL of 0.4 ppm is very close to the original REL of 0.24 ppm.

The level protective against severe adverse effects is based on a reproductive/developmental study of benzene exposure in rats. A 40 ppm NOAEL was observed in this study (Coate *et al.*, 1984). Kuna and Kapp (1981) found teratogenic effects in rats at 500 ppm, and lower fetal weights at 50 ppm. The NOAEL in this study was 10 ppm. We applied a 100-fold uncertainty factor to the higher NOAEL of 40 ppm for interspecies and intraspecies variability. The level protective against severe adverse effects is thus 0.4 ppm. We propose to use this level as the REL. The commentator's suggestion of using a NOAEL for hematopoietic effects in humans based on the Paustenbach *et al.*, 1992 study ignores the potential for benzene to result in adverse reproductive/developmental effects. We do not think that would be a prudent choice.

Comment on Formaldehyde: OEHHA proposed a one-hour REL of 0.25 ppm formaldehyde based on a benchmark concentration approach from the study of Kulle *et al.*, 1987. OEHHA's assessment resulted in a one-hour acute exposure level similar to those developed by other agencies, but the methodology used in the OEHHA assessment was quite different. OEHHA did not consider other available human studies, especially exposures of susceptible subpopulations such as asthmatics. As a result, OEHHA incorporated an additional level of conservatism in their approach by a factor of 3 accounting for variability of susceptible individuals to formaldehyde. While the Kulle *et al.* study presented reasonable dose-response data, alone it only represents what was seen in a small group of individuals. Many other studies were considered by an expert committee which was asked to identify a proposed occupational exposure limit (Paustenbach *et al.*, 1997). The group evaluated 150 journal articles and used data from them to build a dose-response curve for human sensory irritation. The data indicated that eye irritation did not become significant until a concentration of at least 1 ppm. The data indicate irritation was time-independent since exposures to 0.3 ppm did not produce irritation above background following either 10 minute or 6 hour exposures.

The reliance on one study is not warranted when such a rich database is available. Further the application of conservative uncertainty factors to this single study is not justified because of the large database of many human studies. OEHHA applied an uncertainty factor of 3 to account for variability of individuals susceptible to formaldehyde exposure. However, several studies have investigated the human response to formaldehyde in so-called sensitive individuals, like asthmatics. These studies concluded that asthmatics were no more sensitive to airway effects of formaldehyde than non-asthmatics and that bronchoconstriction will only occur at concentrations greater than 2.5 mg/m³ (Green *et al.*, 1987; Sauder *et al.*, 1986; Sauder *et al.*, 1987; Sheppard *et al.*, 1986; Witek *et al.*, 1987).

ACGIH set a ceiling value for formaldehyde of 0.37 mg/m³ based on irritation. AIHA set an ERPG-1 of 1.23 mg/m³. We recommend that OEHHA reevaluate the dose-response relationship for formaldehyde and review the paper by Paustenbach *et al.*, 1997. OEHHA should omit any additional uncertainty factors accounting for variability of individuals susceptible to formaldehyde

since several studies have already established that sensitive individuals such as asthmatics respond no differently than the general population.

Response: As indicated in the introduction to our document, OEHHA conducts an extensive review of the literature before developing an REL. This was the case for formaldehyde as well as the other chemicals in this document. In the interests of space and time, the acute toxicity summaries only discuss key studies used in the analysis. OEHHA conducted a benchmark concentration analysis of the data on mild and moderate eye irritation in Kulle *et al.*, 1987. The lower confidence limit on the 5% response rate was determined to be 0.44 ppm for a 3 hour exposure. Using a modified Haber's Law equation with the exponent, n , set to 2 we estimated a one-hour BC_{05} as 0.76 ppm. We divided this number by an uncertainty factor of 3 to account for sensitive subpopulations. The commentator indicates that because asthmatics are not more sensitive to formaldehyde than nonasthmatics we should not have an uncertainty factor in our analysis. However, the uncertainty factor is not meant to account solely for the response of asthmatics. It is meant to account for human interindividual variability in response. In some cases the asthmatic is more susceptible to the effects of an irritant chemical while in other cases it may be that there is simply a wide variability in the threshold of irritation in the human population. In Paustenbach *et al.* (1997) it is noted that, from the Andersen and Molhave study (1983) (and others), there appears to be a relatively wide variation in individual susceptibility to irritation from formaldehyde. That is what we are attempting to account for in applying the intraindividual uncertainty factor for formaldehyde, and not for the susceptibility of asthmatics.

While many studies fail to demonstrate an increased sensitivity of asthmatics to formaldehyde (Sheppard *et al.*, 1984), other studies indicate that people can become sensitized to formaldehyde (with occupational exposures) and that these people will develop asthmatic symptoms in response to challenge with formaldehyde (Burge *et al.*, 1985; Nordman *et al.*, 1985; Hendrick and Lane, 1977). This is noted in our document on page C-131 - 132.

The commentator refers us to an analysis published by Paustenbach and coworkers (1997) that describes the results of the deliberations of a panel sponsored by the Formaldehyde Institute that was charged with evaluating data to determine an adequate occupational exposure limit. The Kulle study is included in the analysis. The results of the panel's deliberations were applied to an occupational setting. In the panel's deliberations they concluded that reports of eye irritation below 0.3 to 0.5 ppm were not reliable. This appears to be due to reports of irritation in clean air controls in some studies. OEHHA does not agree with applying this conclusion across the board based on what could be poorly controlled environments in some of the studies' controls. The analysis did not consider protecting the general population which, unlike the healthy worker population, includes infants, children, the elderly, and the ill, and others who due to their sensitivity to irritants would likely not be working in an industry where exposure to irritants occurs. In fact, the cited review indicates that the panel acknowledges that the results of the studies involving generally healthy, relatively young volunteers may not reflect the range of results that would be observed if perhaps 100 workers of varying age and health status underwent the same testing. One could take that statement further that a worker population does not provide an adequate population to extrapolate to the general population. Hence, we believe our benchmark

concentration analysis is more appropriate for developing a REL applicable to the general population than the occupational exposure limit described in Paustenbach *et al.* (1997).

Comment on Hydrogen Sulfide: OEHHA identified a one-hour REL of 0.14 mg/m³ (0.1 ppm) to protect against mild adverse effects based on the human study of Jappinen *et al.* (1990). OEHHA based the REL on increased airway resistance in 2 of 10 subjects following a 30-minute exposure to 2 ppm H₂S. However, Jappinen reported no statistically significant changes in airway conductance for the entire group. And thus we recommend that OEHHA consider 2 ppm as a NOAEL rather than a LOAEL. This is further supported by Jappinen *et al.*, 1990, which demonstrated no significant pulmonary function changes or bronchial responsiveness to histamine in a group of smokers, workers with allergies, and atopic individuals exposed to 1-11 ppm H₂S. Using 2 ppm as a NOAEL, the commentator recommends a REL of 1 ppm (1.4 mg/m³) to protect against mild adverse effects.

Response: OEHHA has revisited the hydrogen sulfide REL development. Other commentators pointed out that the Ambient Air Quality Standard (AAQS) of 42 µg/m³ was not merely an odor threshold. Some individuals experience headache, nausea and even vomiting upon exposure to odorous concentrations of H₂S. There is extensive documentation of this problem from local air pollution control districts. It is hard to argue that headache and nausea are not adverse health effects. While the toxicological mechanism may not be easy to understand or explain, the physiological effects are real. Therefore, OEHHA is proposing to use the one-hour AAQS of 42 µg/m³ as the one-hour REL. The toxicological endpoint is thus headache and nausea. The value will not be used in assessing respiratory irritation, which occurs at levels significantly above the AAQS.

Comment on Nickel: OEHHA did not consider the different forms of nickel in the toxicity assessment of a one-hour REL. OEHHA based the REL on pulmonary function changes in workers with occupational asthma exposed to nickel sulfate. The REL was estimated by converting to nickel equivalents. This reduces the observed LOAEL of 0.3 mg/m³ to 0.067 mg/m³.

The acute toxicity of soluble and insoluble forms of nickel will differ significantly due to the extent of absorption of nickel across the lung. A REL based on soluble nickel will overestimate the amount of biologically available nickel and overestimate the potential health risk for less soluble forms of nickel. Ideally, separate RELs should be developed for water-soluble nickel and for relatively insoluble nickel compounds. We recommend a one-hour REL of 0.07 mg/m³ for nickel sulfate to protect against changes in pulmonary function. This is based on a LOAEL of 0.3 mg/m³ adjusted by a modified Haber's Law with n = 2 to 0.212 mg/m³. This value is further adjusted with a safety factor of 3 to account for extrapolation from a LOAEL to a NOAEL, resulting in an REL of 0.07 mg/m³ for nickel sulfate.

Response: OEHHA used a study by Cirila *et al.*, 1985 which evaluated changes in lung function of metal plating workers with occupational asthma. The significant effect was >15% decrease in FEV₁. The volunteers were exposed for 30 minutes to 0.3 mg NiSO₄·6H₂O. The equivalent concentration of nickel is 67 µg/m³. Extrapolating to a one-hour exposure using an exponent, n,

set to 1, the resulting nickel concentration is $33 \mu\text{g}/\text{m}^3$. This was then divided by an uncertainty factor of 3 for extrapolating from a LOAEL to a NOAEL for mild respiratory effects which results in a REL of $11 \mu\text{g}/\text{m}^3$.

The commentator objects to using the nickel equivalents of nickel sulfate hexahydrate as the LOAEL. Nickel is the element that has caused the effect on FEV₁ in the study population, not the sulfate or water moieties of the nickel sulfate hexahydrate. While it may be true that other nickel salts may have different potencies for impacting lung function, in the Hot Spots program, facilities report their emissions as total nickel. Therefore, it is prudent to use a study of soluble nickel compounds as the basis of the REL and apply the nickel proportion of that compound to the derivation of the REL. It may be possible in the future to speciate nickel compounds for the purposes of developing an REL. However, it would then require facilities to speciate their emissions, a potentially costly prospect for most.

Comment on Toluene: There are questions as to the appropriateness of the two studies used by OEHHA to develop the REL for toluene and the “severe adverse effect level”. Based on an analysis of the available data, sensory irritation is the most sensitive endpoint following acute exposure to toluene and more serious adverse effects such as neurological depression occur at higher concentrations following acute exposure.

OEHHA based the REL on Anderson *et al.*, 1983; the stated purpose of this study was to evaluate neurobehavioral effects. Observations on sensory irritation were reported as incidental findings. These data do not provide a sound health risk-based limit for toluene, and OEHHA should not rely on subjective reports of “sensory irritation” for developing a one-hour REL. The Anderson *et al.* study reported incidental observations of headache, dizziness, and feelings of intoxication in individuals exposed to 100 ppm and not the lower dose (40 ppm). The commentator recommends an REL based on Echeverria *et al.*, 1989, a study designed to evaluate sensory irritation. A NOAEL of 75 ppm for a 7 hour exposure was adjusted to a one-hour exposure using an exponent of $n = 2$ in a modified Haber’s Law calculation to derive a NOAEL of $741 \text{ mg}/\text{m}^3$. This was then divided by an uncertainty factor of 10 to arrive at a suggested REL of $74 \text{ mg}/\text{m}^3$ (20 ppm). We recommend that OEHHA consider incorporating data from other representative studies to establish a dose-response relationship for sensory irritation.

OEHHA based the one-hour level protective against severe adverse effects on a study intended to evaluate developmental defects in animals. OEHHA based the REL on a NOAEL of 500 ppm for decreased fetal body weights following repeated exposures to toluene up to 36 days. For many chemical agents, the toxic effects of a single exposure may be quite different than the toxic effects produced by repeated exposures. We recommend that OEHHA consider, as an alternative, available studies on short-term human exposures to toluene concentrations that produce marked adverse effects, such as neurological impairment (Gamberle and Hultengren, 1972).

Response: OEHHA based the REL on Anderson *et al.* (1983), a study of 16 young healthy subjects evaluating nasal mucus flow, lung function, subjective response, and psychometric performance during 6-hour exposures to clean air, 10, 40 or 100 ppm toluene. No effects were noted at 10 and 40 ppm, but at 100 ppm irritation was experienced in the eyes and nose. The test

battery investigated visual perception, vigilance, psychomotor functions, and higher cortical functions. The test battery included five-choice, rotary pursuit, screw-plate, Landolt's rings, Boudon Weisma, multiplication, sentence comprehension, and word memory tests. No statistically significant effects occurred at $p < 0.05$. For three tests (multiplication errors, Landolt's rings, and the screw plate test) there was a borderline significance ($0.05 < p < 0.1$). The subjects reported headache, dizziness, and a feeling of intoxication at 100 ppm. This study was well-controlled and well-conducted. The study was inclusive of irritation and other "subjective" symptoms. The volunteers were asked to rate the following on a continuous scale: their estimate of air temperature, humidity, air movement, light intensity, noise level, air quality, odor level; whether they felt fatigue, sleepiness, work strain, difficulty of work, effort, speed of reaction, irritation of the eyes, nose, throat and lower airway, cough, headache, feeling of intoxication, dizziness, and nausea. Thus, this study was designed to evaluate irritation, contrary to what is implied in the comment. OEHHA believes therefore that this study is useful for developing the REL. It is interesting to note that the authors conclude there is a wide variability in irritation, and that throughout the day there was no adaptation to the irritation. The REL for 6-hours was extrapolated to a one-hour REL using a modified Haber's Law exponent = 2. An uncertainty factor of 10 was applied for interindividual variation in response to derive an REL of 9.8 ppm.

The Echeverria study cited by the commentator, in contrast to the comment, does not identify a higher NOAEL (75 ppm) than the Anderson *et al.*, 1983 study, and so is not useful for developing an REL. In this study, 42 students were exposed to 0, 75, or 150 ppm toluene and changes in CNS function and symptoms were recorded. Verbal and visual memory, perception, psychomotor skill, manual dexterity, mood, fatigue, and verbal ability were evaluated over the course of the seven hour exposures. As in the Anderson study, each subject was their own control. An analysis of variance and test for trend was performed on the difference and score for each concentration where each subject was their own control. Adverse performance was found for a number of tests at 150 ppm, and headache and eye irritation increased in a dose-dependent fashion. The incidence of subjects sleeping also increased in a dose-dependent fashion. The comment above indicates that a NOAEL of 75 ppm is observed in this study. However, the authors of the study indicate that subtle neurological effects were found at 75 ppm. In particular, the pattern recognition latency score for the control group differed significantly by the Scheffe test from the 75 ppm and 150 ppm groups. The authors also note that the incidence of subjects sleeping and of headache and eye irritation increased in a dose-dependent fashion with a positive test for trend. The authors conclude that "this study supports a lowering of the PEL because acute subjective and objective effects have been found at 75 and 150 ppm, bracketing the TLV of 100 ppm". Therefore it is not correct to identify 75 ppm as a NOAEL from this study.

The level protective against severe adverse effects is based on a reproductive/developmental toxicity study. Studies of reproductive/developmental toxicity of necessity involve repeated exposures. It is generally not known at what stage in gestation a developmental defect or an impact on the reproductive capacity of the animal can occur. Thus we have used the one-day exposure concentration (generally 6 or 7 hr/day) in these cases to extrapolate back to a one-hour concentration.

Comment on Xylenes: OEHHA developed a one-hour REL based on findings in Nelson *et al.* (1943) of reported symptoms of eye, nose, and throat irritation at 870 mg/m³ xylenes. Although these results are consistent with other studies, the exposure duration of 3 minutes is a significant shortcoming in its use in developing a one-hour REL. There are several other human studies available with exposure durations closer to one-hour that provide a more appropriate basis for developing a one-hour REL for xylenes. We recommend that the one-hour REL be based on the human studies by Carpenter *et al.* (1975; 1976) and Hastings (1984).

Since irritation is generally time-independent after about 15 minutes of exposure, the concentration of xylenes becomes the important factor in determining the threshold for irritation response. We recommend that OEHHA use an n=2 in the time extrapolation calculation.

In the Carpenter (1975) study, 460 mg/m³ was considered the NOAEL because the number of volunteers that reported irritation was not significantly greater than the control group. In another study, Carpenter *et al.* (1976) found increased observations of eye irritation in all of the volunteers exposed to 930 and 1,800 mg/m³ xylene for 15 minutes, but only observed irritation in one volunteer (10% of total) at concentrations of 220 and 450 mg/m³. The NOAEL is identified as 450 mg/m³ based on eye irritation. Hastings *et al.* (1984) exposed 150 volunteers to 0, 430, 860, and 1,720 mg/m³ mixed xylenes for 30 minutes and found eye irritation in 56% of controls, 60%, 70% and 90% of the volunteers exposed at 430, 860, and 1730 mg/m³ respectively. The xylene concentration of 430 mg/m³ was considered as the NOAEL because reports of eye irritation were the same as controls. This study shows a similar NOAEL to the other studies but uses a 30 minute exposure period. We recommend an REL of 30.4 mg/m³ to protect against eye irritation based on Nelson *et al.*, 1943; Carpenter *et al.*, 1975, 1976; Hastings *et al.*, 1984. The basis of the REL is a NOAEL of 430 mg/m³ for eye irritation. The NOAEL was adjusted from the 30 minute exposure to a one-hour REL with a time extrapolation where n=2, and adjusted by an uncertainty factor of 10 to account for human variability in sensitivity to irritation. The one-hour REL (derived by the commentator) is thus 30.4 mg/m³ for xylene.

Response: OEHHA originally used the study of 10 healthy human volunteers exposed to 100 or 200 ppm xylenes for 3 to 5 minutes. Subjects reported eye, nose, and throat irritation at 200 ppm but not 100 ppm. Thus, this study provides a NOAEL of 100 ppm for extrapolation. OEHHA applied a time adjustment factor to extrapolate from the 3 minute exposure to one-hour equivalent exposure using a value of 1 for the exponent, n, in a modified Haber's Law. The resulting concentration was then divided by an uncertainty factor of 10 for intraspecies variability. The resultant REL is 0.5 ppm or 2.2 mg/m³.

The comment points out one shortcoming of the study in that exposure durations were quite brief. This does present more uncertainty in extrapolating to an equivalent one-hour concentration, than if the duration were much closer to one-hour. The studies cited by the commentator provide a NOAEL for 15 to 30 minute exposures very similar to the NOAEL for a 3 minute exposure in Nelson *et al.* If OEHHA extrapolates using an exponent of 1 from a 3 minute to a 60 minute concentration, the resulting "equivalent" concentration is 10 fold higher than if the extrapolation runs from 30 minutes to 60 minutes. OEHHA agrees that this other data should be taken into account, but prefers to use an exponent of 1 for extrapolating from exposure durations of less

than one hour to a one hour equivalent concentration. Using a NOAEL of 430 mg/m³ for 30 minute exposure, and extrapolating to a 60 minute exposure results in an equivalent concentration of 50 ppm (220 mg/m³). Applying an uncertainty factor of 10 for intraspecies variability yields an REL of 5 ppm (22 mg/m³).