Response to Comments on the October 1997 Draft of the

Air Toxics Hot Spots Risk Assessment Guidelines Part III: Determination of Noncancer Chronic Reference Exposure Levels

Responses to Comments on the Second Set of 40 Chemicals

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Chemical Industry Institute of Toxicology (CIIT)

Comments on the chronic REL for **ethylene oxide** were received from Drs. Preston, Fennell and Janszen of the Chemical Industry Institute of Toxicology (CIIT). OEHHA developed a chronic REL of 5 $\mu g/m^3$ from a 1995 study of hospital workers by Schulte and coworkers.

Comment 1. In regard to exposure, major uncertainties exist in estimating ethylene oxide exposure to the workers and in interpreting the variability in exposure in the human study used to develop the cREL. The ethylene oxide analyses and calculations are not clearly explained. There may not be a significant association between individual exposure and hemoglobin adducts.

Source data for ethylene oxide assessment: The exposure response data used as the source for chronic exposure limits for ethylene oxide are those published by Schulte et al. *(Molecular, Cytogenetic, and Hematologic Effects of Ethylene Oxide on Female Hospital Workers*, Journal of Occupational and Environmental Medicine 37, 313-320, 1995). In order to adequately assess the data and conclusions drawn, it is necessary to also refer to a previous paper that presents much of the original exposure response data (Schulte, P.A. et al., *Biologic markers in hospital workers exposed to low levels of ethylene oxide*, Mutation Research 278, 237-251, 1992). The more significant differences between the two publications is that only female workers were considered in the analysis presented in the 1995 paper (see discussion below), and hematologic effects were analyzed in the 1995 paper. The relevance of the latter markers to risk assessment remains unclear, and for this and other reasons they are not considered further in this commentary.

Response: Staff have again reviewed both the papers by Schulte and coworkers (1992, 1995) to evaluate exposure issues. Based on these comments, those of the CMA, and OEHHA staff's re-evaluation, we decided not to use the study of Schulte et al. as the basis of the REL. Instead we have developed a revised chronic REL for ethylene oxide of 30 $\mu g/m^3$ based on the neurotoxicity study of Klees at al. (1990).

Comment 2. There are three broad areas of concern with the data as presented and these will be considered sequentially as exposure, statistical analyses and biological data. (a) Exposure: As noted in the draft Chronic Toxicity Summary on Ethylene Oxide, major uncertainties exist in estimating exposure, and in interpreting the variability in exposure concentration. In addition, Schulte et al. (1995) did not give adequate information on ethylene oxide analyses and calculations. More details of the exposure assessment and biomarker measurements were provided for this study population in Schulte et al. (1992). The data obtained on hemoglobin adducts may have the power to substantiate the assessment of exposure, since hemoglobin adducts represent a dose integrated over the lifespan of the erythrocyte. However, the uncorrected data were not presented in sufficient detail to enable this comparison to be made, and many of the important features of the data may not be readily apparent as a result of the particular nature of the presentation.

Response. The draft Chronic Toxicity Summary on Ethylene Oxide discussed the major uncertainties that exist in estimating exposure in the 1995 study by Schulte et al. Major areas of uncertainty are the usual uncertainty in estimating human exposure, the potential variability in exposure concentration, and the small number of subjects studied at each location. Schulte et al. also did not give adequate information on their EtO analyses and calculations in their report.

Comment 3. A critical question is whether there is a significant association between the calculated exposures for each individual and the hemoglobin adducts measured. The range observed for the adjusted hemoglobin adduct levels in the U.S. study participants in Figure 2 of Schulte et al. (1992) is extremely broad, and, as noted in the comments on the statistical analysis presented below, a horizontal line indicating a lack of correlation between hemoglobin adducts and the estimated exposure could equally well be valid. A hemoglobin adduct is a measure of the actual internal dose of ethylene oxide achieved in each individual, and is a more reliable estimate of exposure than those generated in Schulte et al. (1992). Unexpected variability of the data is demonstrated by the fact that for 7 individuals with the same log cumulative exposure of 3.4 (30 ppm.hr), the range of hemoglobin adducts was approximately 10 fold, from approximately 0.036 to 0.36 pmol/mg hemoglobin (calculated from the graph). Four of the participants from the >0-32 ppm.hr group had the same exposure assigned as individuals in the 0 ppm.hr category. These values were all plotted together with an exposure value corresponding to approximately 0.5 ppm.hr, and not 0 ppm.hr. No justification was provided for the choice of this value.

Response. Staff assume that the commentators believe that a 10-fold range is unexpectedly high variability of the data. Ten-fold is the common uncertainty factor used for intraspecies (human) variability by both OEHHA and USEPA. OEHHA staff are aware of only one instance in which USEPA has used a UF_H less than 10 when using the NOAEL/UF approach for an RfC. Recent studies by Hattis and coworkers indicate that for many chemicals the variability is more than 10-fold (e.g., Hattis D. 1996. Variability in susceptibility – how big, how often, for what responses to what agents? Environmental Toxicology and Pharmacology. 2:133-145; Hattis D et al. Distributions of individual susceptibility among humans for toxic effects – For what fraction of which kinds of chemicals and effects does the traditional 10-fold factor provide how much protection? Annals NY Academy of Sciences, submitted). As one example, in a study of DNA adducts from PAHs the interindividual variability was about 24-fold (Dickey C, Santella RM, Hattis D, Tang D, Hsu Y, Cooper T, Young TL, Perera FP. Variability in PAH-DNA adduct measurements in peripheral mononuclear cells: implications for quantitative cancer risk assessment. Risk Anal 1997;17(5):649-656).

The choice of 0.5 ppm-h as a cut-off is not an unreasonable choice based on the available data.

Comment 4. The shortcomings of the exposure measurements are discussed by Schulte et al. (1992). The estimates of exposure were based on 2-4 days of ethylene oxide measurements to model cumulative exposure. Exposure that occurred prior to the four-month period of the

exposure assessment may be more relevant for the generation of effects in lymphocytes. Given the uncertainty of the exposure assessment, and the potential utility of the hemoglobin adduct data as a dose measure, it is very surprising that an analysis of this data set has not been reported using hemoglobin adducts as the dose measure against the various measures of effect. Before using these studies (Schulte et al., 1995) as the basis of a risk assessment, it is important that the data stand up to reasonable scrutiny. Using hemoglobin adducts in place of an uncertain exposure measure would provide a means of reducing the uncertainty of a risk assessment.

Response. Exposure assessment is often a problem in epidemiologic studies and we can only use the data presented. If the pattern of exposure is fairly consistent, 2 to 4 days may be a representative sample. Sterilization is a routine procedure in hospitals and the study is published in a reputable journal. On the other hand, if the exposure is sporadic and variable, 2 to 4 days may be a poor sample. These uncertainties, coupled with the availability of Klees *et al*. (1990), were some of the reasons OEHHA is no longer using the studies of Schulte and coworkers.

Comment 5. The hemoglobin adduct measurements were made with an immunoassay method that can have considerable variability in specificity and in background levels of adduct between batches of antibody used (Tornqvist et al., *Ring test for low levels of (2-hydroxyethyl)valine in human hemoglobin*, Anal Biochem 203, 357-360). It is not clear whether a single batch of antibody was used in the Schulte et al. (1992) study. Failure to do so could affect the results and their interpretation.

Response. OEHHA staff appreciate the identification of this shortcoming. However, we use the data that are available in this peer-reviewed article, while aware of limitations.

Comment 6. (b) Statistical Analyses: The following issues raise questions of whether the statistical analyses for the Schulte et al. dataset were appropriate, and whether the results from a statistical viewpoint are soundly based or valid. (i) Use of same data set for model building and hypothesis testing: In epidemiological studies, one is frequently interested in two basic issues: 1) which factors are important for explaining the observed data; and 2) are the observed differences between groups, as defined by one or more categorical variables, statistically different with regard to a particular response variable. Frequently, as in the study performed by Schulte et al., the same data set is used to answer both questions, although it is not valid to do so. The reason is that this practice involves a type of circular reasoning.

Whenever any kind of stepwise regression is performed, one is interested in building a model of those factors that are deemed to be important for explaining the observed results. This process is designed to choose those factors out of many which significantly contribute to the response of interest. To use this data set to create a model is valid. But to create a model and then test to see if there are differences between groups which were determined by the data (via analysis of covariance) is not a valid exercise. Furthermore, the investigators are implying that the regression coefficients obtained from this small investigational study are

representative of the entire population. Unfortunately, a comparable second study group was not available to test this assumption. The investigators did decide to force certain variables into the model, which were occasionally significant.

A further example is given in the Schulte et al. (1992) article. The investigators arbitrarily decided where the breakpoint should be for creating a grouping variable for cumulative exposure to ethylene oxide. Then they tested to see if there was a difference between the two groups.

Response. OEHHA staff agree that the authors have attempted to make their study both exploratory and confirmatory. In addition to the theoretical undesirability of that approach, the authors' data are very variable. If the data had been more distinctively bimodal, the data might be more credible from a biological standpoint, if not from a statistical one. . These limitations constitute another reason for not using the studies of Schulte and coworkers.

Comment 7. Statistical analyses: (ii) Univariate versus multivariate analyses: Since three outcomes (hemoglobin adducts, SCE, and micronuclei) were measured on each subject, a multivariate analysis should have been performed, which would have taken into consideration the correlation between the responses. This is especially true and necessary for the hematologic effects analyses. A separate regression model for each biomarker response was created from the same data set. Because of the multiplicity of models being created from one data set, some sort of protection against over-significance should have been included, e.g., a p-value might need to be <0.005 for a particular variable to be declared significant. This is analogous to the multiple t-test problem.

Response. $p <0.005$ is an very stringent decision criterion. Another approach might be to modify $p < 0.05$ by the Bonferroni correction for multiple analyses, especially if one is hunting for differences. It might not be necessary in this instance. Hemoglobin adducts will have a biologically separate mechanism from that for micronuclei and SCEs. However hemoglobin adducts are a surrogate for DNA adducts. DNA adducts can lead to mispairing of DNA, and both SCE and micronuclei result from alterations in the DNA.

Comment 8. Statistical analyses: (iii) Significance of regression coefficients: For each biomarker or hematological response a multiple regression model was created. P-values for each variable in the model are given, and the implication is made that variables with small p-values are important for explaining the observed outcome. However, what is not stated and is true, is that the "significance" of a variable is totally *dependent* upon the presence in the model of the other variables. In other words, if there is a high degree of correlation between one independent variable and another (multicolinearity), this would explain the observed significance. Unfortunately, there is no statistical method to separate the dependence of one variable from another and still assess the importance of a given variable. However, in the Schulte et al. (1992) article, this assessment has been done graphically. In Figure 2, for example, the adjusted log hemoglobin adducts are plotted against log cumulative ethylene oxide exposure. The slope (from the multiple regression model) is 0.18, and the p-value is

given as 0.0006. This p-value is dependent on the model given in Table 4. This same argument applies to Figure 4, in which the adjusted SCE are plotted values against log cumulative ethylene oxide exposure. The true degree of significance can be determined as follows: if the regression line can be rotated about the point that represents the average value for each axis so that it is horizontal and between the 95% confidence intervals, then the relationship between the independent and dependent variable is not significant. Hence, in truth there appears to be no significant relationship between log cumulative ethylene oxide exposure and the adjusted log transformed biomarker responses. One might consider these p-values to be statistical "oddities" with no real interpretation. A similar argument can be presented for analysis of the hematological data. Although the data were not presented in detail in Schulte et al. (1995), it seems highly plausible that the reported statistically significant regression analysis for hematocrit, lymphocytes and neutrophils fall equally into the category of statistically uncertain.

Response. OEHHA staff do not agree that it is true that the "significance" of a variable is *totally* dependent upon the presence in the model of the other variables. The significance may be dependent on, and influenced by, the other variables but it is not totally dependent on them.

Staff also do not agree that the “if the regression line can be rotated about the point that represents the average value for each axis so that it is horizontal and between the 95% confidence intervals, then the relationship between the independent and dependent variable is not significant.” If the regression line as calculated is horizontal (b = 0), then one can say that there is no association. If the line has a slope, then the slope can be calculated and its significance assessed. The slope can be shallow and statistically significant. The rotation test is interesting but not the accepted method to test significant correlation.

The comment also implies that there is serious confounding. The study controlled for age, smoking and liquor. Smoking is a definite confounder; age and liquor probably less so. Unless identified, it is just a guess that there is another confounder.

The reference to “statistical "oddities" with no real interpretation” is confusing. Something is either statistically significant using the decision criterion specified, or it is not. Whether a statistically significant difference is biologically meaningful is a separate question.

Comment 9. Biological Data: (i) Controls: Population monitoring studies are basically small epidemiological studies that require that confounders of response be accounted for. As noted above, some attempt was made to do this through a statistical approach that has its own inherent problems, but this has to be considered as only a partial attempt to account for confounders. The selection of an appropriate and adequately sized control population can help diminish the influence of confounders. In the study of Schulte et al., the controls are woefully inadequate, being eight in number for the US hospital group and one for the Mexican hospital. Comparing responses from "high" and "low" exposure groups is not a substitute for a comparison between control and exposed, because this will be further complicated by the adequacy of the exposure assessment.

The inadequacy of the control selection is quite possibly the reason for the low mean SCE values presented for the US group (4.61 per cell). In other large control population studies, the mean SCE values are considerably higher, even though the methods used were the same or very similar. Bender et al. *(Chromosomal aberration and sister chromatid exchange frequencies in peripheral blood lymphocytes of a large human population sample,* Mutation Research 204, 425-433, 1988) reported a mean control SCE frequency of 8.29 ± 0.08 for 353 individuals, and Tucker et al. (*Variation in the human lymphocyte sister-chromatid exchange frequency: Results of a long-term longitudinal study,* Mutation Research 204, 435-444, 1988) one of 9.32 for 22 non-smoking individuals. Also of note, smoking was a considerable confounder, accounting for a mean of 1.85 extra SCE per cell. It *appears* to be less so in Schulte et al., but it is not possible to extract the actual data nor to establish the distribution of smokers among the different groups. Suffice it to say that the control data alone are sufficient to provide a very real concern about the validity of the conclusions.

Response. OEHHA staff agree that the number of controls in the Mexican hospital is problematic; as to the U.S. hospitals the adequacy of 8 controls depends on the tightness of the data. OEHHA is not aware of a widely accepted value for SCE in controls. All means in the Schulte study, both unexposed and exposed to ethylene oxide, are <7 which is less than the means of the 2 control groups cited by the commentator. The Bender et al. data seem surprisingly homogeneous while the commentators do not indicate the variability of the Tucker et al. data. Review of the Tucker paper indicated differences in SCE between smokers and non-smokers. Only the eight non-smokers studied by Tucker at al. can be considered controls. The commentators appear to have added the 8 nonsmokers, the 4 smoke-enders and the 10 variable smokers in Table 3 together to arrive at their sum of 22 non-smoking individuals, a questionable summation since the paper shows that smokers have higher levels of SCE and that it takes at least 12 months for SCE to return to normal levels. The Schulte et al. study also had 8 U.S. controls; their smoking status is not obvious.

A 1984 report (Laurent C, Frederic J, Leonard AY. Sister chromatid exchange frequency in workers exposed to high levels of ethylene oxide, in a hospital sterilization service. Int Arch Occup Environ Health 1984;54(1):33-43) found 7.52 ± 0.82 SCEs per cell in 15 non-smoking controls, a value lower than that quoted by the commentator. In the absence of an accepted standard for SCEs in controls, we judge the consistency and believability of the data itself as presented in the study.

Comment 10. Biological data: (ii) Micronuclei: Micronuclei can be formed from acentric chromosome fragments or whole chromosomes that failed to segregate at mitosis, and as such represent a mutagenic endpoint in contrast to SCE that are a genotoxic endpoint since they have not been associated directly with any cellular phenotype. In Schulte et al. (1992) the frequencies of micronuclei were not significantly different among the three sample groups (control, "high" exposure, "low" exposure) in the US sample. In Schulte et al. (1995), a significant difference between the high and low exposure group was reported. This was basically the same data set as that in Schulte et al. (1992) except that the analysis was only for female workers. However, there was no significant effect of gender on micronucleus frequency ($p = 0.57$) and so it is difficult to establish the reasons for the different conclusions

from the two analyses, absent a statistical quirk. There was no increase in micronucleus frequency in the Mexican hospital sample, but the single control individual makes this an unusable conclusion.

Response: OEHHA staff agree that the lack of SCE data for the one control is problematic.

Comment 11. Biological data: (iii) Relationship to risk assessment: As noted in Schulte et al. (1992) with regard to the interpretation of the analysis of responses (micronuclei, SCE and hemoglobin adducts) in peripheral lymphocytes, "It is not known whether these changes may be indicative of increased risk of disease; however, they do appear to reflect exposure to relatively low levels of ethylene oxide. The exact meaning of these changes is unknown." There has been a persistent concern on the utility of cytogenetic data, for example, collected in population monitoring studies. It is generally agreed that they can be used to demonstrate an exposure, but not absence of exposure. However, even in this mode, it can be argued that confounders could be of concern. The reason being that peripheral lymphocytes are terminally differentiated, non cycling cells. Chromosome alterations (micronuclei and SCE) produced by the great majority of chemicals, including ethylene oxide, require DNA replications for their formation. Thus, any cytogenetic alterations observed from the way the assays are conducted are produced as errors of DNA replication *in vitro* (i.e. in culture) from DNA damage that remains at the time of this *in vitro* replication. Given that DNA repair processes are operational in peripheral lymphocytes, most alterations will have been derived from recent exposure. This makes it very difficult to establish a relationship between exposure and response except in the case of rather high, accidental exposures. Thus, even as a measure of exposure, the assessment of cytogenetic alterations in peripheral lymphocytes has serious limitations.

Given that no risk can be assigned to genetic alterations that arise *in vitro,* following an in vivo exposure, it seems highly inappropriate to use such data in the development of chronic reference exposure levels for ethylene oxide, or indeed for a very broad range of chemicals that produce their biological responses by a similar mechanism.

Response: OEHHA appreciates the thoroughness of the comments. OEHHA staff used the Schulte studies because they were the best human data we could find. Indeed the results may be more applicable as an indicator of genotoxic damage and carcinogenic potential than of other types of toxicity. The commentators do not suggest an alternative, superior, human or animal study to use. OEHHA staff has recalculated a chronic REL for ethylene oxide using human and animal data on neurotoxicity, an endpoint reported in both. OEHHA is now proposing a chronic REL of 30 $\mu g/m^3$ based on human data reported by Klees et al. (1990).

Klees *et al.* (1990) observed cognitive impairment and personality dysfunction more frequently in hospital workers chronically exposed to EtO, compared to a control group. A group of 22 hospital workers who had been exposed to an 8-hour TWA of 4.7 ppm EtO for a mean of 6.13 years (range 1-11 years) were matched with 24 control subjects. Worker neuropsychological function was classified as normal or impaired on the basis of the questionnaires and neuropsychological tests by 2 clinical psychologists, who were unaware of

exposure status. (If the classification of the two clinicians did not agree, the subject was classified as "disagreement" which occurred in 7/23 (30%) of the controls and 10/22 (45%) of the exposed.) Exposed subjects were significantly more frequently classified as impaired (5/12) compared to controls (1/16) ($\chi^2 = 6.0861$; $p<0.05$).

Derivation of the revised chronic REL for ethylene oxide

Study population	22 hospital workers (and 24 controls)
Exposure method	Workplace exposure
Critical effects	Impaired neurological function
LOAEL	4.7 ppm
NOAEL	Not observed
Exposure continuity	8-hours/day (10 m^3 occupational inhalation rate), 5 days/week
Exposure duration	6.13 years (range 1-11 years)
Average experimental exposure	1.68 ppm (4.7 x 10/20 x 5/7)
Human equivalent concentration	1.68 ppm
LOAEL uncertainty factor	3
Subchronic uncertainty factor	3
Interspecies uncertainty factor	1
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	100
Inhalation reference exposure level	16.8 ppb (30 $\mu g/m^3$)

Chemical Manufacturers Association - Ethylene Oxide Industry Council

Comments on the chronic REL for **ethylene oxide** were received from the Ethylene Oxide Industry Council (EOIC) of the Chemical Manufacturers Association (CMA) in a letter signed by Courtney M. Price dated January 29, 1998. OEHHA developed a chronic REL of 5 $\mu g/m^3$ from a 1995 study of hospital workers by Schulte and coworkers.

Comment 1. The OEHHA guidelines establish criteria for the determination of RELs. The 1995 Schulte study cited in the TSD, and the equally relevant 1992 study that is not cited, must be evaluated subject to Cal EPA guidelines on interpretation of human studies. Cal EPA OEHHA guidelines recognize that "[e]xposure measures frequently represent the greatest weakness of available epidemiological studies." Short-term exposure monitoring must frequently be used where long-term data are not available. "The degree to which air concentrations can be adequately measured is critical in determining the usefulness of an epidemiological study." "Covariables and confounding variables should be controlled or removed from the study." A limitation of controlled human exposure studies, in addition to their short duration, is that they usually involve small sample sizes. In evaluating evidence, OEHHA considers "strengths and uncertainties of each REL.... Issues such as observation of dose-response relationship, reproducibility of findings, and mechanism of action" are given weight in evaluating RELs. "Consistency of an association between chemical exposure and adverse effect is also evaluated. Relevant observations include similarity of effects noted in different studies and among different populations and/or species ...." When these guidelines are applied to the 1992 and 1995 Schulte studies, significant questions are raised concerning the validity of the findings.

Response. OEHHA acknowledges that human studies (including the 1992 and 1995 Schulte studies) often suffer from deficiencies in the assessment of exposure. The deficiencies were detailed by OEHHA in the TSD. We have since re-evaluated the utility of the Schulte et al. (1995) study in deriving the chronic REL and, as a result, are proposing to use a study by Klees et al. (1990) on neurotoxicity.

Comment 2. Cal EPA should not utilize the Schulte studies to establish a REL for EO since the control population is too small. A valid epidemiologic study must have an adequate number of controls to yield reliable estimates of risk and permit adjustment for potential confounders that can bias results. The number of controls was much too small in the 1995 Schulte study - eight U.S. workers and one in the Mexican worker group. There is indication that the insufficient number of controls is not merely a formal deficiency, but undermines reliance on the TSD's conclusion that Schulte found a significant excess in SCE values and hernatocrit values. Taking SCE values, Schulte's U.S. control group shows SCE mean values of 4.61 per cell. Other larger studies report SCE values of 8.29 ± 0.08 for 353 individuals, and 9.32 for 22 non-smoking individuals. It is recognized that smoking is a considerable confounder and thus an adequate number of controls is especially important to a valid study. As a result of the small size of Schulte's control group and the anomalous level of SCEs reported in these controls, Schulte's findings lack the indicia of validity to be selected as the basis for the EO REL.

Response. The smaller the control group is, the more obvious the effect must be in the exposed group. The possibility that these controls have unusually low SCE values is important and may be a reason to doubt the small, purported increase in SCE in the EO exposed workers. As noted above, OEHHA is now proposing the use of a study on neurotoxicity as the basis for the chronic REL.

Comment 3. Cal EPA should not utilize the Schulte studies to establish a REL for EO since the relevance of SCE data to risk assessment has not been demonstrated. Schulte et al. recognized in the 1992 paper a significant limitation not quoted by Cal EPA: micronuclei, SCE, and hemoglobin adducts appear to reflect exposure to relatively low levels of EO but it is not known whether they are indicative of increased risk of disease. Thus SCE data are biomarkers of EO exposure but it is not known whether they have any clinical significance or indicate any disease endpoint. Schulte himself recognizes that "the predictive value of SCEs and micronuclei to cancer is undetermined." Mutation Research, Vol. 278 at 239. Schulte states that "the significance of our findings [increased numbers of hemoglobin adducts and SCEs] for the long term health of workers is unknown." Id. at 248. Other investigators in addition to Schulte acknowledge that these cytogenetic changes have no known clinical significance. E.g., Stolley et al., "Sister-chromatid exchanges in association with occupational exposure to ethylene oxide," Mutation Research 129:89-102 (1984). It is unwarranted to treat these biomarkers of exposure as indices of health risk.

Response. Although the relevance of SCE data to risk assessment of ethylene oxide has not been demonstrated, the finding of increased SCE in Bloom's syndrome, in which the risk of cancer is increased several fold, indicates that SCE, a rearrangement of the genetic material, may be linked to cancer. However, OEHHA agrees that for noncancer, chronic risk assessment, the use of this endpoint is questionable. As such, OEHHA is proposing to use the Klees et al. (1990) study of neurotoxicity.

Comment 4. Cal EPA should not utilize the Schulte studies to establish a REL for EO since the 1992 Schulte study does not indicate dose response for micronuclei. In the 1992 Schulte Study, frequencies of micronuclei were not significantly different in the U.S. population between controls, low and high exposure. Although the 1995 study overlapped the 1992 data set, an unexplained difference in results was observed which is not rationalized by the fact that the 1995 study was limited to female workers. When the 1992 data are considered, there is not an adequate dose-response to suggest causal association under OEHHA guidelines.

Response. In the U.S. data there is a statistically significant difference between the 0 exposure and the >32 category. The SCE are higher in the high exposure group in the 1995 report (Table 3). The p value is 0.02.

Comment 5. Cal EPA should not utilize the Schulte studies to establish a REL for EO since the exposure assessment in the Schulte assessment was recognized by the author as a

weakness of the study. In the 1992 Schulte study, the estimate of four months of cumulative exposure was based on only two to four days of EO measurements. Schulte acknowledges as study "weaknesses" the fact that "the estimate of exposure was based on 2-4 days of EO measurements to model the cumulative exposure. The impact of peak exposures or other variations from the mean of those measurements could not be assessed." U.S. OSHA adopts a short term excursion limit of 5 ppm for EO given relevance of peaks of exposure. The Schulte data are flawed in their inability to adequately characterize exposure and to take intensity of exposure into account. The 1992 Schulte study simply does not account for the short term exposures (STEs) in conclusions or reporting. There is no indication of the magnitude or frequency of the exposures, even with multiple statements that the STEs are the primary source of exposure. Schulte simply takes all exposure measurements and calculates the ppm hour or cumulative time weighted exposure. Schulte then concludes from this number that effects are observed at exposure levels below the OSHA standard. This is a flawed conclusion because it ignores the implications of the OSHA excursion limit. OSHA has recognized the significance of STEs relative to health effects in the establishment of the EL. If an employer exceeds either the 8-hour limit or the 15 minute limit, the employer has violated the OSHA limits. It is unjustified to assume that health effects caused by exposures above an OSHA standard would apply below the standard. In addition, improper sampling techniques used by Schulte may have lead to inappropriate conclusions. In the study, results from different sampling techniques (personal monitoring, breathing zone, area samples) were used for the same study population and considered together, which would not be considered an appropriate method.

Response. OEHHA acknowledges the limitations of the exposure data in these 2 studies (and in many other human studies), the problems with measuring exposure to humans in such situations, and the problems associated with short-term excursions, especially with ethylene oxide in health care settings. OEHHA prefers to use human studies in developing RELs. We have revisited the use of this study as the basis of the chronic REL and have decided to use the study of Klees at al. (1990) instead.

Comment 6. Cal EPA should not utilize the Schulte studies to establish a REL for EO since the complete blood count data are not significant given the small number of controls and the frequency of iron deficiency in a population of young women. Data on minor hematologic changes do not provide a sound basis for the REL, especially given inadequate sample size. The level of reduction in hemoglobin is well within the expected range for a population of female workers who may be iron-deficient for a variety of reasons.

Small differences were noted in hemoglobin and hematocrit between mid-dose and high-dose exposed workers but not between unexposed workers and either low-dose or high-dose groups. The differences between mid-dose and high-dose groups were not clinically significant. See attached report by Dr. Mark Udden, Baylor College of Medicine. None of the subjects' hemoglobin levels were below the range of normal women as reported in the authoritative reference, Williams' Hematology. Moreover, Schulte does not appear to have addressed some other potential causes for their hematologic status such as folate or other nutritional deficiency.

Schulte's claim that EO causes changes in the CBC data of a population are primarily based on granulocyte and lymphocyte changes. However, as Dr. Udden observes, it is not clear that these changes have biological significance given that there was no statistically significant effect on the total white cell count of EO-exposed women versus unexposed women. The shifts in granulocyte levels (10%) did not decrease to the low level associated with neutropenia, nor was there evidence of lymphocytosis. The study also lacks internal consistency. Although Mexican workers had higher average cumulative exposures than U.S. women, the Mexican workers did not show statistically significant percentage changes in lymphocytes or neutrophils as might be expected if there were a real biological effect. The findings, based on multiple linear regression (Table VII), do not indicate a statistically significant relationship with increasing cumulative exposure.

In addition, there is lack of external consistency or consistency across studies. Schulte identified in his 1995 paper three other studies that did not find the effects he reported. Thus there is not found a consistency of association between EO exposure and hematologic effects across studies. See TSD Guideline § 2.2.2,

A much larger number of women would need to be studied before any conclusion can be drawn that CBC data represent meaningful biological effects of EO exposure.

Response. The inconsistency of the data in the 2 Schulte reports with data in other reports in the literature is important. For this and other reasons OEHHA staff have reconsidered the basis of the chronic REL and are now proposing to use neurotoxicity data from Klees et al. (1990).

Comment 7. Cal EPA should not utilize the Schulte studies to establish a REL for EO since the relevance of EO blood count data to worker health has been questioned. In June 1997 hearings at U.S. OSHA reviewing the current occupational standard on EO, Dr. Anthony LaMontagne appeared as the principal witness for the unions. In discussing recommended revisions to various ancillary requirements, Dr. LaMontagne stated that he questioned the usefulness of the complete blood count and differential in EO medical surveillance. See June 30, 1997 OSHA hearing transcript at 70-73 and exhibit to Dr. LaMontagne's testimony, "The Massachusetts Hospital Eto Health and Safety Study: A Summary Report for Study Participants and Supporters" (1996) at 37. Dr. LaMontagne recommended that the CBC count be eliminated from surveillance requirements, citing his publication, LaMontagne et al., "The utility of the complete blood count in routine medical surveillance for ethylene oxide exposure," Am. J. Ind. Med. 24:191-206 (1993). In this article, LaMontagne concludes that "a cross-sectional comparison of the CBC data from the EtO exposed workers to data from non-EtO exposed hospital workers showed no significant differences, ruling out an association of relative lymphocytosis with EtO exposure." The authors conclude that the CBC with lymphocyte differential is not useful in EO medical surveillance.

Response. Staff appreciate being apprised of Dr. LaMontagne's testimony. However, blood count was only one of the endpoints OEHHA considered. Also, as noted above, we have decided not to use the study by Schulte and coworkers as the basis of the chronic REL.

Comment 8. CONCLUSION: Individual epidemiologic studies addressing potential carcinogenicity of EO include hundreds or thousands of workers. It is inappropriate for Cal EPA to use the 1995 Schulte study with its small handful of workers in setting a REL for chronic effects given the significant limitations of the Schulte data.

Response. OEHHA appreciates the thoroughness of the comments. OEHHA staff used the Schulte studies because they were the best human data we could find. Indeed the results may be more applicable as an indicator of genotoxic damage and carcinogenic potential than of other types of toxicity. The commentators do not suggest an alternative, superior, human or animal study which OEHHA should use. OEHHA staff has recalculated the REL using human and animal data on neurotoxicity, an endpoint reported in both. OEHHA is now proposing a chronic REL of 30 $\mu g/m^3$ based on human data reported by Klees et al. (1990).

Klees *et al.* (1990) observed cognitive impairment and personality dysfunction more frequently in hospital workers chronically exposed to EtO, compared to a control group. A group of 22 hospital workers who had been exposed to an 8-hour TWA of 4.7 ppm EtO for a mean of 6.13 years (range 1-11 years) were matched with 24 control subjects. Worker neuropsychological function was classified as normal or impaired on the basis of the questionnaires and neuropsychological tests by 2 clinical psychologists unaware of exposure status. (If the classification of the two clinicians did not agree, the subject was classified as "disagreement" which occurred in 7/23 (30%) of the controls and 10/22 (45%) of the exposed.) Exposed subjects were significantly more frequently classified as impaired (5/12) compared to controls (1/16) ($\chi^2 = 6.0861$; $p<0.05$).

Derivation of the revised chronic REL for ethylene oxide

Study population	22 hospital workers (and 24 controls)
Exposure method	Workplace exposure
Critical effects	Impaired neurological function
LOAEL	4.7 ppm
NOAEL	Not observed
Exposure continuity	8-hours/day (10 m^3 occupational inhalation rate), 5 days/week
Exposure duration	6.13 years (range 1-11 years)
Average experimental exposure	1.68 ppm (4.7 x 10/20 x 5/7)
Human equivalent concentration	1.68 ppm
LOAEL uncertainty factor	3
Subchronic uncertainty factor	3
Interspecies uncertainty factor	1
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	100
Inhalation reference exposure level	16.8 ppb (30 $\mu g/m^3$)

Chemical Manufacturers Association - Alkanolamines Panel

Comments on the chronic REL for diethanolamine were made by the Alkanolamines Panel (Panel) of the Chemical Manufacturers Association in a letter from Courtney M. Price dated January 29, 1998. The Panel is comprised of the major domestic producers of diethanolamine (The Dow Chemical Company, Huntsman Corporation, Union Carbide Corporation, and Occidental Chemical Corporation). The Panel urges OEHHA to withdraw its draft toxicity summary and proposed reference exposure level (REL) for diethanolamine. The Panel states that the study on which OEHHA has relied is inadequate to derive a REL, and the draft toxicity summary does not reflect accurately diethanolamine's toxicity database, particularly for reproductive and developmental effects. Also, the summary should be revised to characterize diethanolamine's vapor pressure accurately. In restricting its comments to the toxicity summary and related REL, however, the Panel does not endorse the risk assessment practices, policies, and methods set forth in those Guidelines in whole or in part. Moreover, the Panel reserves the right to challenge OEHHA's use of the Guidelines to assess or regulate any chemical, including DEA. OEHHA developed a chronic REL for diethanolamine of 20 $\mu g/m^3$ based on hematologic changes in female rats exposed to the chemical in drinking water.

Comment 1. OEHHA should derive its REL for DEA from inhalation studies, not from a drinking water study. The California Toxic Air Contaminants Program provides that OEHHA shall evaluate the health effects of and prepare recommendations regarding ... toxic air contaminants. In conducting its evaluation, OEHHA must consider all available scientific data, including but not limited to, data provided by state and federal agencies, private industry, and public health and environmental organizations. The evaluation must include an assessment of the availability and quality of data on health effects, including potency, mode of action, and other biological factors. OEHHA has stated that, because it is required to develop chronic inhalation RELs, "[s]trong weight is given to inhalation exposure-based health effects data. Oral exposure data are used only if adequate inhalation data are unavailable.

In deriving its REL for DEA, OEHHA stated that no inhalation studies with diethanolamine were located. For this reason, OEHHA derived its REL for DEA from a subchronic drinking water study conducted in rats. As shown below, however, a substantial database exists on DEA's potential inhalation toxicity. None of these studies is referenced in the toxicity summary. These studies provide data that is far more relevant to DEA's potential inhalation effects than the drinking water study on which OEHHA has relied. OEHHA must review these studies to fulfill its obligations under the Toxic Air Contaminants Program, comply with its own Guidelines, and derive an up-to-date and scientifically defensible REL.

A substantial database exists on DEA's potential inhalation toxicity. According to OEHHA's chronic toxicity summary, the direct effects of DEA on the respiratory system are unknown since no subchronic or chronic inhalation studies have been conducted. A number of inhalation studies have been conducted with DEA, however. These studies include:

BG Chemie (1993): In this 14-day inhalation study, DEA was administered to rats in an aerosol. No effects were observed in response to the 0.2 mg/l dose. For the 0.4 mg/l dose, rats exhibited slightly decreased body weight and retarded body weight gain in the males, slightly decreased serum cholesterol in both sexes, and increased relative and absolute liver weight in the females. The study concludes that "[u]nder the conditions of the test the degree of toxic effects as reported in the literature after inhalation of *6* ppm, *25* ppm, and *200* ppm DEA-vapor could not be confirmed." It further finds that "[n]eurotoxic effects as reported after 13 week application in the drinking water were not found after 2-weeks inhalation."[BG Chemie (1993). Study on the inhalation Toxicity Including Neurotoxicological Examinations of Diethanolamine as a Liquid Aerosol in Rats (14 Day Test). Project No. 3610233/90008. A copy of this study is appended as Attachment 1.]

Gamer et al. (1996): In this 90-day liquid aerosol inhalation study, thirteen male and thirteen female Wistar rats were exposed head-nose to liquid aerosols of DEA for six hours per working day for 90 days. The target concentrations were 15, 150, and 400 mg/m^3. The study found no functional or morphological evidence of neurotoxicity. Retardation of body weight was observed in animals that received high concentrations. No systemic effects occurred at the low dose, but liver, kidney, male reproductive system and red blood systemic effects occurred in the high concentration dose group. In the mid dose group, mild liver and kidney effects were present. Local irritation of the larynx and trachea was found in the high and mid dose groups, with irritating laryngeal effects also detected in the low dose group. [Gamer, et al. (1996). Diethanolamine – 90-Day Liquid Aerosol - Inhalation Study in Wistar Rats. BASF Project No. 5010075/93011. A copy of this study is appended as Attachment 2.]

BASF (1966): In this study, rats were administered a saturated vapor of DEA for eight hours. No mortality was reported.

Foster (1972): In this study**,** rats administered 1,471 ppm of DEA via inhalation experienced lung edema and died less than two hours after exposure. [Foster, G. (1972) . "Studies of the Acute and Subacute Toxicologic Responses to Diethanolamine in the Rat." Dissert. Abst. B32:6549.]

Union Carbide Corp. (1950): Rats were administered a saturated vapor of DEA at 25°C for six hours. No deaths resulted. Rats were also administered DEA in a saturated mist for eight hours with no deaths resulting. [Union Carbide Corp. (1950). Bushy Run Research Center Report 13-67.]

Schaper and Detwiler-Okabayashi (1996): This three-hour inhalation study in mice compared the sensory and pulmonary irritating effects of amines found in metalworking fluids containing DEA. The RD50 (sensory irritation) for ethanolamines ranged from 500 to 1,500 mg/m^3. [Schaper, M. and Detwiler-Okabayashi, K. (1996). "Comparison of Sensory and Pulmonary Irritating Effects of Amines Found in Metal Working Fluids (MWF) . " Toxicologist 301:18 (abstract)] .

Knaak et al. (1997): The authors reported a study in which rats were administered 25 ppm. of DEA vapor for a period of nine days by continuous inhalation (23.5 hours/day). Increased

liver and kidney weights, elevated blood urea nitrogen, and serum glutamate oxaloacetate transferase reported. [Knaak J, et al. (1997) "Toxicology of Mono-, Di-, and Triethanolamine" in Ware, G (ed.). Reviews Environ. Contam. Toxicol.

Eastman Kodak Co. (1967): In this 90-day subchronic inhalation study, dogs, weanling rats**,** adult rats, and guinea pigs were administered saturated vapor concentrations of about 0.26 ppm DEA. Exposure did not produce any identifiable gross or microscopic alterations in organs that could be attributed to DEA in any species. [Eastman Kodak Company (1967). Health and Safety Studies for Diethanolamine, Laboratory Tests to Determine Effect of Inhalation of Two Ethanolamines - Diethanolamine (DEA), Methylaminoethanol (MAE), Formulation 485K - Histological Addendum to Final Report. TSCA 8d Submission 86-890000205, Microfiche Number OTS0516742. Washington, D.C.: OPPT, U.S. EPA.]

Eastman Kodak Co. (1967): As an extension of the study summarized above, rats, guinea pigs, and dogs were, for 45 days, administered atmospheric concentrations of approximately 0.5 ppm DEA. All animals survived the study, and their behavior and appearance appeared normal. No systematic toxic effects or irritation were observed. The clinical examination also revealed no abnormal response, except that a "slight retardation in growth rate in rats may have occurred." [Subacute - Inhalation Toxicity of Diethanolamine and Bimat Imbibant (485 K))

Hartung et al. (1970): The authors report a subchronic study in which inhalation of 6 ppm vapor by male rats on a workday schedule for 13 weeks caused depressed growth rates, increased lung and kidney weights, and some mortality. [Hartung, *R., et al. (1970).* "Acute and Chronic Toxicity of Diethanolamine." Toxicol. Appl. Pharmacol. 17:308]

The significance of the more recent studies conducted with DEA in predicting DEA's potential health effects was acknowledged recently during the deliberations of the Organization for Economic Cooperation and Development (OECD) Programme for the Investigation of High Production Volume Chemicals. This program, initiated in 1990, was established to gather data on chemicals produced in large quantities by member nations, provide for an initial screening of the potential risks to human health or the environment presented by these chemicals, and develop recommendations for further testing. The sponsor country for DEA, the United Kingdom, completed its Screening Information Data Set (SIDS) Dossier in 1993 [OECD, Screening - Information Data Set (SIDS) Dossier, OECD Am Chemicals Programme (June 1993) (prepared by the United Kingdom, Department of the Environment) (OECD SIDS Dossier)], and in 1995 submitted a SIDS Initial Assessment Report (SIAR). The SIAR, based on a comprehensive review of data, concluded that no further testing was necessary.

Some additional testing was nevertheless proposed at the SIDS Initial Assessment Meeting (SIAM) where the SIAR was discussed, although initially it was agreed at the SIAM that no further testing was necessary. In the OECD SIAR prepared to address the concerns raised at the SIAM, the National Centre for Ecotoxicity and Hazardous Substances of the United Kingdom's Environment Agency reiterated:

"Since SIAM 4 the results of good quality 2- and 13-week inhalation toxicity studies have been incorporated into the SIAR. These studies [OECD (1997). SIDS - Initial Assessment Report: Diethanolamine] included specific evaluations of subgroups for neurotoxicity. Also good quality developmental toxicity data has been incorporated. It is therefore concluded that further animal testing of diethanolamine is unnecessary."

The Panel believes that OEHHA must review and evaluate all available inhalation data including recent unpublished studies that OEHHA has characterized as being "of good quality," in order to reach sound conclusions about DEA's potential inhalation effects.

Response. OEHHA appreciates the suggestion of additional inhalation studies and the furnishing to OEHHA of some of the studies. However, many of the studies are acute or subacute studies:

- Foster (1972) - 2 hours;
- Schaper and Detwiler-Okabayashi (1996) – 3 hours;
- Union Carbide Corp. (1950) – 6 hours;
- BASF (1966) - 8 hours;
- Knaak et al. (1997) – 9 days;
- BG Chemie (1993) 14 days.

These studies are of little use for developing a chronic REL.

Of more relevance to the development of a chronic REL may be:

- the Gamer et al. (1996*)* 90-day liquid aerosol inhalation study in rats,
- the Hartung et al. (1970) 13 week (90 day) inhalation study of 6 ppm DEA in rats, and
- the Eastman Kodak Co. (1967*)* 90-day subchronic inhalation study in dogs, weanling rats**,** adult rats, and guinea pigs administered saturated DEA vapor concentrations of about 0.26 ppm.

The Gamer et al. study has not appeared in the peer-reviewed medical and toxicological literature as of March 1999. The Eastman Kodak study also has not appeared in the peer-reviewed literature; it provides a free-standing NOAEL for inhalation of 0.26 ppm. The Hartung et al. (1970) report on the effects of 6 ppm DEA is likely an abstract since it could not be located on Medline. Hartung and Cornish reported on the acute and short-term oral toxicity of 2-N-ethylaminoethanol in rats in 1969 (Food and Cosmetic Toxicology 7(6):595-602).

The Gamer et al. (1996) aerosol inhalation study can be used as a check against the chronic REL of 20 $\mu g/m^3$ proposed by OEHHA. The NOAEL from the Gamer et al. (1996) study was 15 mg/m^3 diethanolamine based on a 6 hour/day, 5 day/week exposure. The equivalent continuous exposure would be 2.7 mg/m^3. After dividing by 1,000 (10 each for subchronic to chronic, animal to human, and intraspecies uncertainty/variability), the REL would be 2.7 $\mu g/m^3$, one-seventh of the REL proposed. If this study is published in the peer-reviewed literature, OEHHA will consider lowering the REL to 2.7 $\mu g/m^3$.

As another check, the Hartung et al. (1970) free-standing LOAEL of 6 ppm (25.8 mg/m^3) for a 13 week exposure of male rats would require time adjustment for continuous exposure to 4.6 mg/m^3 and the maximum UF of 3,000 which results in a REL of 1.5 µg/m^3 (also below the proposed chronic REL).

Comment 2. OEHHA should derive its REL for DEA from the Gamer et al. (1996) inhalation study. The Panel believes that the recent Gamer et al. (1996) study provides adequate data on which to base a REL and should be used for that purpose instead of the Melnick et al. (1994) study. As OEHHA has acknowledged in its Guidelines, oral data are considered only where inhalation data are unavailable. Moreover by using a cumulative uncertainty factor of 3,000 to derive a REL for DEA from this study - the highest uncertainty factor used by OEHHA for any chemical - OEHHA also has acknowledged the relative weakness of this study for predicting DEA's potential toxicity.

OECD (1997) (Section Addressing Recommendations for Further Work) Recent studies reviewed in connection with the OECD SIAR include the BG Chemie (1993) and Gamer et al. (1996) studies.

In the Gamer et al. study, conducted in the Republic of Germany, male and female Wistar rats were exposed by head-nose to liquid aerosols of DEA for 6 hours per working day for 90 days. The target concentrations of treatment groups were 15, 150, and 400 mg/m^3. A complete necropsy and gross pathological examination was conducted on animals in the experimental and control groups.

The only clinically detectable effect was a reduction of body weight development among high dose (400 mg/m^3) males. No systemic effects occurred at the low dose, but liver, kidney, male reproductive system, and red blood systemic effects occurred in the high dose group. In the mid dose group, mild liver and kidney effects were observed. Local irritation of the larynx and trachea was found in the high and mid dose groups, with irritating laryngeal effects also detected in the low dose group.

The authors concluded that the liver, kidney, male reproductive system, and red blood were target organs for systemic effects at the high concentration tested, but that no systemic effects occurred in the low concentration. They concluded further that the no observed effect level (NOEL) for its systemic effects lies between 15 and 150 mg/m^3. The Panel believes that OEHHA should use the no observed adverse effect levels (NOAELs) from this study, together with the standard uncertainty factors set forth in the Guidelines, to compute a REL for DEA.

Response. OEHHA calculated a REL based on the Gamer et al. study in the response to the first comment. Systemic effects on the blood were seen in both the Melnick and Gamer studies, which indicates that DEA causes the same effects by both routes. The laryngeal irritation effects, detected in the low dose group, is of interest because it is an effect specific to the route of exposure.

Comment 3. OEHHA should revise its draft toxicity summary to describe accurately DEA's potential health effects and vapor pressure. The Panel also urges OEHHA to revise its draft chronic toxicity summary for DEA to characterize more accurately the chemical's potential chronic health effects. Although OEHHA states, for example, that there is a lack of reproductive and developmental toxicity studies on DEA, the database on these endpoints is robust. Among studies that provide data relevant to DEA's potential developmental toxicity are:

Bushy Run Research Center (1991): In this study, pregnant rats were dosed cutaneously with 150, 500, and 1,500 mg/kg/day of DEA in distilled water on gestation days 6-15. No mortality was observed during the study, and the pregnancy rate was equivalent for all groups. No evidence of embryotoxicity or malformations was observed; there were no decreases in the mean fetal body weight; and no treatment related differences in the incidence of external or visceral variations were seen. There was an increase in the incidence of fetal skeletal variations at 1,500 mg/kg/day. Maternal toxicity was observed primarily at 1,500 mg/kg/day. [Bushy Run Research Center. Definitive Developmental Toxicity Evaluation of Diethanolamine (DEA) Administered Cutaneously to Sprague Dawley Rats (Final Draft Report) (Unpublished) (Sept. 9, 1991)] .

BASF (1993): In this study, pregnant Wistar rats were dosed with DEA in an aerosol (nose-only on gestation days 6-15. The concentrations tested were 0.01, 0.05, and 0.2 mg/l (10, 50 and 200 mg/m^3). Maternal toxicity (vaginal hemorrhage) and embryo fetotoxicity (increased incidence of skeletal variations) were observed at the highest dose level. No teratogenic effects were seen at any dose level. NOAELs were computed as follows: maternal toxicity (50 mg/m^3); embryofetal effects (50 mg/m^3); and teratogenicity (greater than 200 mg/m^3). [BASF (1993). Study of the Prenatal Toxicity of Diethanolamin in Rats after Inhalation. Project No. 31RO233/90010].

*Neeper-Bradley and Kubena (1993)**:*** Pregnant rabbits were treated by occluded cutaneous application to three concentrations of DEA for 6 hours a day on gestation days 6-18. Maternal toxicity (severe skin irritation) was seen at the highest dose. No teratogenic or embryofetal toxic effects were seen at any dose tested. NOELs were computed as follows: maternal toxicity (100 mg/kg) ; embryofetal effects (350 mg/kg) ; and teratogenicity (greater than 350 mg/kg). [Neeper-Bradley, T. L. and Kubena, M. F. (1993) . Diethanolamine**:** Developmental Toxicity Study of Cutaneous Administration to New Zealand White Rabbits. Union Carbide Corp. Bushy Run Research Center Project Report 91NO136.]

Environmental Health Research and Testing, Inc. (1990): In a range–finding developmental toxicity study, Sprague-Dawley rats were administered aqueous solutions of DEA by gavage at levels of 0, 50, 200, 500, 800, or 1,200 mg/kg from gestation days 6-15. The dosing volume was held constant at 5 ml/kg. Fetuses were delivered by Cesarian section on day 20 of gestation. The number of implantation sites, resorptions, dead or live fetuses, and the gravid uterine weight were recorded. All animals at the 500 mg/kg or higher level died or were moribund and sacrificed. No maternal mortality was observed in the 50 or 200 mg/kg groups. Maternal body weight gain was significantly reduced in the 200 mg/kg group. At scheduled sacrifice, a litter was found to be completely resorbed in one dam in the 200 mg/kg

group. None of the recorded gestational parameters were significantly different between the treatment groups and controls, however. [Environmental Health Research and Testing, Inc. (1990) . Report: Range Finding Studies: Developmental Toxicity Diethanolamine When Administered Via Gavage in CD SpragueDawley Rats. NTP-89-RF/DT-002].

Burnett et al. (1976): No embryotoxic or teratogenic effects were produced by topical administration of 2 ml/kg semipermanent hair dye preparations containing 2 percent DEA (equivalent to about 40 mg/kg DEA) to the shaved backs of pregnant Charles River CD rats on gestation days, 1, 4, 7, 10, 13, 16, and 19. [Burnett, C. et al. (1976) "Teratology and percutaneous toxicity studies in hair dyes." J. Toxicol. Environ. Health 1:1027-1040.]

The Panel notes in this regard that the OECD SIAR reviewed these studies, particularly the BASF (1993) study, which it characterizes as "good quality developmental toxicity data," in repeating its recommendation that "further animal testing of diethanolamine is unnecessary. OEHHA should, therefore, assess and incorporate these studies into its chronic toxicity summary and also revise the text of its summary to reflect accurately the robust nature of DEA's toxicological database.

OEHHA similarly has failed to discuss or even reference reproductive studies conducted with DEA. These include:

Battelle Columbus (1989): Reproductive effects were reported in male rats administered DEA concentrations of 2.5 and 5 mg/ml in drinking water (233 mg/kg and 487 mg/kg body weights, respectively). " -Effects included atrophy of the seminal vesicle, hypospermia, and a decrease in sperm motility and sperm count. The doses at which adverse effects were seen, however, approximate toxic levels - evidenced by the fact that the rats exhibited a large depression in their group mean body weight. Body weight gains relative to controls were significantly depressed in all male and female treatment groups. Weight depressions ranged from 66 percent in male rats administered 5 mg/ml DEA, to 11 percent in females administered the lowest dose (0.16 mg/ml). The authors acknowledged that "these doses are much too high for a chronic study," and recommended that doses for a chronic study should not exceed 0.16 mg/ml (the lowest dose used in the Battelle Columbus study). As noted in a toxicology review recently conducted in connection with the OECD's Programme on the Cooperative Investigation of High Production Volume Chemicals, the results observed in this study for DEA are "unlikely to be indicative of specific reproductive toxicity," and "further reproductive effects toxicity studies in animals cannot be justified. [Battelle Columbus (1989). Diethanolamine: Subchronic Dosed Water and Dermal Studies in F344 Rats and B6C3Fl Mice - Final Report for Prechronic Dosed Water Study for Diethanolamine in Fischer 344 Rats. TSCA FYI Submission FYI-OTS-1189-0721, Microfiche Number OTS0000721. Washington, D.C.: OPPT, U.S. EPA.]

Battelle Columbus (1989): In a 14-day oral dosed water study, for example, DEA was administered to mice at concentrations ranging from 0.63 to10 mg/ml of water. Exposure to the test solutions resulted in a calculated intake of 110 to 1,362 mg/kg/day for male mice and 197 to 2,169 mg/kg/day for female mice. No effects on the reproductive system were

detected in either gross necropsy or during histopathologic examination of high dose mice of both sexes. Battelle Columbus (1989) at 4 and Tables 5 and 6.

Hejtmancik et al. (1988): In a follow-up 13-week subchronic oral dosed water study, B6C3F1 mice were administered DEA concentrations of up to 10 mg/ml. As in the 14-day screening study, reproductive effects were found following gross necropsy or histologic examination. [Hejtmancik, M, et al. (1988a) . Prechronic Dosed Water Studv of Diethanolamine (CAS 111-42-2) in B6C3F1 Mice (Report prepared by Battelle, Columbus, Ohio)].

Response. OEHHA appreciates the additional information on the effects of DEA on development. As much as possible OEHHA based its chronic RELs on articles appearing in the peer-reviewed toxicologic and medical literature. Published reports on the reproductive/developmental effects of DEA are lacking. The studies cited by the commentator are nearly all unpublished, in-house reports. They also are either by the cutaneous (skin) or oral (gavage, drinking water) routes. An exception to these routes is the unpublished BASF (1993) study of inhalation of aerosolized DEA, which resulted in NOAELs of 50 mg/m^3 both for embryofetal effects and for maternal toxicity. However, OEHHA would prefer to use data other than a 10 day study for developing a chronic REL.

Comment 4. OEHHA should also ensure that the draft toxicity summary adequately characterizes DEA's physical characteristics. OEHHA's draft summary states, for example, that DEA's vapor pressure is less than 0.01 mm Hg at 20 degrees Celsius. DEA’s vapor pressure is, however, much lower - less than 0.00015 mm Hg at that temperature. OEHHA should revise the summary to correct this error. The public must be provided with accurate information regarding DEA's vapor pressure because it ensures that ambient air concentrations of DEA are extremely low.

Response. The commentator requests that we be more accurate in reporting the vapor pressure of DEA. Indeed HSDB (1997) reports the value of 0.00014 mm Hg at 25°C, which is found in Dow Chemical’s Alkanolamine Handbook (1980). OEHHA will revise the value.

Chemical Manufacturers Association – Arsenic

Comments on the chronic REL for **arsenic** were made by the Arsenic Acid Task Force of the Chemical Manufacturers Association Biocides Panel in a letter from Courtney M. Price dated January 28, 1998. The members of the Chemical Manufacturers Association Biocides Panel Arsenic Acid Task Force are: American Chrome & Chemicals; Chemical Specialties, Inc.; Hickson Corporation; J.H. Baxter & Company; Osmose Wood Preserving, Inc.; Occidental Chemical Corporation; Peninsula Copper Company; and Phibro-Tech, Inc. OEHHA proposed a chronic REL of 0.03 $\mu g/m^3$ based on reduced fetal body weight in mice exposed to arsenic during days 9-12 of gestation.

Comment 1. The Task Force has reviewed the OEHHA draft chronic inhalation and oral Reference Exposure Level (REL) for arsenic. With regard to the chronic inhalation REL, the Task Force is concerned that OEHHA's analysis relies primarily on one study and fails to account for the well-known differences in toxicity among arsenic compounds based on the chemical oxidation state and the differences in animal metabolism of arsenic. Similarly, the Task Force is concerned about the development of an REL under the "Hot Spots" program that is dependent on oral exposure, as wells as the primary reliance in the chronic oral REL on the Taiwanese drinking water studies, especially in light of questions raised about those studies. The Task Force's concerns about each of these points is discussed in more detail below. The Task Force asks that OEHHA carefully consider these comments and make the appropriate revisions to the chronic REL for arsenic.

Response. OEHHA staff recognize that there are differences in toxicity among arsenic compounds based on the chemical oxidation state. However, in the Hot Spots program industries do not speciate their arsenic emissions. Also there are differences in animal metabolism of arsenic. A PBPK model is needed to address this but only one has appeared in the peer-reviewed literature. OEHHA staff address the more detailed comments below.

Comment 2. OEHHA's chronic inhalation REL for arsenic is based primarily on a single publication by Nagymajtenyi et al. that describes the results of an inhalation developmental toxicity study in mice exposed to arsenic trioxide (As_2O_3). In this study, pregnant mice were exposed to trivalent inorganic arsenic (As,O) at concentrations of 28.5, 2.9 or 0.26 mg/m^3, which equates to total arsenic concentrations of 21.6, 2.2 or 0.2 mg/m^3 as arsenic. Even if one discounts maternal toxicity and considers delayed ossification as a fetal malformation, adverse effects were seen at the highest dose level only:

As_2O_3, mg/m^3 Exposure	As mg/m^3 Exposure	Fetal effect reported
28.5	21.6	29% (fetal body weight; delayed ossification)
2.9	2.2	9% (fetal body weight)
0.6	0.2	3% (fetal body weight)

Only the effects observed at the highest dose have biological significance and of those, only reduced fetal body weight can be viewed as meaningful because the recoverability of the delay in bone maturation was not assessed in the study. Weight decrements of 9% and certainly 3% are not biologically meaningful.

OEHHA interpreted the Nagymajtenyi data as demonstrative of an adverse effect at each dose level; accordingly, a No-Observed-Adverse-Effect-Level (NOAEL) was not considered in the interpretation of the study data. Also, well-known differences in toxicity among arsenic compounds based on the chemical oxidation state and differences in animal metabolism of arsenic were not taken into account by OEHHA in the proposed arsenic chronic inhalation REL.

Response. The weight decrements of 9.9% and 3% were both statistically significant. A weight difference of 9.9% may be biologically meaningful in a very small, developing animal. The weight decrement of 3% might not be biologically significant if the loss is generally distributed. If it were specific, it could be. In humans, the logarithm of infant mortality (death) increases linearly as birth weight decreases from 3500 to 1000 grams (Hogue *et al*., 1987; Rees and Hattis, 1994). This log-linear relationship exists on both sides of the weight (2500 g) conventionally used as a cutoff defining low birth weight. There is no evidence for a threshold. Thus any reduction in fetal weight is a cause for concern since it increases mortality. (Hogue CJ, Buehler JW, Strauss LT, Smith JC. Overview of the National Infant Mortality Surveillance (NIMS) project--design, methods, results. Public Health Rep 1987 Mar-Apr;102(2):126-138; Rees DC, Hattis D. Chapter 8. Developing Quantitative Strategies for Animal to Human Extrapolation. In: Principles and Methods of Toxicology. Third Edition. AW Hayes, editor. New York: Raven, 1994). In the absence of certainty, OEHHA staff take the health protective approach that the reduced weight effect in the animal fetuses may be biologically significant.

In order to investigate the effects of environmental arsenic on human reproduction, Ihrig et al. (1998) conducted a hospital-based case-control study of stillbirths in a central Texas community. (Ihrig MM, Shalat SL, Baynes C. A hospital-based case-control study of stillbirths and environmental exposure to arsenic using an atmospheric dispersion model linked to a geographical information system. Epidemiology 1998 May;9(3):290-294). The community included a facility with a more than 60 year history of producing arsenic-based agricultural products. Data were collected on 119 stillbirth cases and 267 controls (randomly selected from healthy live births at the hospital, matched for year of birth). Arsenic exposure levels were estimated from airborne emission estimates and an atmospheric dispersion model; the results were linked to a geographical information system (GIS) database. Exposure was linked to residence address at time of delivery. A conditional logistic regression model was fit to the data including maternal age, race/ethnicity, parity, income group, exposure as a categorical variable, and exposure-race/ethnicity interaction. The prevalence odds ratio (OR) for stillbirths observed for Hispanics in the high-exposure group (>0.1 $\mu g/m^3$ As) was 8.4 (95% confidence interval = 1.4-50.1). Based on these statistically significant results in people, the proposed REL of 0.03 $\mu g/m^3$ for arsenic does not appear to be too conservative

since LOAEL/NOAEL and intraspecies UFs would need to be applied to the human data to develop a chronic REL.

Comment 3. According to Garcia-Vargas and Cebrian (in Toxicology of Metals, 1996) and the US EPA (EPA, 1984), inorganic trivalent arsenic is generally regarded as being more acutely toxic than inorganic pentavalent arsenic. According to Marie Vahter (in Arsenic Exposure and Health, 1994), a prominent and perhaps leading authority on arsenic metabolism: The methylation of inorganic arsenic in mammals functions as a detoxification mechanism. The methylated metabolites are less acutely toxic than inorganic arsenic. They are also less reactive with tissue components and faster excreted in urine than is inorganic arsenic.

The inorganic arsenic, especially As(III), is the main form of arsenic interacting with tissue constituents. This means that factors influencing the methylation (of arsenic) may influence arsenic toxicity.

Vahter presents comparative metabolism data that show mice methylate inorganic arsenite (trivalent arsenic) about 3.6 times more efficiently than humans for a given dose of arsenic (Vahter, 1994).

Response. Comment noted. OEHHA acknowledges that there are differences in metabolism and in toxicity between trivalent and pentavalent arsenic. However, arsenic emissions are not speciated in the Hot Spots program. Thus we prefer to use data on the more toxic species.

Comment 4. OEHHA should have considered these facts in proposing a chronic REL for arsenic. Using these facts, the derivation of a chronic inhalation REL for arsenic would be:

LOAEL	2.2 mg/m^3 as arsenic (Nagymajtenyi, 1985)
NOAEL	0.2 mg/m^3 as arsenic (Nagymaitenyi, 1985)
LOAEL Uncertainty Factor	1
Interspecies Uncertainty Factor	3.6
Intraspecies Uncertainty Factor	10
Cumulative Uncertainty Factor	36

Inhalation Reference Exposure Level 0.2 mg/m^3 x 36 = 7.2 mg/m^3

OEHHA should revise the chronic inhalation REL for arsenic to take into account the points presented above and repropose a chronic inhalation REL of 7.2 mg/m^3 total arsenic. An REL of 7.2 mg/m^3 takes into account relevant inhalation toxicity data for arsenic compounds and contains a safety factor in addition to those listed by California. In OEHHA's calculations, the REL is based on trivalent inorganic arsenic toxicity data and assumes that all exposure to arsenic is to the trivalent form - the most toxic form of inorganic arsenic. Real-world exposures are not limited exclusively to trivalent arsenic, but include exposure to the less toxic forms as well. Thus, calculating the chronic inhalation REL using the

above-referenced conservative assumptions will protect against adverse effects from trivalent arsenic, which also overprotects against exposure to all other forms of arsenic.

Response. The commentator appears to have confused calculation of a REL with calculation of a Margin of Exposure. The chronic REL of 7.2 mg/m^3 proposed in the comment is 720 times the ACGIH TLV for arsenic of 0.01 mg/m^3. The 50 minute LC_{50} for arsenic in mice (acute lethality) is 99 mg/m^3, only 12x the chronic REL proposed by the commentator. If the suggested NOAEL of 0.22 mg/m^3 is divided by the suggested cumulative UF of 36, a tentative REL of 5.5 $\mu g/m^3$ is estimated. However, OEHHA staff do not agree with the choice of the NOAEL for the study. In addition the suggested interspecies UF would require special consideration.

In the absence of a superior study in the peer-reviewed literature on which to base a REL, the chronic inhalation REL proposed for arsenic is still 0.03 $\mu g/m^3$

Comment 5. OEHHA has reestablished, in addition to an inhalation REL, an oral REL for arsenic. As a threshold matter, the Task Force objects to the inclusion of a chronic oral REL in the guidelines at all, since the purpose of the guidelines is to derive risk levels for airborne toxic contaminants. These risk levels, in turn, will be used to characterize the hazards associated with routine industrial releases of chemicals to the atmosphere. Nothing in the "Hot Spots" program requires or authorizes OEHHA to develop oral RELs. Even if OEHHA was otherwise authorized to develop oral RELs, the chronic oral REL for arsenic is based exclusively on the US EPA Oral Reference Dose (RfD) for arsenic in drinking water. The US EPA RfD for arsenic is based on the Taiwanese drinking water studies published by Tseng (1968,1977). These studies have been the subject of much scientific review and are not without criticism as to methodology (analytical chemistry and epidemiology) and applicability to US populations. This criticism is presented by Brown (1994, 1996) and suggests that reliance on the Taiwanese studies to establish US regulatory limits for arsenic exposure is not appropriate because of the necessity to extrapolate from high-dose exposures to low-dose exposures and across cultural lines.

Specifically, Brown has stated that a more detailed exposure classification than previously used is needed for reliable descriptions of cancer mortality in Taiwanese villagers and arsenic concentrations in drinking water. Brown also states that the cancer mortality dose-response curve for the Taiwanese cohorts is nonlinear at the low-dose end (arsenic drinking water concentrations of <0.05mg/L) suggesting that there may be a low-dose threshold for the observation of human cancer. US EPA surveys of US drinking water have shown that 95% of the samples collected and analyzed have arsenic levels of less than 0.005mg/L; the highest value recorded was 0.082mg/L (Borum and Abernathy, 1994). Finally, Brown has pointed out evidence that arsenic may be adequately methylated and detoxified at drinking water concentrations below 0.05mg/L. The adverse health risks, particularly cancer, ascribed to ingestion of arsenic in drinking water may be inaccurately stated for US populations when based on the Taiwanese studies. Accordingly, OEHHA's reliance on the Tseng studies (via US EPA) is inappropriate for establishing a chronic oral REL, even if oral RELs were authorized under the "Hot Spots" program.

Response. The Air Toxics Hot Spots risk assessments of facilities include an analysis of all potential pathways of exposure. Oral RELs are needed in the Hot Spots program to do multipathway analysis of chemicals that are emitted as particulates. Not only are these materials inhaled but they also are deposited on and ingested from home-grown crops and from soil, and can be absorbed following dermal contact with contaminated surfaces. Multipathway analyses have been part of the Hot Spots program since its inception. Proper parameters to use are discussed in the 1993 CAPCOA Guidelines and in the draft Exposure Assessment and Stochastic Analysis Technical Support Document. USEPA RfDs are being used as oral RELs. The Risk Assessment Advisory Committee (RAAC) recommended that CalEPA harmonize where possible with USEPA on risk assessment. Governor's Executive Order W-137-96 concerned the enhancement of consistency and uniformity in risk assessment between Cal EPA and USEPA. Use of RfDs as oral RELs was one action that OEHHA took to address the RAAC recommendations and to implement the Executive Order.

Comments on the deficiencies in the RfD for arsenic should be directed to USEPA.

Chemical Manufacturers Association (CMA) - Carbon Disulfide Panel

Comments on the chronic REL for **carbon disulfide** were made by the CMA Carbon Disulfide Panel. OEHHA proposes use of the US EPA Reference Concentration of 700 $\mu g/m^3$, based on effects on the nervous system

Comment 1. These comments address the chronic toxicity summary and proposed reference exposure level (REL) for carbon disulfide presented in the "Air Toxics Hot Spots Program Risk Assessment Guidelines Part III: Technical Support Document for the Determination of Noncancer Chronic Reference Exposure Levels" (Guidelines). In restricting its comments to the toxicity summary and related REL, however, the Panel does not endorse the risk assessment practices, policies, and methods set forth in those Guidelines in whole or in part. Moreover, the Panel reserves the right to challenge OEHHA's use of the Guidelines to assess or regulate any chemical, including carbon disulfide.

OEHHA should not characterize the database supporting the REL as "limited." The carbon disulfide database is robust, as other agencies reviewing it have found. In its toxicity summary, OEHHA states that one major uncertainty in the REL is the "limited nature of health effects studies conducted. The database supporting the REL cannot fairly be characterized as "limited," however, given the numerous epidemiological and animal studies of carbon disulfide‘s inhalation effects. The findings of other agencies that have reviewed this substantial body of data support this conclusion. For example, in proposing a test rule under Section 4 of the Toxic Substances Control Act (TSCA) for chemicals listed as hazardous air pollutants (HAPs) under the federal Clean Air Act (CAA), EPA decided not to pursue toxicity testing for carbon disulfide. EPA stated unequivocally that carbon disulfide has "a large inhalation toxicology database." As another example, the Toxicological Profile prepared by the Agency for Toxic Substances and Disease Registry (ATSDR) reviewed the numerous animal and human studies conducted with carbon disulfide. With respect to neurological effects, for example, the Toxicological Profile discussed occupational epidemiological studies in a variety of settings and summarized a number of animal studies. With respect to other endpoints, the Toxicological Profile stated that human data provide information on acute and chronic effects from inhalation exposure to carbon disulfide, as well as immunologic, neurologic, developmental, and reproductive effects. Animal inhalation data are available on intermediate systemic, neurologic, developmental, and reproductive effects.

Moreover, the key epidemiological study underlying the proposed REL, conducted by Johnson et al. (1983), has been subject to both external and internal peer review, and EPA concluded in its Integrated Risk Information System (IRIS) that it is "well designed and conducted, uses adequate numbers of subjects, and is well supported by other occupational studies examining the same effect. Because of its greater confidence in human data, ATSDR relied on this study to establish a minimum risk level (MRL) for carbon disulfide. In light of the large body of human and animal data on carbon disulfide's inhalation effects, and given the review of and reliance on by other agencies of the key study on which the REL is based, OEHHA should delete the reference to the "limited nature" of health effects studies conducted.

Response. OEHHA has reexamined the description of the quality of the health effects database and agrees with the commentator that the term "limited" is not warranted. The text has been changed to reflect this. However, the database for this chemical also can not be viewed as exhaustive. As noted by US EPA, significant areas of uncertainty include the exposure histories of workers examined in the key study and the possibility of developmental effects in humans.

Comment 2. OEHHA should eliminate the use of the modifying factor of 3. This factor is not needed, given carbon disulfide's extensive database. The Panel also believes that no uncertainty or modifying factor should be applied to address any purported deficiencies in the toxicological database for carbon disulfide. OEHHA does not discuss why it has accepted EPA's 3-fold modifying factor for database deficiencies, or why any modifying factor at all is appropriate. Indeed, OEHHA itself has expressed skepticism about the propriety of any modifying factor to address purported database deficiencies. When deriving chronic RELs using its own Guidelines, OEHHA does not employ a modifying factor to address database weaknesses. Given the extensive toxicological database on carbon disulfide's inhalation effects, such an uncertainty factor is particularly inappropriate here.

Response. As a result of both scientific judgement and legislative mandate, OEHHA considers US EPA an authoritative scientific body whose prior scientific assessments carry great weight. Furthermore, OEHHA has been directed to harmonize with US EPA as regards guidance levels for exposure of the general public to chemicals by both the Risk Assessment Advisory Committee (RAAC) and Governor's Executive Order W-137-96. Minor differences in scientific conclusions between two agencies such as OEHHA and US EPA are likely to arise, but such differences add a burden to those attempting to address two differing sets of recommendations. Thus, unless the difference of opinion is substantial, OEHHA will incorporate US EPA guidance into its programs. This does lead to the result that risk assessment recommendations for two different chemicals may be based on slightly different assumptions, as noted by the commentator.

Comment 3. OEHHA should revise the chronic toxicity summary for carbon disulfide to provide a more balanced and accurate summary of the scientific database on carbon disulfide's chronic health effects. The Panel believes that the toxicity summary provided in EPA's recent Sector Notebook for the Plastic, Resin and Manmade Fiber Industry provides such a summary and urges OEHHA to adopt that discussion.

Response. The health effects reviews presented in the chronic reference exposure level document are not intended to be exhaustive but rather to highlight the most important scientific data. Information on health effects of and risk assessment guidelines for more than 100 chemicals are presented in the document, which totals more than 700 pages in length. In addition, for chemicals such as carbon disulfide which have previously been addressed by USEPA in its Reference Concentration (RfC) program, OEHHA gives considerable weight to

US EPA's position as a recognized authoritative body and in most cases has proposed adopting the USEPA RfC.

Comment 4. OEHHA's summary of "effects of human exposure from carbon disulfide" is inaccurate and misleading. OEHHA's chronic toxicity summary for carbon disulfide fails to provide a balanced or accurate summary of the scientific database on carbon disulfide's chronic health effects. For example, the summary of the section entitled "Effects of Human Exposure" states:

"[A] primary target of carbon disulfide (CS_2) toxicity is the nervous system. The major neurotoxic action of carbon disulfide is the development of mental disturbances, such as change of personality, irritability, and forgetfulness, often with accompanying neurophysiological and neuropathology changes after prolonged exposure. Alterations in behavioral indices have been historically associated with high levels of CS_2, often in the excess of 20 ppm."

OEHHA's summary is misleading in not stating clearly that it is only high levels of exposure, well in excess of current regulatory levels, that may result in such effects. EPA's recent Sector Notebook for the Plastic, Resin and Manmade Fiber Industry (Sector Notebook) more accurately states that long-term (chronic) exposure to high levels [of carbon disulfide] in excess of regulatory standards may result in peripheral nerve damage (involving the nerves that control feet, legs, hands, and arms) and cardiovascular effects. The Panel thus urges OEHHA to revise the summary, and in this regard, the Panel urges OEHHA to consider adopting the Sector Notebook summary.

Response. The examples cited do not indicate the OEHHA summary was inaccurate. The current TLV is 10 mg/m^3. However, the sections have been reviewed in light of the comment and changes made in the presentation to better clarify the type of exposures that have been associated with observable adverse health effects.

Comment 5. OEHHA's summary of carbon disulfide's reproductive toxicity is similarly misleading and inaccurate. With respect to this end-point, OEHHA says simply that "carbon disulfide causes reproductive toxicity in both males and females. This statement fails, however, to reflect accurately the robust database on carbon disulfide's potential reproductive toxicity and the scientific uncertainty regarding the no effect level that should be used based on these studies. Although there are substantial data bearing on carbon disulfide's potential reproductive effects, as discussed above, there remains substantial uncertainty about the significance of these effects and the no effect level that can be derived from these studies. This uncertainty should be reflected in any statements regarding carbon disulfide's potential reproductive toxicity.

Similarly, the EPA Sector Notebook notes that "[A] few studies contend that chronic exposure may also result in potential reproductive effects. The Panel urges OEHHA to revise its summary and in this regard to consider adopting the Sector Notebook summary,

which accurately reflects the scientific uncertainty underlying carbon disulfide's potential reproduction effects.

Response. Again, the examples cited do not demonstrate that the OEHHA summary was inaccurate. Similarly, however, the sections have been reviewed in response to the comment and changes made in the chapter to better clarify the evidence for reproductive toxicity from carbon disulfide exposures.

Comment 6. The Panel additionally urges OEHHA to review and rely on the following two recent publications on carbon disulfide's potential toxicity, which are appended as Attachments 1 and 2:

Price, B., *et al.* (1996). A Benchmark Concentration for Carbon Disulfide: Analysis of the NIOSH Carbon Disulfide Exposure Database. *Regulatory Toxicol. Pharmacol.* 24:171-176.

Price, B., *et al.* (1997). A Review of Carbon Disulfide Exposure Data and the Association between Carbon Disulfide Exposure and Ischemic Heart Disease Mortality. *Regulatory Toxicol. Pharmacol.* 26:119-128.

Response. The two papers cited have been reviewed and their findings have been summarized in the revised toxicity summary for carbon disulfide.

Chemical Manufacturers Association – Cresols Panel

Comments on the chronic REL for **cresols** were made by the Cresols Panel of the CMA in a letter from Courtney M. Price dated January 29, 1998. The members of the Cresols Panel are Concord Chemical Company, CRI Fine Chemicals, Dakota Gasification Company, General Electric Company, Merichem Company, Mitsui Petrochemicals (America) Ltd., PMC Specialties Group, Inc., and Sumitomo Chemical Americas, Inc. In the draft TSD OEHHA proposed a chronic REL of 4 $\mu g/m^3$ based on the Uzhdavini et al. (1972) discontinuous, 4 month inhalation study in rats which resulted in alterations in bone marrow cellularity.

Comment 1. As discussed in the appended comments, the Panel urges OEHHA to withdraw its draft toxicity summary and proposed reference exposure level (REL for cresol mixtures (cresols). The studies on which OEHHA has relied cannot support a REL, and cresols do not merit priority attention for evaluation or regulation. These comments address the chronic toxicity summary and proposed inhalation reference exposure level (REL) of 4 $\mu g/m^3$ for cresol mixtures (cresols) presented in the Guidelines. In restricting its comments to the toxicity summary and related REL, however, the Panel does not endorse the risk assessment practices, policies, and methods set forth in those Guidelines in whole or in part. Moreover, the Panel reserves the right to challenge OEHHA's use of the Guidelines to assess or regulate any chemical, including cresols.

The Panel urges OEHHA to withdraw its draft toxicity summary and proposed REL for cresols for the following reasons:

- The proposed REL for cresols is based on a single, poorly reported study that does not comply with Good Laboratory Practices, and other data do not support the findings of that study or the proposed REL.

- In any event, cresols do not merit priority attention for assessment or regulation because they are present in the ambient air only in very small concentrations. Available data show very low workplace and general population exposure concentrations - well below those that implicate health concerns.

Response. The detailed comments are individually addressed below.

Comment 2. The Uzhdavini et al. and Kurliandskii et al. studies are of insufficient quality to derive or support a REL. OEHHA derived its REL for cresols from a Russian inhalation study conducted with rats in 1972. OEHHA refers to a second Russian study of the same era as providing support for the REL. Neither study, however, is of sufficient quality to derive or support a REL and OEHHA should, therefore, withdraw the proposed REL.

The Uzhdavini et. al (1972) study is of insufficient quality to support a REL. OEHHA's proposed chronic toxicity REL for cresols is based on the Uzhdavini et al. (1972) observations regarding o-cresol exposure in rats. Uzhdavini et al. reported that rats exposed to 9 mg/m^3 o-cresol by inhalation showed an increase in white blood cells, and a statistically

significant change in the leuko-to-erythmo ratio in the bone marrow. The authors also reported an extension of hexobarbital narcosis duration in treated animals. The Uzhdavini et al. study - which was performed more than 25 years ago in the then Soviet Union under conditions that do not approximate current scientific methods and standards - cannot be used to support a REL. The study findings are difficult to interpret for a variety of reasons. The study parameters reported are vague; the specific data are not included (only summary statements) and the conclusions relate only to imprecisely measured concentrations of "vapor/ aerosol." Additionally, the published study report does not describe chamber generation methods, precise analytical methods, exposure details, animal characteristics (weight, age, sex, strain), observational information (times, frequency, duration, specific conditions examined), or specific experimental conditions. From the summary nature of the information presented and the absence of information about the study design, a dose-response relationship cannot be determined. This study would be judged inadequate under GLP requirements for use in determining potential risk to humans. Relying on the study clearly contravenes OEHHA's own Guidelines, which state unequivocally that any animal data supporting a REL "should have a clear rationale and protocol, use [GLP] Standards, and use appropriate analysis methods.

With respect to the specific findings at issue, the results - even if credited - do not indicate adverse effects from exposure to cresols. For example, while white blood cell counts reportedly were elevated in some treated animals, these effects were observed in male animals only, and blood counts returned to normal after cessation of exposure. The reversibility of the effects, and the fact that effects were seen in male animals only, suggests that they were neither serious nor clearly associated with exposure to cresols. Moreover, the authors report with respect to this study that no changes were found in the leuko-erythmo ratio in the second species tested - guinea pigs. Additionally, Uzhdavini reported that:

- the vapor pressure of cresols was so low that acute inhalation toxicity could not be induced with vapor alone, only with a mixed vapor aerosol of cresols could adverse effects be produced;
- nonspecific irritation was produced in the respiratory tract by high concentrations of cresols aerosols;
- in repeated exposure experiments, cresols did not exhibit cumulative toxicity; and
- in rats, where recovery studies were made, recovery from cresols effects (blood parameters) was seen.

Thus, the Uzhdavini et al. findings simply cannot support OEHHA's proposed REL. Indeed, other agencies have discounted the Uzhdavini et al. (1972) study observations regarding o-cresol exposure in rats, as well as the additional limited information reported in the Uzhdavini study regarding effects from inhalation exposure to o-cresol in several species, including humans. [For example, the study reported a human threshold for respiratory irritation (dryness, constriction in the nose, irritation of the throat, a taste in the mouth) of 6 mg/m^3 (1.4 ppm) Uzhdavini et al. (1972).] The American Conference of Governmental Industrial Hygienists (ACGIH) considered the Uzhdavini et al. study, but elected not to rely on it to establish its 8-hour threshold limit value (TLV) for exposure to cresols of 22 mg/m^3 (5 ppm). Similarly, the National Institute for Occupational Safety and Health (NIOSH) rejected

the Uzhdavini data when it recommended an "immediately dangerous to life or health" (IDLH) population exposure limit of 1,123 mg/m^3 (250 ppm), and a number of countries, in addition to the United States, have established inhalation exposure levels for cresols at 22 mg/m^3.

ACGIH (1991) (Documentation of the Threshold Limit Values and Biological Exposure Indices (1991) at 341) noted that eight of ten human subjects exposed to 1.4 ppm of o-cresol in the Uzhdavini et al. study complained of upper respiratory tract irritation, but criticized the study because the minimal exposure levels and duration associated with the irritation had not been reliably documented. The U.S. Occupational Safety and Health Administration (OSHA) also has established a time-weighted average (TWA) for all cresol isomers of 5 ppm (29 C.F.R. Part 1910).

Moreover, the U.S. Environmental Protection Agency's (EPA) Health Effects Assessment for Cresols, on which OEHHA also relied in drafting the toxicity summary, has criticized the two Russian studies. Because of the absence of detail regarding the severity or type of changes reported, EPA concluded that "it would be imprudent to use either of these studies to derive a value for an AIS [Acceptable Intake Subchronic] without further information. EPA also noted that NIOSH had concluded that the two Russian studies "were considered inadequate as a result of the incomplete presentation of experimental design and the confusing presentation of results.

Given the many defects and omissions in the Uzhdavini et al. study discussed above, the results cannot be deemed reliable for predicting the chronic health effects potentially associated with exposure to cresols. It is not surprising that the study has been accorded little weight in decision-making by regulatory agencies in the United States and elsewhere. OEHHA likewise should not rely on the results obtained in the Uzhdavini et al. study to reach conclusions about cresols, potential chronic effects, or to derive a REL.

Response. OEHHA originally selected the Uzhdavini et al. (1972) study in order to base as many chronic RELs as possible on inhalation data. The study reports unusual endpoints by today's standards. However, the study had been reported on by both NIOSH and ATSDR in their documents. Therefore the study was selected as the basis for the REL despite its shortcomings. On reconsideration we have decided to base the chronic REL on the USEPA RfD. The U.S. EPA RfD was based on 90 day animal toxicity studies done by USEPA and reported in 1986.

The commentator states: "The reversibility of the effects, and the fact that effects were seen in male animals only, suggests that they were neither serious nor clearly associated with exposure to cresols. Moreover, the authors report with respect to this study that no changes were found in the leuko-erythmo ratio in the second species tested - guinea pigs." OEHHA staff do not agree that these are useful criteria for addressing toxicity results. Elevated carboxyhemoglobin levels are both potentially adverse and reversible. Certain chemicals have the propensity to be more toxic to, or only toxic to, one sex versus the other. Limonene and dichlorobenzene cause kidney tumors only in rats and only in male rats. Other agents may cause adverse effects in only one species or strain or not cause adverse effects in

only one species. Benzo(a)pyrene is highly carcinogenic in all species and strains except DBA2 mice. Thalidomide is teratogenic except in rabbits. Even the lethal level of a chemical can vary among species. The LD_{50} of TCDD varies widely (guinea pig = 0.001-0.002 mg/kg; male rat = 0.022 mg/kg; female rat = 0.045 mg/kg; mouse = 0.114 mg/kg; hamster = 1.157 mg/kg).

Comment 3. The Kurliandskii et al. (1975) study is of insufficient quality to support a REL. Although OEHHA did not rely on the Kurliandskii et al. (1975) study to derive the REL, it cited the study as further support for the REL and as evidence that chronic adverse health effects may occur in animals exposed to cresols at levels lower than those reported by Uzhdavini et al.

The Kurliandskii et al. study, however, suffers from the same inadequacies that plague the Uzhdavini et al. study. Among other methodological defects, the study lacks information necessary to interpret the findings; fails to report how many hours per day animals were exposed; and fails to report whether the exposure was daily. NIOSH found the findings difficult to assess "because of unexplained differences in the experimental results" and "unanswered questions concerning the procedures used to measure central nervous system function." Like the Uzhdavini et al. study discussed above, the Kurliandskii study also fails to comply with fundamental GLPs and, pursuant to the OEHHA Guidelines, is thus inadequate to derive or support a REL.

Response. OEHHA agrees that the Kurliandskii et al. study also has shortcomings. In addition it indicates that 0.05 mg/m^3 is a LOAEL and 0.0052 mg/m^3 is a NOAEL for some endpoints, whereas 9 mg/m^3 was considered a LOAEL in the Uzhdavini et al. study.

Comment 4. Other data show no adverse effects from exposure to cresols. Not only do the Uzhdavini et al. and Kurliandskii et al. studies not support a REL, but other data show no adverse effects following inhalation exposure to cresols. These include:

- Mellon Institute of Industrial Research (1949): In this acute toxicity study conducted with rats, animals were exposed to a saturated vapor of m-cresol on a single day for eight hours (saturated vapor concentration of m-cresol at room temperature is estimated to be 0.3 mg/L (300 mg/m^3 or 68.2 ppm)). No effects were observed, except that one rat failed to gain weight.

- CONOCO (1975): Rats exposed to a single 6-hour exposure of o-cresol vapor by inhalation at doses up to 4,500 ppm (19,800 mg/m^3 or 19,800,000 mg/L) did not experience mortality or clinical signs of toxicity other than eye irritation, which cleared up within 24 hours after exposure.

Similarly, a number of oral studies conducted with cresols show none of the blood chemistry changes reported in the Uzhdavini et al. (1972) study. These studies include:

- Hornshaw et al. (1986) Spleen weight and white blood cell (WBC) count were unaffected when o-cresol was administered in feed at doses up to 400-720 mg/kg/day in ferrets and 320-480 mg/kg/day in mink. Similarly, no effect was seen on spleen weight or WBC count in a reproduction study where mink were administered 105-190 mg/kg/day of o-cresol in feed for six months.

- Microbiological Associates, Inc. (1988a, b, c): No mortality or illness due to infections were seen in mice or rats receiving either o-cresol or m/p-cresol mixture in feed for 90 days at concentrations up to 20,000 ppm or 30,000 ppm (for mice and rats, respectively). Hematology parameters including WBCs, lymphocytes, monocytes, and eosinophils were unremarkable at all dose concentrations. In mice, changes in spleen or thymus were observed at 15,000 and 30,000 ppm, but there were no changes observed following gross or microscopic examination.

- Bushy Run Research Center (BRRC) (1989a, b, c). Two-generation reproduction studies were conducted by oral gavage in rats with each cresol isomer. The dose levels used achieved systemic toxicity in adult animals (lethality). First and second generation parents were necropsied, and selected organs, tissues, and all gross lesions were examined. The adrenal gland, spleen, mandibular and mesenteric lymph nodes, pituitary, thyroid, and thymus region were among the tissues examined. The study pathologist reported no compound-related effects in any of these tissues for any of the cresol isomers. [BRRC (1989a). Two-generation reproduction study of o-cresol (CAS No. 95-48-7) administered by gavage to Sprague-Dawley (CD) rats. Project Report 51-614. Unpublished data submitted to the Chemical Manufacturers Association Cresols Panel. Washington, D.C.; BRRC (1989b). Two-generation reproduction study of p-cresol (CAS No. 106-44-5) administered by gavage to Sprague-Dawley (CD) rats. Project Report 52-512. Unpublished data submitted to the Chemical Manufacturers Association Cresols Panel. Washington, D.C.; BRRC (1989c). Two-generation reproduction study of m-cresol (CAS No. 108-39-4) administered by gavage to Sprague-Dawley (CD) rats. Project Report 51-634. Unpublished data submitted to the Chemical Manufacturers Association Cresols Panel. Washington, D. C. These data were submitted to EPA by Union Carbide. See Union Carbide Corporation, "Two-generation reproduction studies on ortho-, meta-, and para-cresols administered by gavage to Sprague-Dawley (CD) rats (final reports) with attachments and cover letter dated 12-06-89." TSCA 4 submission 40-8960311, microfiche number OTS0529224. Washington, D.C. OPPT, U.S. EPA (Nov. 9, 1989).]

- U.S. National Toxicology Program (NTP) (1992): In these studies, groups of mice and rats were administered oral doses of cresol isomers and mixture for 13 weeks. A full battery of hematology parameters were evaluated. No blood alterations were seen in rats exposed to o-cresol or a m/p-cresol mixture up to 30,000 ppm. Mice exposed to 20,000 ppm of o-cresol also displayed no hematological changes. Mice exposed to up to 10,000 ppm m/p-cresol showed a mild decrease in hemoglobin at study termination, but no blood changes similar to those reported by Uzhdavini. The author of the NTP study report concluded that the hematology changes observed in mice following exposure to m/p cresol were "largely unremarkable."

Response. The commentator presents 2 acute inhalation studies of 8 and 6 hours (Mellon and CONOCO, respectively), which showed no adverse effects, and several oral studies that indicate that cresols do not affect hematology parameters, which the Uzhdavini et al. study (1972) claimed cresols affect. As stated above, due to the shortcomings in the Russian studies OEHHA has decided to base the chronic REL on the U.S. EPA RfD.

Comment 5. Cresols are present in the ambient air at very low concentrations, and do not merit priority consideration for evaluation or regulation. The California Toxic Air Contaminants Program (Program) provides that, in evaluating the health effects of toxic air contaminants, OEHHA "shall give priority to the evaluation and regulation of substances based on factors related to the risk of harm to public health, amount or potential amount of emissions, manner of, and exposure to, usage of the substance in California, persistence in the atmosphere, and ambient concentrations in the community." Because cresols concentrations in the ambient air are very low - well below those that implicate health concerns -cresols merit neither evaluation nor regulatory action under the Program.

Response. ARB estimates that at least 12,000 pounds of cresols are released annually into California air. While statewide ambient concentrations are probably low overall, the Hot Spots program addresses ambient concentrations around facilities that are potential "Hot Spots" for emissions of cresols.

Comment 6. Available monitoring data show very low cresols ambient air concentrations Available data show very low cresols concentrations in the atmosphere, even near manufacturing facilities. Monitoring data include:

- EPA 1982 Survey: In a survey of volatile organic compounds (VOCS) found in the atmosphere commissioned by EPA, cresols were found near source-dominated sites (adjacent to chemical plants) at levels ranging from 0.1 to 30 parts per billion (ppb), with a median of 1.6 ppb. [Brodzinsky, R. and Singh H. (1982). Volatile organic Compounds in the Atmosphere: An Assessment of Available Data, EPA Office of Research and Development. Research Triangle Park, North Carolina]

- EPA's Hazardous Substances Databank Entries: Entries for cresols note that o-cresol was detected near a phenolic resin factory in Japan at a maximum concentration of 40 ppba8 ~ and that m-cresol and p-cresol were not detected at all in air samples taken in both urban and rural areas of western Colorado and Utah.

- Gordon (1976): On behalf of EPA, Gordon (1976) estimated cresols air concentrations at a hypothetical facility producing 80 million pounds of cresols annually and emitting 160,000 pounds of cresols per year - an amount greater than actual emissions reported by any one facility for 1994. The estimated air concentration 500 meters downwind of the hypothetical plant was 0.163 mg/m3 or 37 ppb - an amount well below the OSHA, ACGIH, and NIOSH limits for full day occupational exposures. Thus, the population

living near a major source is at a very low risk of exposure from industrial cresols emissions.

- Merichem Data: Merichem Company modeled cresols concentrations at its Houston facility in 1991. At 2,000 feet from the facility, at the fenceline, the concentration of cresol isomers was 38 pg/m^3. This is far below the OSHA, ACGIH, and NIOSH worker exposure limits (10,000 - 22,000 pg/m^3).

- ATSDR Toxicological Profile: In its 1992 Toxicological Profile discussion of general population exposure to cresols, the Agency for Toxic Substances and Disease Registry (ATSDR) concluded that "[m]onitoring data have not shown cresols to be widely occurring. .The median air concentration of o-cresol at source-dominated sites is 0.359 ppb for 32 samples."

The Program requires consideration of exposure data (including emissions data and data on estimated actual exposure) when selecting chemical substances for priority for evaluation and regulation. In light of their low documented emissions and exposure potential, cresols do not merit priority consideration for evaluation or regulation.

Response. It is encouraging that cresols are not wide-spread toxic air contaminants like benzene or butadiene. However, as stated above, the Hot Spots program addresses ambient concentrations around facilities that may be Hot Spots for emissions of cresols. Also cresols are not being given priority consideration.

Comment 7. Modeling data show that even under extreme conditions, highly unlikely to occur, exposure levels are very low. Accidental release modeling shows that even under extreme conditions, cresol vapors would quickly disperse to levels below regulatory levels of concern. Dakota Gasification Company modeled two accident scenarios using the ARCHIE computer program and assuming EPA's worst-case weather conditions of 68° F and 3.4 miles per hour wind speed. The first scenario modeled was a 100,000 gallon tank rupturing and 879,452 pounds of cresols spilling out within one minute. The cresols product temperature was modeled at 68°F. The model predicted that peak cresols concentrations at 1,536 feet (468 meters) from the tank would be 4 ppm (18 mg/m^3), which is below the previously established OSHA and ACGIH 8-hour average limit of 22 mg/m^3. At 2,333 feet (711 meters), the concentration would be only 2.1 ppm (9.3 mg/m^3), less than the NIOSH recommended 10-hour average limit of 10 mg/m^3.

The second scenario assumed that a distillation column failed instantaneously, releasing 75,762 pounds of cresols at 365°F. Modeled concentrations from this extreme scenario were 9.6 ppm (42 mg/m^3) at 2,194 feet (669 meters), which is well below the NIOSH IDLH of 250 ppm. By 3,450 feet (1,052 meters), the concentration is less than 5 ppm, and by 5,962 feet (1,817 meters), the modeled concentration is 2 ppm (8.8 mg/m^3), which is below the NIOSH recommended limit.

These modeled accidental release scenarios represent conditions under which the highest air concentrations of cresols could reasonably be expected (that is, large amounts released within a short interval of time during worst-case weather conditions) . Even under these extreme conditions, the modeled air concentrations of cresols in the near vicinity of the facility - concentrations which would persist for only a brief period of time - are on the order of concentrations which are considered acceptable for occupational exposure, i.e., acceptable for 40 hours per week.

The amount of cresols modeled to be released in the second scenario - 75,762 pounds - is more than the amount reported by most facilities as their annual emission quantity. The amount modeled as released in the first scenario - 879,452 pounds far exceeds the total reported cresols air emissions for all cresols manufacturing facilities for 1994. Clearly, then, cresols air concentrations in the vicinity of emitting facilities due to normal operations - that is, concentrations due to emissions of much smaller quantities over an extended period of time - are low, demonstrating that cresols should not be given priority consideration for evaluation or regulation under the Act.

Response. Comment noted. Again cresols are listed as listed Hot Spots chemicals. OEHHA staff attempted to develop as many health guidance values for Hot Spots chemicals as it could find data for. Since the industrial emissions of cresols are low, the ground level concentrations should be well below the chronic REL.

Comment 8. Cresols' physical characteristics ensure low concentrations in the ambient air. The physical characteristics of cresols help explain the very low concentrations found in the ambient air. Cresols air concentrations are limited by the short lifetime of cresols in the atmosphere. During the day, cresols are removed by reaction with hydroxyl radicals. At night, nitrate radical reactions predominate. ATSDR reports cresols half-lives (calculated from kinetic data) as being less than ten minutes at night and less than ten hours during the day. As ATSDR summarized, "cresols have a short residence time in both day- and night-time air; despite continual releases of cresols to the atmosphere, levels are probably low."

Because cresols air concentrations are so low and cresols so rapidly degrade when emitted, the Panel does not believe that cresols in the air present general population exposure concerns. Indeed, EPA stated that it "has also determined that cresols released to the atmosphere are not expected to create an exposure problem." EPA further stated: "Cresols are not expected to persist in the atmosphere because (1) cresols have low estimated half-lives of less than 1 day; (2) they are sensitive to photolysis; and (3) the water solubility of cresols may be expected to cause transport from the atmosphere to the soil or aqueous environment."

Accordingly, the available data show that exposure to cresols is uniformly low, that cresols have a low potential for "persistence in the atmosphere" within the meaning of the Act, and that cresols should not, therefore, be considered a priority for evaluation and regulation.

Response. OEHHA staff attempted to develop as many health guidance values for listed Hot Spots chemicals as it could find data for. Some chemicals will be of more concern than others. Cresols may well be of lesser concern than most listed compounds. Otherwise the commentator encourages OEHHA not to develop a chronic inhalation REL for cresols because there is not a problem. But OEHHA's way of addressing the situation is to develop a chronic inhalation REL and then compare it with ambient levels and with modeled levels around Hot Spots facilities to determine if the levels are above or below the REL.

Comment 9. A majority of the general population exposure is not the result of manufacturing operations, but naturally occurring and other sources. Cresols are ubiquitous in the environment. The vast majority of cresols found in the environment are derived from natural sources. Cresols are formed as metabolites of microbial activity and are excreted in the urine of mammals, including humans. They are present in the lipids of a number of different plant species and are found in foods such as tomatoes, cooked asparagus, cheese, butter, oil, red wine, coffee, and black tea. The Panel has estimated that releases from naturally-occurring sources of cresols are at least 15 million pounds a year - nearly an order of magnitude greater than the 1.7 million pounds reported on EPA's Toxics Release Inventory (TRI) in 1995.

Cresols also are products of combustion both from natural and anthropogenic sources. Cresols are released to the air from fires associated with lightning and volcanic activity.

According to a study performed on behalf of EPA, the "major ambient source [of cresols] is automotive emissions. Cresols also have been detected in stack emissions from municipal waste incinerators, in emissions from vegetable material incineration, in fly ash from coal combustion, in emissions from wood combustion, and in cigarette smoke.

Thus, there are numerous and diverse sources of cresols air emissions. A significant portion of cresols air emissions is due to natural sources -- which are not a concern of California's laws governing toxic air contaminants. Indeed, releases from natural sources dwarf those from manufacturing operations and further confirm that cresols emissions from industrial facilities should not be given priority for evaluation and regulation under the Program.

Response. Since the chronic REL will be compared to off-site, annual ground level concentrations based on modeled facility emissions and not on monitoring data, the background concentrations should not interfere with use of the REL. On the other hand, if cresols are monitored, facility contributions to the outdoor concentration could be detected based on comparison of upwind and downwind concentrations of cresols. Many other compounds emitted by facilities also have measurable natural emissions.

Comment 10. New NESHAPS will further reduce the potential for exposure to cresols. Concentrations of cresols would be expected to be greatest in the vicinity of a facility that emits relatively large quantities of cresols to the air. A review of the TRI database for cresols indicates that, of the facilities which individually have relatively high emissions of cresols,

nearly all are or will be subject to NESHAPs pursuant to the 1990 Clean Air Act (CAA) Amendments. Implementation of these NESHAPs will reduce even further potential exposure to cresols. (These attachments are based on data received from the EPA TRI User Support Library and the National Library of Medicine's ToxNet database.)

Attachments 2, 3, and 4 summarize the top twenty emitters of cresol isomers and mixed cresols in 1993, 1994, and 1995, as reported to the TRI. Only one facility in California was among the top twenty emitters in 1993 and 1994 and no California facility is among the top twenty emitters in 1995 - the latest year for which TRI data is available. In each year, the top twenty emitters represented nearly 100 percent of all reported cresol isomers emissions and between 60 to 94 percent of mixed cresols emissions. Review of the Standard Industrial Classification (SIC) codes associated with each of these facilities indicates that they already are, or soon will be, subject to maximum achievable control technology (MACT) standards under various NESHAPs.

Attachment 5 lists the twenty SIC codes with the highest reported TRI emissions of cresol isomers and mixed cresols in 1995. These SIC codes include primarily pulp and paper operations, chemical manufacturers, surface coating operations, and other sources that are or will be subject to MACT standards established by forthcoming NESHAPs. These include the following:

- The HON: Many manufacturers of cresols themselves are subject to the hazardous organic NESHAP (HON) for the Synthetic organic Chemical Manufacturing Industry. For individual isomers, between 33 percent and 81 percent of emissions are associated with facilities in SIC Code 2865 for Cyclic Crudes and Intermediates or SIC Code 2869 for Industrial Organic Chemicals, both of which are subject to the HON. Cresols emissions will be reduced even further because many of the principal uses of cresols are as chemical intermediates in the manufacture of other chemicals that also are subject to the HON.

- Metal Coil (Surface Coating) Source Category: In 1995, approximately 60 percent of emissions of m-cresol and 28 percent of p-cresol and mixed cresols air releases are reported by facilities in SIC Code 3357 - Nonferrous Wire Drawing and Insulating. Cresols are used at these facilities as a solvent for wire enamel. MACT standards for the Metal Coil (Surface Coating) source category are scheduled for promulgation by the year 2000.L3-1 This category will address hazardous air pollutants (HAP) emissions from facilities that engage in the surface coating of continuous metal strips that are packaged in a roll or coil, such as wire.

- Amino and phenolic resin production: O-cresol is used in the production of epoxy-o-cresol resins and other resins. A presumptive MACT standard has been issued for amino and phenolic resin production that will require controls for cresols emissions.

- Pulp and paper mills: Over 55 percent of releases of mixed cresols isomers in 1995 were produced as a byproduct of pulp, paper, paperboard, and related manufacturing operations. Air emissions from pulp mills, paper mills, and paperboard mills are now subject to a NESHAP. This NESHAP is expected to reduce VOC emissions, including cresols, by

716,000 megagrams (Mg) annually. Existing mills became subject to the NESHAP in December 1996 and reductions in emissions will be reflected in future TRI reports.

- Petroleum refining: Cresols are produced as a byproduct of petroleum distillation. A NESHAP for petroleum operations has been promulgated and is expected to reduce total air emissions by 59 percent.

- Agricultural chemical production: Cresols are used in the production of agricultural chemicals such as 4,6-dinitro-o-cresol, which are subject to MACT controls.

- 4-chlor-2-methyl phenoxyacetic acid production: Cresols are used in the production of 4-chlor-2-methyl phenoxyacetic acid, for which MACT standards will be issued.

- Anthropogenic sources of cresols: Cresols also are produced as a byproduct of various combination operations. These sources of cresols will be reduced by MACT standards for hazardous waste boilers and incinerators; and off-site waste recovery operations.

In summary, most of the individual sources of cresols emissions will be regulated under a NESHAP within the next few years. The Panel believes that cresols emissions also will be reduced significantly in the near future as a result of voluntary efforts undertaken by industry. Panel members who are CMA member companies, for example, are committed to CMA's Responsible Care program, pursuant to which they have agreed to reduce emissions continually. All of these efforts will reduce concentrations of cresols in the ambient air and the need for evaluation or regulatory action under either the Program or the Act.

Response. OEHHA acknowledges that many individual emission sources of cresols will be regulated under various NESHAPs. A chronic REL will still be useful to gauge how far below the health benchmark the ambient concentration of cresols actually falls. In addition there are other environmental sources of cresol, such as cigarette smoke, for which a chronic REL will be useful as a health benchmark.

Comment 11. Measures implemented to reduce ozone levels will reduce emissions that include cresols from mobile and stationary sources. During the past several years, EPA has implemented an aggressive set of programs for achieving the National Ambient Air Quality Standard (NAAQS) for ozone, driven in large part by the new nonattainment provisions enacted by the 1990 CAA Amendments. These programs address ozone precursor emissions from both stationary and mobile sources, and thus are directed toward the reduction of smog levels in affected areas. The very low environmental concentrations of cresols will fall even lower as EPA makes continuing progress toward attaining the NAAQS for ozone, thus further reducing smog exposure levels in current "nonattainment" areas. EPA recently issued a final rule that has tightened the NAAQS for ozone, for example.

These programs will reduce cresols emissions, to which the general population is exposed, from automobile and diesel exhaust, coal-fired power plants, and other operations. These measures will reduce the levels of VOCs, such as cresols, and their contribution to

ozone formation and to urban smog. Since actual emissions inventory data (and TRI data) must be considered in selecting chemical substances for priority evaluation and regulation, these current and future reductions in cresols emissions further demonstrate the inappropriateness of according priority treatment to cresols.

Response. Cresols are not being given priority treatment. OEHHA staff developed health guidance values for as many chemicals as possible listed under the Hot Spots program, which includes cresols. OEHHA has decided to base the chronic REL, not on the Uzhdavini et al. (1972) study, but on the USEPA RfD. The U.S. EPA RfD was based on 90 day toxicity studies done by USEPA and reported in 1986. The RfD is 0.05 mg/kg/day and the equivalent chronic REL is 180 $\mu g/m^3$. The critical effects are decreased body weight and neurotoxicity and the target organ is the nervous system.

Chemical Manufacturers Association – Diisocyanates Panel

Comments on the Proposed Toxicity Summaries and Reference Exposure Levels for **methylene diphenyl isocyanate (MDI) polymer** and **2,4- and 2,6-toluene diisocyanate (TDI)** were made by the Chemical Manufacturers Association Diisocyanates Panel. The Dissocyanates Panel represents the major domestic producers of methylene diphenyl isocyanate ("MDI") and toluene diisocyanate ("TDI"). Members of the Panel are: ARCO Chemical Company; BASF Corporation; Bayer Corporation; The Dow Chemical Company; and ICI Americas, Inc. OEHHA used the original USEPA RfC of 0.02 $\mu g/m^3$ based on hyperplasia of the olfactory epithelium in rats as the chronic REL for MDI polymer. For TDI OEHHA used the original USEPA RfC of 0.07 $\mu g/m^3$ based on decreased lung function in occupationally exposed workers as the chronic REL.

Comment 1: CALCULATION OF THE REL FOR POLYMERIC MDI. OEHHA's proposed Chronic Toxicity Summary and REL for polymeric MDI are based on the U.S. EPA's IRIS Summary and inhalation RfC. In April 1996, U.S. EPA announced a Pilot Program to update the IRIS database entries for eleven chemicals, including MDI. Pursuant to this program, U.S. EPA currently is reviewing and revising the IRIS summary and RfC for MDI. U.S. EPA expects to finalize the IRIS entry for MDI in February 1998. The Diisocyanates Panel urges OEHHA to defer its recommendation of an REL for MDI pending completion of the updated IRIS assessment and revised RfC.

In connection with the IRIS Pilot Program, U.S. EPA has circulated, for peer review, a draft Toxicological Review for MDI. The Draft Toxicological Review provides an updated summary of the available data for 4.4'-MDI ("monomeric MDI") and polymeric MDI. Based on this review, U.S. EPA proposed a revised RfC of 2×10^{-4} mg/m^3 for MDI. The proposed RfC was based on the adjusted NOAEL of 0.036 mg/m^3 for nasal effects reported by Reuzel *et al.* (1994). EPA recalculated the human equivalent concentration for the NOAEL group ("NOAEL HEC") in the Reuzel Study based on a revised Regional Deposited Dose Ratio (RDDR) for MDI of 0.453. U.S. EPA's revised NOAEL HEC for MDI is 0.016 mg/m^3. In calculating its revised RfC, EPA applied three uncertainty factors to the NOAEL HEC: (1) a factor of 10 was applied for intraindividual variation; (2) a factor of 3 was applied for database deficiencies; and (3) a factor of 3 was applied for intraspecies variation. Thus, U.S. EPA proposed an RfC for polymeric and monomeric MDI of 2×10^{-4} mg/m^3, rather than the value of 2×10^{-5} mg/m^3 that was previously calculated by EPA and on which OEHHA has relied for its proposed REL

The CMA Dissocyanates Panel met with U.S. EPA and submitted comments on the IRIS assessment for MDI. The Panel presented a benchmark analysis of the Reuzel data developed by Drs. Bruce Allen and Melvin Andersen of ICF Kaiser. Based on this analysis, the Panel calculated an RfC for MDI of 9.64×10^{-4} mg/m^3. The Panel urged U.S. EPA to adopt the benchmark methodology in calculating the RfC for MDI. The benchmark approach has received broad scientific support and U.S. EPA and others have recognized the advantages of the benchmark analysis as an alternative to relying on the NOAEL for non-cancer risk assessment. Advantages of the benchmark approach include reduced dependency on dose selection and spacing, more appropriate reflection of sample size, and better inclusion

of dose-response information. The Panel's comments to EPA presenting its proposed RfC calculation based on the benchmark approach are included in Attachment I (Allen and Andersen (1997) is appended thereto).

EPA has not yet finalized the Toxicological Review and RfC for MDI. However, EPA staff have informed Panel representatives that the Agency intends to use the benchmark analysis in deriving the RfC. The Panel recommends that the State of California similarly adopt the benchmark approach in establishing its REL for MDI. For the reasons presented in the Panel's comments to EPA, the Panel believes that the REL for MDI should be 9.6×10^{-4} mg/m^3.

Response: All USEPA Reference Concentrations (RfCs), available when the draft Technical Support Document (TSD) on chronic Reference Exposure Levels was released in October 1997, are being used as chronic RELs. RfCs are already used by the USEPA and by California's Department of Toxic Substances Control and were earlier incorporated by reference in Appendix F of the Emissions Inventory Criteria and Guidelines for the Air Toxics "Hot Spots" Program for use in screening risk assessments in the Hot Spots Program. These Guidelines were effective July 1, 1997. The Risk Assessment Advisory Committee (RAAC) recommended that CalEPA harmonize where possible with USEPA on risk assessment. Governor's Executive Order W-137-96 concerned the enhancement of consistency and uniformity in risk assessment between Cal EPA and USEPA. Use of RfCs as chronic RELs was one action that OEHHA took to address the RAAC recommendation and to implement the Executive Order. RfCs released after October 1997, including ones that are revisions of those in the October 1997 draft, will be evaluated for use in the Hot Spots program. Staff plan to review the scientific basis of each revised RfC when it becomes available and determine whether the scientific literature cited in the RfC is current. Appropriate RfCs will be submitted to the SRP for review and possible endorsement. OEHHA has reviewed the updated IRIS value for this chemical but it was released after October 1997 and OEHHA has not automatically accepted new RfCs. The new RfC for MDI is based on a benchmark dose approach, specifically a BMC10. OEHHA staff believe that consensus has not been reached on benchmark dose methodology. Both BMC10 and BMC05 approaches have their advantages and their proponents. The BMC10 is usually in the linear range of most models while the BMC05 more closely resembles a NOAEL than the BMC10 does. We will continue to review the updated RfC and present it to the SRP in our first update of chronic RELs. In the interim we have revised our proposed chronic REL from 0.02 $\mu g/m^3$ to 0.5 $\mu g/m^3$. (See next response.)

Comment 2: APPLICATION OF THE REL TO 4,4'-MDI MONOMER. OEHHA has stated that the "major limitation" of the proposed REL for MDI *"is* that it is based on data on exposures to MDI polymers." OEHHA states that, because "monomers frequently are much more toxic than polymers, ... OEHHA considers the value is only predictive of adverse effects of polymeric *MDI*. Effects of monomeric MDI may occur at concentrations several orders of magnitude lower than in the reported study on MDI polymer." This conclusion is not supported by the available data. The study by Reuzel *et al.* (1994) was conducted using the substance described commercially as polymeric MDI. This substance is not, however, a true

MDI polymer. Rather, it is more accurately characterized as MDI oligomer and is comprised of approximately 40 to 60% monomeric MDI and diminishing proportions of MDI dimer and other low-order MD1 oligomers. Polymeric MDI also is the more commercially relevant *NMI* product and accounts for greater than 90% of MDI sold domestically.

In addition, the pulmonary effects reported by Reuzel *et al.* (1994) are generally consistent with those reported in the whole body inhalation study of monomeric MDI in rats by Hoymann *et al.* (1995) (abstract only) which reported effects, which were related primarily to the impairment of *MDI* clearance, only in the highest dose group. The International Isocyanate Institute ("III") currently is sponsoring a comparison of the Hoymann data with the Reuzel (1994) data. Pathologists are reviewing the salient slides from the respiratory tract and the lung to assess the toxicology and also to understand the likely origin of the lesions observed in the two studies. Thus, it appears that monomeric *MDI* has a toxicity that is approximately the same as that of the polymeric MDI evaluated by Reuzel, and monomeric MDI does not have an effect level that is several orders of magnitude lower.

Further evidence of a lack of significant difference between polymeric and monomeric *MDI* is in parallel teratology studies performed by Garner *et* al. (1995) and Buschmann *et al*. (1996), respectively. In similar exposure scenarios, the no embryotoxic effect level was observed at 3 mg/m^3 for monomeric MD, and 4 mg/m^3 polymeric *MDI*. Maternal effects also were comparable between the polymeric MDI used in the Gainer study and the monomeric MDI in the Buschmann study. This further supports the conclusion that the toxicity of monomeric and polymeric MDI is similar.

Response: OEHHA has revised the text to account for the fact that nearly half the airborne material was monomer. OEHHA has also removed the database modifying factor of 10 since new studies on teratology have been published by Buschmann and others. The HEC calculation has also been revised. OEHHA has recalculated the chronic REL to be 0.5 $\mu g/m^3$.

Comment 3: 2,6- AND 2,4-TOLUENE DIISOCYANATE: ON-GOING EPIDEMIOLOGY STUDIES OF TDI-EXPOSED WORKERS. OEHHA also relied on the IRIS RfC in proposing an REL for 2,4- and 2,6-TDI. The RfC for TDI is based on a 1982 epidemiology study by Diem *et* al. showing lung function decrement in workers occupationally exposed to TDI. ARCO Chemical Company is looking into the feasibility of updating the Diem study. In addition, efforts currently are underway to complete several other epidemiology studies of TDI-exposed workers. Studies of workers in TDI production facilities are being conducted by Dow Chemical Company and BASF. These studies are expected to be completed in 1998. These additional studies will expand and improve the available epidemiology database related to the human health effects of TDI exposure. Thus, the Panel urges OEHHA to await the results of these studies before finalizing its REL for TDI.

Response: The adoption of USEPA RfCs by OEHHA was described above. OEHHA is pleased that better data may become available and will review the studies when they are finished. We assume that USEPA will do the same. As of April 1999 OEHHA had not

received the updated studies. The current chronic REL is based on the data currently available.

Comment 4: CALCULATION OF THE RfC FOR TDI. U.S. EPA based the RfC for TDI on the epidemiology study of occupationally exposed workers by Diem *et al.* (1982). In calculating the RfC, U.S. EPA relied on the analysis of the data from the Diem study by Hasselblad (1993) to derive a NOAEL of 0.006 mg/m (0.9 ppb) for TDI.

The Diisocyanates Panel does not agree with Hasselblad's conclusion that the Diem study supports a NOAEL of 0.006 mg/m^3. As explained in the attached letter by Dr. Gerald Ott of BASF Corporation (copy enclosed as Attachment 1), the statistical analysis of the epidemiology data conducted by Hasselblad is flawed in several respects. First, it selectively applies the data from Diem *et al.* and the other available epidemiology studies (in particular, by failing to consider the findings within the "former smoker" subpopulation). It also employs questionable procedures to estimate TDI concentrations consistent with the reported decline in forced expiratory volume (FEV1) and overlooks important biological parameters in deriving the NOAEL.

Moreover, the Diem Study was not designed to support the derivation of an overall NOAEL for TDI. The study evaluates cumulative exposure categories, which limits examination of exposure intensities. According to Garabrant and Levine (1994), the lung function decrement observed in the study was more likely related to episodic exposure to TDI at 6 levels above 20 ppb than to exposures in the 5 to 10 ppb range. Although the Diem *et al.* study does not permit the examination of exposure intensities, we believe that it is consistent with an overall NOAEL for TDI of 5 ppb.

The Panel further believes that U.S. EPA's use of the Diem Study to derive a NOAEL of 0.9 ppb for TDI is inconsistent with the TDI epidemiological database as a whole. The results reported by Diem *et al.* have not been replicated in larger and more recent studies of TDI-exposed workers, which rely on more precise methods for estimating exposures below 5 ppb. *see* Bulger *et al.* (1991); Jones *et al.* (1992); *see* also Allport *et al.* (1993). Overall, eight studies have failed to demonstrate lung function decrement from exposure to TDI at concentrations below 5 ppb. Thus, the overwhelming epidemiological evidence supports the conclusion that 5 ppb (0.036 mg/m^3) is the no-effect-level for exposure to TDI with decreased living function being the most sensitive endpoint.

Response: These concerns should be addressed to the USEPA for possible reevaluation of the RfC.

Comment 5: The Diisocyanates Panel believes that the additional studies currently being conducted will strengthen the TDI database and provide a better data set from which to derive a NOAEL for TDI. For this additional reason, the Panel suggests that OEHHA await the results of these studies before finalizing its REL for TDI.

Response: USEPA last updated the RfC for TDI on IRIS in September 1995. OEHHA is proceeding with the finalizing of the chronic REL based on information currently available but will review the new data when made available.

Chemical Manufacturers Association (CMA) - Ethylene Glycol Ethers Panel

Comments on the chronic REL for **ethylene glycol butyl ether** (EGBE) were received from the Ethylene Glycol Ethers Panel of the Chemical Manufacturers Association (CMA). The Chemical Manufacturers Association (CMA) Ethylene Glycol Ethers Panel is made up of the Dow Chemical Company, Eastman Chemical Company, Occidental Chemical Corporation, Shell Chemical Company, and Union Carbide Corporation. In the original TSD OEHHA derived a chronic REL of 200 $\mu g/m^3$ for EGBE based on a 1983 study by Dodd *et al*. showing decreased red blood cells in female rats. (The chronic REL has been revised to 700 $\mu g/m^3$ as described below.)

Comment 1: Significant new information should be employed in the calculation for EGBE**.** The TSD (pp. A-274 to A-278) proposes an REL for EGBE of 0.04 ppm (200 $\mu g/m^3$). This REL is derived by applying a cumulative uncertainty factor of 100 to an average experimental exposure No Observed Adverse Effect Level (NOAEL) of 4.5 ppm, which is equated to a Human Equivalent Concentration (HEC) based on default assumptions. The NOAEL is obtained from the Dodd (1983) 90-day inhalation study in rats that found a NOAEL of 25 ppm with 30 hour/week exposures (converted to continuous exposure by multiplying by 6/24 x 5/7). The cumulative uncertainty factor represents uncertainty factors of 10 each for (a) absence of a chronic study (the subchronic uncertainty factor) and (b) potential intraspecies differences.

A more appropriate REL for EGBE can be established by taking into account significant data on EGBE developed in recent years. These data, described below, should be employed to determine the HEC more accurately and to diminish the need for ten-fold uncertainty factors for intraspecies differences and for the absence of chronic data.

First, a validated physiologically-based pharmacokinetic (PBPK) model has been developed for EGBE. This PBPK model makes EGBE a compound for which "[c]omparison of human and animal pharmacokinetics and metabolism may be useful in selecting the relevant animal model for predicting human health effects" (TSD, at p. 17). As the enclosed publication describing the model (Corley et al.) shows, a more accurate determination of the HEC can be achieved by use of the PBPK model than is obtained by the standard default calculations employed in the TSD to convert discontinuous to continuous exposures (TSD, at p. 23).

Response: According to the Summary, Corley et al developed a PBPK model to describe the disposition of EGBE and its major metabolite, EGBEA (2-butoxyacetic acid), in rats and humans (Corley RA, Bormett GA, Ghanayem BI. Physiologically based pharmacokinetics of 2-butoxyethanol and its major metabolite, 2-butoxyacetic acid, in rats and humans. Toxicol Appl Pharmacol 1994;129(1):61-79). The model predicts that rats metabolize EGBE and eliminate the EGBEA faster per kg body weight than humans do. The balance of these two processes plus physiological differences between species result in higher predicted peak blood concentrations as well as total areas under the blood concentration time curves for EGBEA for rats versus humans. These species differences (and the fact that human blood is significantly less susceptible than rat blood to the hemolytic effects of EGBEA) indicate that

there is considerably less risk for hemolysis in humans from exposure to EGBE than predicted solely from standard toxicity studies with rats. In the original REL, instead of the interspecies UF default value of 10, OEHHA used an interspecies UF of 1, which indicates no likely interspecies differences. There is presently no guidance for using a factor of less than 1. To use a factor of less than 1, there would need to be reproducible data showing that the AUC of BAA in animals was a specific multiple of the AUC of BAA in humans.

Comment 2: Second, research conducted by Dr. Mark M. Udden at Baylor College of Medicine has demonstrated that blood from the elderly and from patients with hemolytic disorders does not show an increased sensitivity to the hemolytic effects of EGBE (which, as the TSD finds, are the critical toxicologic effects for establishment of an REL for EGBE). Enclosed are Dr. Udden's 1994 publications, which demonstrate that an uncertainty factor of ten for intraspecies differences is unwarranted.

Response: The demonstration that blood from the elderly and from patients with hemolytic disorders does not show an increased sensitivity to the hemolytic effects of EGBE is reason to depart from the intraspecies UF default value of 10. Since there may still be other sources of intraspecies uncertainty or variability, OEHHA staff have changed the intraspecies UF to 3. The cumulative UF is then 30 and the revised chronic REL is 0.15 ppm (724.5 $\mu g/m^3$, which rounds to 700 $\mu g/m^3$).

Comment 3: The PBPK and Udden work are both described in more detail and employed in the enclosed Draft IRIS Support Document developed jointly by U.S. EPA scientists (Drs. Jeff Gift, Annie Jarabek, and Vicki Dellarco) and scientists from Panel member companies. Although the Support Document is not yet final and EPA's scientists have not yet reviewed all sections of it, the Panel believes its recommendations for an IRIS Reference Concentration (RfC) for EGBE are consistent with the views of all the scientists working on the IRIS Document. We anticipate working with EPA in 1998 to complete the Document and establish an RfC for EGBE.

We call to your attention, particularly, the derivation of an RfC in Chapter 6 of the IRIS Draft Document. The Draft calculates RfC's by several methods: (1) the standard IRIS RfC method, which is quite similar to California's REL methodology; (2) a methodology that incorporates information from the PBPK model; (3) a benchmark dose methodology; and (4) a methodology incorporating both the PBPK model and the benchmark dose methodology.

The Draft IRIS Support Document recommends adoption of the fourth method because it most fully employs the complete database. That methodology yields an RfC (or REL) of 15 ppm (73 mg/m^3). We urge California to do the same. At a minimum, the State should take advantage of the PBPK model to adopt an REL of 6 ppm (27 mg/m^3); such an REL would represent a more refined determination of the HEC based on the PBPK model and an acknowledgment that the Udden data shows an intraspecies uncertainty factor of 3 is fully sufficient.

The Panel urges CalEPA to make use of the significant information we enclose in adopting an REL for EGBE. Alternatively, the State may wish to await EPA's adoption of an IRIS RfC. EPA announced this month that it intends to complete its IRIS review of EGBE in 1998 (63 Fed. Reg. 74, 75, Jan. 2, 1998). By waiting for a short period, CalEPA could also take advantage of the results of chronic bioassays with EGBE in mice and rats to be announced soon by the National Toxicology Program.

Response: The draft TSD was released in October 1997. As of June 1999 IRIS has no listing for EGBE or butoxyethanol. If and when it is finalized, OEHHA will review it, consider whether or not OEHHA should adopt the USEPA RfC, and forward its findings to the Scientific Review Panel for its consideration. We are not willing to wait for the USEPA RfC since there is no date certain for its completion. For now we are proposing a revised chronic REL of 0.15 ppm (700 $\mu g/m^3$).

Chemical Manufacturers Association - Hydrazine Panel

Comments on the chronic REL for hydrazine were made by the Hydrazine Panel of the Chemical Manufacturers Association in a letter dated January 29, 1998. OEHHA developed a chronic REL of 0.2 $\mu g/m^3$ based on the critical effects of amyloidosis of the liver and thyroid in hamsters (Vernot at al., 1985). OEHHA considered the lowest dose used (0.25 ppm) in hamsters to be a LOAEL since at this level the authors noted weight depression, mineralization of the kidney, and amyloidosis of the thyroid.

Comment 1: The Panel agrees that Vernot et al. is the appropriate study for derivation of the hydrazine chronic REL, but disagrees with OEHHA's interpretation of that study. The Panel believes that the 0.25 ppm dose level should be considered a NOAEL, not a LOAEL. Although the frequency of amyloidosis in hamsters exposed at this level was increased compared to controls, the frequency levels nonetheless were within the range reported in the literature for control animals.

Response: Controls reported in the same study are more relevant than historical controls for several reasons. Same study controls were exposed to the same environmental and dietary conditions and potential pathogen exposures as the exposed group. Also, the study control and exposed groups use the same strain of animal, whereas historical controls may have significant genetic differences from the test group. In addition to amyloidosis of the liver, thyroid and adrenal glands, male hamsters exposed to 0.25 ppm hydrazine showed other statistically significant increases over controls in liver hemosiderosis, bile duct hyperplasia, lymphadenitis of the lymph nodes, and mineralization of the kidney.

Comment 2: Even if the 0.25 ppm dose level is considered a LOAEL, an uncertainty factor often is overly conservative to extrapolate from a LOAEL to a NOAEL for these effects. The reported amyloidosis was at most an acceleration of a natural aging process, the incidence of the effect was within the levels normally seen in control populations, and hamster amyloidosis is an effect that may have questionable relevance for human health hazard assessment. For these reasons, an uncertainty factor of no more than three is appropriate to extrapolate from a LOAEL to a NOAEL.

Response: The relevance of historical controls was discussed in response to Comment 1. The basis for the statement that amyloidosis is not relevant to human health hazard assessment is unclear. A diverse array of human medical disorders, both neurologic and systemic, are associated with extensive amyloidosis. Human amyloidosis can be severe, with some forms associated with a median survival duration after diagnosis of as low as 25 months (Raikumar SV, Gertz MA, Kyle RA. Prognosis of patients with primary systemic amyloidosis who present with dominant neuropathy. Am J Med 1998 Mar;104(3):232-7). Amyloid deposits may cause direct harm or may be markers for an underlying metabolic disorder. Thus amyloidosis does not fit the mild effect category described in the OEHHA chronic REL document.

Comment 3. Alternatively, it may be advantageous to calculate the hydrazine REL using a benchmark concentration approach. Such an approach uses all of the available study data and avoids the difficulties associated with determining whether a NOAEL has been identified in a given study.

Response. The potential use of benchmark concentration (BMC) modeling was extensively evaluated. Dose-response modeling of the data of Vernot and associates (1985) illustrates some of the complexities of using BMCs. Several mathematical models (probit, Wibull, quantal quadratic, quantal linear, and gamma models using USEPA BMDS software) were fit to the data. None of the models fit well the unusual dose-response relationship where all three concentrations, covering a 20-fold range, were associated with a significantly increased incidence of liver amyloidosis relative to controls, but where the dose-response slope appears very shallow over this range. The models able to converge on a solution tended to project a BMC_{10} of 1 to 3 ppm. However, all the fits are questionable since they are based on assuming (1) that the true control and low dose incidence are both 30-35%, when the observed incidences were 23% and 42% respectively, and (2) that the dose-response slopes are modeled to be much steeper than actually observed. This represents one possible explanation: that the true dose-response relationship is steeper than observed due to sampling error. However, alternative explanations, more consistent with the observed data, can not be ruled out. One explanation would be that the dose-response relationship is not unimodal; there may be a susceptible subgroup at increased risk of amyloidosis at relatively low concentrations and a second more resistant subgroup. Secondly, caution against using poorly modeled BMCs or those exceeding a LOAEL has been emphasized (Gaylor et al., 1998, Procedures for calculating benchmark doses for health risk assessment, Regul. Toxicol. Pharmacol. 28, 150-164). For the above reasons a BMC can not substitute for the experimental observations in this case.

Comment 4: OEHHA should remove the reference to endocrine effects from its chronic toxicity summary for hydrazine. Although amyloidosis was seen in the thyroid of hamsters, no effects on the endocrine system were noted even at the highest doses studied. Nor have any other studies reported adverse effects on the endocrine system from exposure to hydrazine.

Response: The categorization of adverse health effects is intended to denote only the general category of organ system affected. Thus, as thyroid amyloidosis was observed and the thyroid is an endocrine gland, the effect is noted as “endocrine,” and is only meant to imply an endocrine gland was affected, and not to imply that abnormalities in hormone production are anticipated.

Comment 5: The chronic toxicity summary gives undue weight to the poorly-reported findings in the Sotaniemi case report. Other epidemiological studies that are not discussed by OEHHA do not corroborate the findings of Sotaniemi. The Panel therefore requests that OEHHA revise its discussion on the effects of human exposure to hydrazine to provide a more balanced presentation of the available data.

Response: The Sotaniemi paper is not an epidemiological study but rather a case report. Both this paper and the description of this case report as presented in the draft chronic REL document were reviewed. The case was well presented in the original report and the chronic REL review was found to be accurate. Some additional text is being added to clarify some aspects of the case: (1) a cause and effect relationship between the hydrazine exposures and the sudden death of the worker is strongly suggested but not proven; (2) the worker was 59 years old and healthy prior to hydrazine exposure; and (3) the worker's once per week exposure was reported to be routinely followed by 1-2 days of conjunctivitis and tremor.

Only a single epidemiological study of human hydrazine exposures was found and a description is being added to the OEHHA document. This study (Wald, 1984, *IARC Scientific Publication* 65:75-80; Wald et al., 1984, *British Journal of Industrial Medicine* 41:31-34) was based on a review of medical records of 406 of 427 male workers at a single chemical factory. Only 78 of these workers were believed to have had more than incidental exposure to hydrazine. Only cumulative mortality was reviewed. Health effects reported during or after hydrazine exposure were not examined. No increase in mortality was noted for lung cancer, other cancers, or causes other than cancer. However, this small study has little power to detect increased mortality, and age of death was not examined.

Chemical Manufacturers Association (CMA) - Hydrogen Fluoride Panel

The Chemical Manufacturers Association Hydrogen Fluoride Panel (Panel) on January 29, 1998 submitted comments on the October 1997 draft OEHHA chronic inhalation reference exposure level (REL) for fluorides, including hydrogen fluoride (HF). The Hydrogen Fluoride Panel includes 3M Company, Allied Signal Inc., Aluminum Company of America, Chemtech Products, Inc., Daikin America Inc., DuPont, Elf Atochem, NA, Inc., General Chemical, Industrial Quimica de Mexico, S.A. de C.V., LaRoche Industries Inc., LCI/Norfluor, Occidental Chemical Corp., OSRAM Sylvania Inc., and Quimica Fluor S.A.

Comment 1. In general, the Panel believes the chronic toxic summary for fluorides prepared by OEHHA is well-written. However, for reasons set forth below, the Panel believes the REL should be higher by a factor of three. In the case of hydrogen fluoride and other fluorides, an uncertainty factor of three should be sufficient to protect sensitive individuals.

The Technical Support Document discusses the application of an uncertainty factor to account for "the potential for greater susceptibility in subpopulations, including infants and children (p. 29-30). OEHHA indicates it generally will use an uncertainty factor of ten to protect sensitive individuals (p. 30). In the presentation at the OEHHA Workshop held in Long Beach, California on December 4, 1997, however, OEHHA staff presented a slide showing the possibility of using uncertainty factors of one, three or ten for "sensitive subgroups" when justified. The Panel believes a factor of three is scientifically appropriate in the case of fluorides.

As noted in the Technical Support Document, the steepness of the dose-response relationship affects the adequacy of the uncertainty factor for sensitive individuals. The Panel believes that the abundant information available on fluorides, with studies of large and varied human populations, documents a dose-response which would justify an uncertainty factor of three, rather than ten. Much of this information is summarized in a recent National Research Council (NRC) publication ("Health Effects of Ingested Fluoride," National Research Council, National Academy Press, 1993). The NRC publication addresses oral data, and the Panel recognizes that OEHHA typically would prefer to base an inhalation REL on inhalation studies. Nevertheless, it is generally recognized that oral exposure data can provide valuable information (Technical Support Document, p. 30-31) and, specifically in the case of fluorides, it is known that 75 to 90 percent of ingested fluoride is absorbed (Ekstrand, J., Boreus, A.L.O. and Norlin A., 1977, Pharmacokinetics of Fluoride in Man after Single and Multiple Oral Doses, Eur. J. Clin. Pharmacol. 12:311-317). The level of absorption is certainly equivalent to the amount absorbed via inhalation (approximately 99%) (Morris, J.B. and Smith, F.A., 1982, Regional Deposition and Absorption of Inhaled Hydrogen Fluoride in the Rat, Toxicol. Appl. Pharmacol. 62:91-99). Thus, the Panel believes the extensive oral data provide a scientifically sound basis for evaluating the appropriate uncertainty factor for protecting sensitive individuals. Further, since fluoride elimination is primarily via renal clearance, people with impaired renal function or nutritional deficiencies, e.g., Vitamin C or calcium, may be expected to have a greater susceptibility to fluoride toxicity. However, data from Spencer et al. (Spencer, H., Kramer, L., Gatza, C.A., 1980, Fluoride Metabolism in Patients with Chronic Renal Failure. Arch. Intern. Med. 140:1331-35) indicate that retention is not

more than about three-fold between those with normal renal clearance and those with impaired clearance. Therefore, these data would support the use of a less conservative uncertainty factor.

As a scientific "reality check," one can compare OEHHA's proposed REL of 0.03 mg/m^3 with the oral reference dose (RfD) of 0.06 mg/kg/day published by U.S. EPA in its Integrated Risk Information System (IRIS) database. Assuming a person breathes 20 cubic meters of air per day and the air contains HF at a concentration equal to the proposed REL, that person would inhale (but not absorb) 0.6 mg fluoride per day. By comparison, ingesting fluoride at the level of the oral RfD, a 50 kg adult would ingest 3.0 mg per day. One could also use for comparison California's Drinking Water Standard of 1400-2400 µg/L fluoride ion (compared to USEPA's 4000-8000 µg/L, under which an adult could safely ingest at least 2.8 mg (2 liters x 1400 µg) fluoride ion per day. These comparisons show that the proposed chronic inhalation REL for fluorides is approximately five-fold more conservative than USEPA's RfD or the State of California's existing drinking water standard. Using an uncertainty factor of three to account for potential human variability would produce an REL that is consistent with these other regulatory standards.

Response. The intent of the OEHHA reference exposure levels is to provide health-based guidance. Thus regulatory standards, which consider other issues in addition to health effects, were not considered in the development of the RELs. OEHHA RELs are intended to protect the general public, including potentially sensitive groups such as children, the elderly, and those with chronic illness. Chronic RELs, similar to USEPA RfC values, are meant to be protective to the general public rather than predictive of risk. Thus, exposure to a REL concentration may or may not be associated with adverse effects. But because of uncertainties in available data, RELs are calculated at some lower concentration than that at which adverse effects have been observed. The cumulative uncertainty factor of 10 for HF is one of the lowest used among more than 100 OEHHA chronic RELs and USEPA RfCs.

Comment 2. In summarizing the article by Derryberry et al. (1963), the chronic toxicity summary overstates the extent to which bone density increases were observed in workers. The chronic toxicity summary characterizes bone density for several workers as "high" (Table 1). However, the actual Derryberry et al. article simply notes with an asterisk those individuals who had "bone density changes." The study originally planned to include three categories of osseous changes: 1) normal skeletal density; 2) minimal or questionable bone changes indicative of increased bone density; and 3) positive characteristics of increased bone density. Derryberry reported no individuals in the latter category. According to the radiologist, none of the x-rays showed sufficient increase in bone density to be recognized as such in routine radiological practice. Thus, the authors did not express the opinion that "[t]he increased bone density observed was considered as indicating adverse effects had occurred" (Chronic Toxicity Summary, p. A-315). The study by Riggs et al. (1990), which also is cited in the chronic toxicity summary, employed pharmacologic doses of fluorides at levels almost four times those known to result in crippling fluorosis (USEPA, National Primary Drinking Water Regulations; Fluoride; 50 Fed. Reg. 47,142, Nov. 14, 1985). While it may be reasonable to use such questionable radiologic changes as the endpoint for determining a

lowest observed effect level (LOEL) or no observed effect level (NOEL), OEHHA has provided insufficient justification to show that the levels chosen represent a lowest observed adverse effect level or a no observed adverse effect level.

Response. Changes are being made in response to this comment. Text modifications will better clarify the minimal changes in bone density reported by Derryberry and associates. However, the minimal extent of the findings do not mean they are not relevant to developing RELs to protect the general public. In general, it is necessary to consider studies where statistically significant changes of questionable biological significance are consistent with frank adverse effects at higher exposures in other studies. A similar situation would be where high exposures to a chemical were established as causing clear liver toxicity and lower exposures in another study caused minimal effects such as increased liver weight without other observable effects. In these cases it is a reasonable public health goal to avoid exposures which begin going down the path from minimal to frank adverse effects, especially as subgroups in the populations may have preexisting conditions that render them especially susceptible to changes in a particular organ.

Comment 3. Section IV of the chronic toxicity summary ("Effects of Human Exposure") summarizes the few, and mostly older, reports of the effects of human inhalation exposure to generally very high levels of hydrofluoric acid. There is no mention of the abundant literature on human exposure to fluorides by the oral route, nor is there any indication that a certain level of fluoride intake is recommended by public health authorities for the prevention of dental caries (NRC publication, supra, n.6). This information should be included so that readers will be aware that fluoride is among those substances, which have beneficial effects at certain levels, with harmful effects only at higher levels.

The study on which OEHHA is relying to set the REL (Derryberry et al.) reports airborne exposures to fluorides. However, the authors note, "The principal routes through which these compounds are introduced into the human system are by ingestion or swallowing of dust containing fluorides and by inhalation of fluoride compounds." Thus, ingestion of fluorides was a major source of fluoride exposure even for those workers studied by Derryberry et al.

Response. *Text is being added to review normal dietary exposures* to fluorides and the use of fluoride supplements and to augment generally the health effects of fluorides other than hydrogen fluoride.

Comment 4. The document should be revised to state more clearly that the REL applies to all fluorides, not just to hydrogen fluoride. The title of the chronic toxicity summary is "FLUORIDES including HYDROGEN FLUORIDE, " with subtitles referencing hydrofluoric acid (aqueous solution) and hydrogen fluoride (as a gas). The only substance discussed under "Major Sources and Uses" is hydrogen fluoride, and the literature review also mostly addresses hydrogen fluoride. The article by Derryberry et al., however, is based on exposures to fluorides, not exposure to HF. Fluoride from HF and fluoride from other sources are

essentially indistinguishable by the human body (as well as by air sampling methods). There are many sources of fluoride other than HF. The Panel agrees that it is appropriate to recommend an REL for all fluorides, not just hydrogen fluoride. The Panel recommends that an additional statement be added to the introduction to the chronic toxicity summary to make clear that the REL applies to all fluorides, not just to hydrogen fluoride, even though much of the underlying data is derived from HF studies.

Response. Changes have been made in response to this comment. As noted in the comment, OEHHA relied primarily on health effects data on hydrogen fluoride because most of the available fluoride inhalation data are for this chemical.

Chemical Manufacturers Association (CMA) - Maleic Anhydride Panel

The Chemical Manufacturers Association (CMA) Maleic Anhydride Panel (Amoco Chemical Company, Ashland Chemical Company, Bayer Corporation, Huntsman Corporation) submitted comments on the OEHHA proposed chronic Reference Exposure Level for **maleic anhydride** on January 29, 1998. In the draft TSD OEHHA developed a chronic REL of 0.2 $\mu g/m^3$ based on respiratory tract effects in rats, hamsters, and monkeys. (The chronic REL has been revised as described below in the Responses to Comments 4 and 5.)

Comment 1. As we detail below, the strongest basis for a REL is the monkey data by Short et al., which leads to an inhalation REL of 0.06 mg/m^3 (60 $\mu g/m^3$). This is the preferred approach for maleic anhydride, which is highly reactive in nasal tissues, because of the strength of the Short monkey data and because the monkey respiratory system is more like that of humans than are rats or hamsters.

Response. In light of these comments, OEHHA has undertaken a reevaluation of the proposed maleic anhydride chronic REL, as presented below. However, as noted below in the response to Comment 2, OEHHA staff do not believe that the monkey data should be used to develop the REL.

Comment 2. California proposes an REL for maleic anhydride of 0.0002 mg/m^3 (0.2 $\mu g/m^3$, 0.05 ppb) based on the 1.1 mg/m^3 Lowest Observed Adverse Effect Level (LOAEL) it found for rats, hamsters and monkeys in the Short, et al., six-month inhalation studies (R.D. Short, et al., 1988, A six-month multispecies inhalation study with maleic anhydride, Fundamen. Appl. Toxicol. 10:517-524). The State says the study did not find a No Observed Adverse Effect Level (NOAEL) and cites as the critical effects hyperplastic change and neutrophilic infiltration of the nasal epithelium and respiratory irritation. It proposes converting the 6-hour/day, 5 days/week LOAEL exposures of 1.1 mg/m^3 to an average experimental exposure of 0.20 mg/m^3 and converting that value to a human equivalent concentration (HEC), using standard default values for gases, of 0.019 mg/m^3. To calculate the REL, the HEC is divided by 100 to account for uncertainty factors of 3 for use of a LOAEL rather than a NOAEL, 3 for interspecies variability, and 10 for intraspecies variability.

In developing its REL, California relied on highly conservative assumptions that do not present an accurate and balanced assessment of the human health risks from exposure to maleic anhydride. As we explain below, the REL should be based on the Short monkey data that are more relevant to humans. Maleic anhydride is highly irritating to nasal tissue. The Short studies of inhalation exposure for six months resulted in histological changes to nasal tissue that were indicative of such irritation.

In rats and hamsters, the histological changes observed by Short consisted of nasal epithelial hyperplasia (trace to mild) and/or metaplasia and inflammation (neutrophilic infiltration). Such lesions occurring as a result of inhalation exposure to a known strong irritant such as maleic anhydride are considered a reversible and adaptive response rather than

an adverse effect. (Monticello, T.M., K.T. Morgan, L. Uriah, 1990, Nonneoplastic lesions in rats and mice, Environ. Health Perspect, 85:249-274; Reuben, Z. and C.G. Rousseaux, 1991, The limitations of toxicologic pathology, In Handbook of Toxicologic Pathology, pp. 131-142, San Diego, Academic Press). Considerations of the adversity of hyperplastic and metaplastic lesions in rodent nasal cavities have been evaluated in the context of determining a critical effect for setting an EPA RfC (Foureman, G.L., M.M. Greenberg, G.K. Sangha, B.P. Stuart, R.N. Shiotsuka and J.H. Thyssen, 1994, Evaluation of nasal tract lesions in derivation of the inhalation reference concentration for hexamethylene diisocyanate, Inhalation Toxicology, 6(suppl): 341-355) and have been adopted by EPA for an RfC (Greenberg, M.M. and G.L. Foureman, 1995, Derivation of the inhalation reference concentration for hexamethylene diisocyanate, Toxic Substances Mechanisms, 14: 151-167).

By contrast, only slight inflammation, consisting of an infiltration of neutrophils, was observed by Short in the nasal tissues of monkeys. Pulmonary function tests in monkeys revealed no compound-related effects.

California chose the hamster data from the Short study as the basis for the REL, but the hamster data provides an inappropriate model for human health risk assessment and significantly overstates potential risks. The Panel recommends use of the monkey data because these results would provide a better estimate of the possible effect of maleic anhydride on the human nasal airway. Both monkeys and humans are nose and mouth breathers, whereas rodents are obligate nose breathers (Proctor, D.E., and Chang, J.C.F., 1983, Comparative anatomy and physiology of the nasal cavity, In: Nasal Tumors in Animals and Man, Vol. III, pp. 1-33 (G. Reznik and S.F. Stinson, Eds.), CRC Press, Boca Raton, FL; Bridger, M.W., and van Nostrand, A.W., 1978, The nose and paranasal sinuses - applied surgical anatomy, J Otolaryngol. 7 (suppl. 6): 1-33; Morgan, K.T., and Monticello, T.M., 1990, Airflow, gas deposition, and lesion distribution in the nasal passages. Environ. Health Persp. 88: 209-218; Harkema, JR., 1991, Comparative aspects of nasal airway.) Further, the anatomical structure of the nasal cavity of the monkey is more like the human nasal cavity compared to rodents (Harkema, JR., 1990, Comparative pathology of the nasal mucosa in laboratory animals exposed to inhaled irritants. Environ. Health Perspect. 85: 231-238). Thus, for a highly reactive chemical such as maleic anhydride, which produces nasal irritation with no systemic toxicity, human risk assessment should use the monkey data.

Response. The observation by Short and colleagues that monkeys, unlike rats and hamsters, did not develop hyperplastic changes of the nasal epithelium was discussed in the presentation of the proposed chronic REL. The difficulties in adopting the primate data as the sole basis for deriving a REL are: (1) neutrophilic infiltration of the nasal epithelium and irritation were observed in primates at all dose levels, and (2) only 3 monkeys per sex per dose were studied by Short et al. (1988) thus giving little evidence whether such changes might occur in a significant minority of monkeys. With only 3 animals per group there are only 16 possible outcomes of the experiment and, on chance alone, each one would occur with a probability of 0.0625. Thus no outcome has a $p < 0.05$. In addition, as noted in the document, challenge with particulate maleic anhydride at an average concentration of 0.83 mg/m^3 has resulted in acute asthmatic response in a sensitized worker.

Comment 3. The Short study finds a NOAEL for monkeys of 9.8 mg/m^3. Monkeys exhibited mucosal and/or submucosal infiltration of neutrophils into the nasal tissues at all exposure levels, but no morphological changes such as hyperplasia were observed. Since maleic anhydride is known to be very irritating to nasal tissue, this slight inflammatory response in monkeys is considered to result from the acute irritating properties of maleic anhydride.

Response. The common situation where the primary adverse effect observed for a chemical is an *acute* irritation response presents a special difficulty in developing an appropriate *chronic* REL. The chronic REL must still be protective against such effects that can be repeatedly or chronically induced as a result of long-term exposures to acutely irritating substances. The scenario in which a subset of sensitized individuals develop an atopic response to lower levels than might be a concern for non-sensitized individuals is an additional complication. Both of these issues apply to maleic anhydride.

Comment 4. The Panel thus proposes that the REL be based on the monkey data as follows:

NOAEL	9.8 mg/m^3
Average experimental exposure:	1.75 mg/m^3 for NOAEL group
Human equivalent concentration:	1.75 mg/m^3 for NOAEL group (monkeys considered equal to humans based on similar anatomy of the nasal cavity and similar surface area to volume ratio)
Subchronic uncertainty factor:	1
Interspecies uncertainty factor:	3
Intraspecies uncertainty factor:	10
Cumulative uncertainty factor:	30
Inhalation REL:	0.06 mg/m^3 (60 µg/m^3)

This monkey data-derived REL is both based on the best animal model for human risk assessment of maleic anhydride and within an order of magnitude of the REL values that would apply if the Short rat or hamster data were used, as shown below. Because the only systemic effects found in rodents in the Short studies are the weight losses at the highest doses in male and female rats, a REL derived from that data would be:

NOAEL	3.3 mg/m^3
Exposure continuity:	6 h/day, 5 days/week
Average experimental exposure:	0.6 mg/m^3 for NOAEL group
RGDR:	(0.395 m^3 /15 cm^2)/(20 m^3/200 cm^2)=0.263
Human equivalent concentration:	0.6 mg/m^3 x 0.263 = 0.16 mg/m^3
Exposure duration:	6 months
Subchronic uncertainty factor:	1
Interspecies uncertainty factor:	3
Intraspecies uncertainty factor:	10

Cumulative uncertainty factor: 30
Inhalation reference exposure level: 0.005 mg/m^3 or 5 µg/m^3

Similarly, a hamster-based REL would be based on a NOAEL as described below. The mild to trace hyperplasia and metaplasia observed in hamsters are not considered to be adverse effects for the reasons described above at page 2. The incidence of these lesions appears to be slightly lower in hamsters than in rats. As there were no compound-related effects observed for body weight in hamsters, the concentration of 9.8 mg/m^3 is a NOAEL for hamsters. Thus, the REL would be calculated as follows:

NOAEL: 9.8 mg/m^3
Exposure Continuity: 6 hr/day, 5 days/week
Average experimental exposure: 1.75 mg/m^3
RGDR 0.096 (hamster)
Human equivalent concentration: 1.75 mg/m^3 x 0.096 = 0.168 mg/m^3
Exposure duration: 6 months
Subchronic uncertainty factor 1
Interspecies uncertainty factor 3
Intraspecies uncertainty factor 10
Cumulative uncertainty factor 30
Inhalation reference exposure level 0.006 mg/m^3 or 6 µg/m^3

Response. The derivation of the chronic REL for maleic anhydride was reexamined in light of these comments. The results of three alternative analyses are presented in the following tables.

A. Alternative analysis for the repeated acute effects of irritation and inflammatory responses among the larger experimental group size rodent study.

Study	Short *et al.*, 1988
Study population	Rats (15/sex/group), hamsters (15/sex/group)
Exposure method	Discontinuous inhalation exposure (0, 1.1, 3.3, or 9.8 mg/m^3)
Critical effects	Neutrophilic infiltration of the nasal epithelium, respiratory irritation in all species
LOAEL	1.1 mg/m^3
NOAEL	Not observed
Exposure continuity	6 hr/day, 5 days/week
Average experimental exposure	Relevant exposure assumed to be 1.1 mg/m^3 for repetitive acute exposures
Human equivalent concentration	0.100 mg/m^3 for LOAEL group (gas with extrathoracic respiratory effects, RGDR = 0.096, based on hamster data)
Exposure duration	6 months
LOAEL uncertainty factor	3
Subchronic uncertainty factor	1

Interspecies uncertainty factor	3
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	100
Inhalation reference exposure level	0.001 mg/m^3 (1 µg/m^3, 0.0002 ppm, 0.2 ppb)

B. Alternative analysis for repeated acute irritation and inflammatory responses in the smaller experimental group size monkey study

Study	Short *et al.*, 1988
Study population	Monkeys (3/sex/group)
Exposure method	Discontinuous inhalation exposure (0, 1.1, 3.3, or 9.8 mg/m^3)
Critical effects	Neutrophilic infiltration of the nasal epithelium, respiratory irritation in all species
LOAEL	1.1 mg/m^3
NOAEL	Not observed
Exposure continuity	6 hr/day, 5 days/week
Average experimental exposure	Relevant exposure assumed to be 1.1 mg/m^3 for repetitive acute exposures
Human equivalent concentration	Not determined (inadequate data for monkeys)
Exposure duration	6 months
LOAEL uncertainty factor	3
Subchronic uncertainty factor	1 (due to acute inflammatory character of response)
Interspecies uncertainty factor	10 (default since HEC could not be calculated)
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	300
Inhalation reference exposure level	0.004 mg/m^3 (4 µg/m^3, 0.001 ppm, 1 ppb)

C. Alternative analysis for chronic effects in the smaller group size monkey study

Study	Short *et al.*, 1988
Study population	Monkeys (3/sex/group)
Exposure method	Discontinuous inhalation exposure (0, 1.1, 3.3, or 9.8 mg/m^3)
Critical effects	Hyperplastic changes of the nasal epithelium
LOAEL	Not observed (1.1 mg/m^3 in rats and hamsters)
NOAEL	9.8 mg/m^3
Exposure continuity	6 hr/day, 5 days/week
Average experimental exposure	1.75 mg/m^3 for NOAEL group
Human equivalent concentration	Not determined (inadequate data for monkeys)
Exposure duration	6 months
LOAEL uncertainty factor	1
Subchronic uncertainty factor	10 (less than 8% of lifetime)

Interspecies uncertainty factor	10 (default since HEC could not be calculated)
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	1,000
Inhalation reference exposure level	0.002 mg/m^3 (2 µg/m^3, 0.0005 ppm, 0.5 ppb)

Comment 5. In sum, the strongest basis for a REL is the monkey data by Short et al., which leads to an inhalation REL of 0.06 mg/m^3 (60 µg/m^3). This is the preferred approach for maleic anhydride, which is highly reactive in nasal tissues, because of the strength of the Short monkey data and because the monkey respiratory system is more like that of humans than are rats or hamsters. RELs based on rats (5 µg/m^3) or hamsters (6 µg/m^3) are consistent between these two species and within an order of magnitude of the REL based on the monkey data. The rat and hamster values are lower primarily because they are nasal breathers and have a more tortuous architecture in their nasal cavities that tends to enhance the retention of reactive vapors and gases, factors not applicable to humans.

Response. The response to Comment 4 presented a reassessment by OEHHA with 3 alternative analyses that incorporate consideration of the lack of evidence of cumulative chronic effects or systemic toxicity differing substantially from acute irritative effects. These analyses using guidelines developed by USEPA and OEHHA resulted in possible chronic REL values of 1, 2, and 4 µg/m^3. Because of the small size of the monkey group studied and several reports implicating maleic anhydride in asthmatic responses in sensitized individuals, OEHHA recommends the first reanalysis (*A.* Alternative analysis for the repeated acute effects of irritation and inflammatory responses among the larger experimental group size rodent study). This reanalysis resulted in a chronic REL for maleic anhydride of 1 µg/m^3 to protect against both chronic and repetitively induced acute adverse effects.

Chemical Manufacturers Association - Olefins Panel

Comments on the chronic RELs for **ethylene** and **1,3-butadiene** were received from Courtney M. Price, on behalf of the Olefins Panel of the Chemical Manufacturers Association (CMA), in a letter dated January 29, 1998. (Comments on propylene were dealt with previously.)

In addition to the comments below, the commentator provided a list of the references cited. This list is available upon request. The commentator also provided two slides of data in an appendix. These slides were presented by Dr. James Swenberg of CMA in March of 1996 regarding ethylene and ethylene oxide research. The appendix is also available upon request.

I. Comments regarding the ethylene REL. OEHHA developed a chronic inhalation REL of 100 $\mu g/m^3$ for ethylene based on the chronic REL of ethylene oxide, to which ethylene is metabolized.

Comment 1. OEHHA should not use an ethylene oxide study to establish the REL for ethylene. It is fundamental to sound science that, when sufficient data are available, the risk assessment for a chemical should be based on studies of the chemical itself. To do otherwise is scientifically unjustified and introduces unnecessary uncertainties into the risk assessment. Use of surrogates (e.g., structural analogue relationships or metabolite studies) may be appropriate if there is insufficient data on the chemical itself, but, even then, such approaches should be used with caution.

Although sufficient data exist to conduct a risk assessment for ethylene [discussed in more detail below], OEHHA has used data for ethylene oxide. Such an approach - using data on a metabolic product when data on the chemical are available - is highly unusual and is unprecedented in U.S. EPA and other agency evaluations of ethylene. The Panel strongly objects to this approach.

Response. OEHHA staff agree that such approaches are unusual and should be used with caution. However, when the chronic REL was developed, OEHHA staff wanted to base as many RELs as possible on human data. Since ethylene is metabolized to ethylene oxide, we originally decided to base the REL for ethylene on the REL for ethylene oxide, which was based on human data. However, based partly on critiques of the Schulte et al. by the Chemical Industry Institute of Toxicology (CIIT) and the Ethylene Oxide Industry Council of the CMA, we are revising the chronic REL for ethylene oxide and basing it on the report of neurotoxicity in EtO exposed workers by Klees at al. (1990).

Comment 2. The data do not support OEHHA's use of an ethylene oxide study to establish the ethylene REL. OEHHA's rationale for using the ethylene oxide data is that 1) ethylene is metabolized to ethylene oxide and 2) humans may be more sensitive to effects from ethylene oxide inhalation than are animals in experimental studies. The OEHHA summary states that, at the maximum rate of metabolism of ethylene in the rat, the theoretical ethylene oxide exposure is 5.6 ppm, which is below observed NOAEL levels in the rat of 10-50 ppm

ethylene oxide. OEHHA then speculates that humans may be more sensitive to ethylene oxide exposure than experimental animals, because "[n]on-cancer adverse effects (LOAELs) have been found at concentrations of 10 to 0.17 ppm (Zampollo *et al.*, 1984; Estrin *et al.*, 1987; Schulte *et al.*, 1995)." A comprehensive review of these studies shows they do not support this contention.

The 0.17 ppm value is taken from Schulte *et al.* (1995), which OEHHA also used as the basis for the ethylene oxide REL. The Schulte *et al.*, study is discussed extensively in comments which are being submitted separately by the Ethylene Oxide Industry Council, which are incorporated herein by reference. Those comments show: 1) the Schulte study is of questionable validity because of its small control population; 2) the effects noted by Schulte *et al.*, have not been demonstrated to have clinical significance -- that is, they are not adverse effects; and 3) the exposure assessment, which was acknowledged by the study authors to be a weakness of the study, did not account for peak exposures. Schulte *et al.* state in their paper that their results are not conclusive and may merely reflect chance physiological variation. Therefore, the Schulte *et al.*, study does not support 0.17 ppm as an adverse effect level in humans.

Zampollo *et al.* (1984) reported two cases of peripheral neuropathy in twelve nurses who removed objects from an ethylene oxide sterilizer and sorted the objects on a tray. The paper provides very little information on the collection of ethylene oxide concentration data, but does clearly state that values were 30 to 400 ppm in the vicinity of the sorting tray while a nurse sorted sterilized objects. Thus, this study does not support a human LOAEL of 10 ppm or less.

Estrin *et al.* (1987) measured nervous system function in 8 hospital workers that worked in proximity to ethylene oxide sterilizers and in 8 nonexposed controls. The authors report that, "Six exposed subjects reported olfactory detection of the gas on repeated occasions indicating exposures near or above the odor threshold of 700 ppm." In addition, industrial hygiene sampling records showed peak exposures in the employees' breathing zones in excess of the upper detection limit of 200 ppm. Estrin *et al.* (1987) note that, "Exposure to EtO [ethylene oxide] in hospitals generally occurs in predictable, relatively high, short-term peaks." Thus, although the average exposure may be low, the observed effects in studies of hospital workers quite possibly are due to the high peak concentrations and are not indicative of potential effects from chronic exposure to low levels of ethylene oxide. Thus, this study does not support a LOAEL of 10 ppm or less for human exposure to ethylene oxide.

Response. Because of the difficulties with the use of the study of Schulte et al. (1995) in the development of a REL for ethylene oxide (see CIIT and CMA comments and responses on the ethylene oxide REL), OEHHA has decided not to base the chronic inhalation REL for ethylene on that report.

Comment 3. In contrast to the Zampollo *et al.* and Estrin *et al.* case studies of workers exposed to high peak concentrations, Joyner (1964) conducted a retrospective morbidity study of 37 workers with 5 to 16 years of occupational exposure to ethylene oxide at 5 to 10 ppm.

There was no statistically significant increase in the incidence of neurological disorders compared to controls. After a review of the data for ethylene oxide, Golberg (1986) concluded that neurological effects were unlikely to occur at ethylene oxide exposures up to 100 ppm. Thus, the weight of evidence does not support OEHHA's proposition that humans are more sensitive to ethylene oxide exposure than are experimental animals.

Response. Other studies have been reported since Golberg made his conclusion in 1986. OEHHA staff believe that neurological effects may occur in workers due to chronic exposures to ethylene oxide below 100 ppm. Such studies are described in the ethylene oxide summary under effects of human exposure and include Estrin *et al*. (1987, 1990) and Klees *et al*. (1990). OEHHA is now proposing a revised chronic REL for ethylene oxide of 30 $\mu g/m^3$ based on nervous system effects in humans as reported by Klees et al. (1990).

Comment 4. Furthermore, even if there were evidence that humans are more sensitive than rodents to inhaled ethylene oxide, it would not follow that humans are most sensitive to effects from inhaled ethylene. The metabolism of a compound to a toxic metabolite occurs within the cells of metabolically-active tissues such as the liver. The effects of directly inhaling ethylene oxide, therefore, are not necessarily the same as the effects of ethylene oxide generated by metabolism of inhaled ethylene.

There are a number of endogenous sources of ethylene in the human organism: lipid peroxidation, oxidation of free methionine, oxidation of hemin in hemoglobin, and metabolism of intestinal bacteria (Filser *et al.*, 1992). In addition, natural exogenous sources of ethylene exist. It is a natural product of vegetation of all types and acts as an endogenous plant growth regulator. Sawada and Totsuka (1986) estimate that approximately 74 percent of ethylene emissions are from natural sources. Thus, humans evolved in the presence of both exogenous and endogenous sources of ethylene.

Studies being conducted by Dr. James Swenberg of the University of North Carolina demonstrate that humans have endogenous levels of significant quantities of ethylene oxide adducts. Dr. Swenberg has found that endogenous levels of the ethylene oxide-DNA adduct in the human liver are equivalent to levels produced in rats exposed to 10 ppm ethylene oxide or mice exposed to 33 ppm ethylene oxide. [Note: The level of 7-hydroxyethylguanine (7-HEG) in DNA from liver of nonexposed humans was 1.4 to 4.5 pmol/μmol Guanine, with a mean value of 3.0 pmol/μmol G. The mean level of 7-HEG in the liver of rats exposed to 10 ppm EtO was 3.3 pmol/μmol G, and the mean level of 7-HEG in the liver of mice exposed to 33 ppm EtO was 3.75 pmol/μmol G. A copy of a presentation by Dr. Swenberg that includes this data is provided as Appendix A.] Assuming equivalent concentrations of ethylene oxide produce equivalent concentrations of DNA adduct in humans and rodents, the humans were exposed endogenously at the rodent equivalent of 10 to 33 ppm inhaled ethylene oxide. Using a factor of 3 percent ethylene converted to ethylene oxide (human conversion saturation), the human endogenous exposure would be equivalent to an environmental exposure of 333 to 1100 ppm ethylene. Thus, OEHHA's proposed REL of 0.1 ppm ethylene appears to be some 3,300 to 11,000 times lower than what the human body spontaneously produces.

Response. OEHHA acknowledges that the body can produce ethylene. The body also produces the toxic chemical carbon monoxide (CO) from heme and uses nitric oxide (NO) as a hormone. Levels of hydrogen chloride, which can cause inflammation in other tissues, are normally present in the stomach. The relevant information of interest is the adverse effect(s) of exogenous ethylene which is inhaled.

Comment 5. The Panel therefore believes OEHHA is not justified in using ethylene oxide data to establish the REL for ethylene. Because adequate data exist to directly evaluate ethylene, OEHHA should base the REL on the ethylene studies. [Note: If OEHHA nevertheless persists in using ethylene oxide, then its analysis should be revised in accordance with the comments being separately submitted by the Ethylene Oxide Industry Council.]

Response. OEHHA has revised its chronic REL for EtO based in part on the comments from CMA's Ethylene Oxide Industry Council and those from the Chemical Industry Institute of Technology (CIIT). We will be discussing this with the Scientific Review Panel on Toxic Air Contaminants.

Comment 6. OEHHA should derive the REL for ethylene from the chronic study on ethylene. The toxicological database for ethylene includes both a comprehensive lifetime inhalation study in rats (Hamm *et al.*, 1984) and an inhalation reproductive/developmental study in rats (Aveyard and Collins, 1997). These studies provide an adequate and appropriate basis for deriving the REL for ethylene, especially since the pharmacokinetics of ethylene in rats and humans has been shown to be similar (Shen *et al.*, 1989). The existence of the reproductive/developmental study provides confidence that the chronic study did not miss potential sensitivity to reproductive or developmental effects. Because the route of exposure for both studies is inhalation, they are particularly relevant for derivation of the REL, which is an air concentration risk parameter.

Hamm *et al.* (1984) exposed rats to 300, 1000, or 3000 ppm ethylene for 6 hours/day, 5 days/week, for 24 months with no observed toxic effects. Hematology, blood chemistry, and urinalysis tests were performed at six-month intervals throughout the study. Over 24 months, no differences were observed between exposure groups with respect to mortality, clinical blood chemistry, urinalysis, body weights, organ weights or histopathology of a variety of tissues and organs. Inflammatory lesions typical of this strain of rat were distributed equally among all exposure groups. The NOEL in this study was 3000 ppm.

As discussed by OEHHA, a 13-week inhalation study of Sprague-Dawley rats found no treatment related effects at levels up to 10,000 ppm ethylene (Rhudy *et al.*, 1978). Parameters measured included body weight, total weight gains, food consumption, hematology, clinical chemistry, urinalysis, and histopathology.

Aveyard and Collins (1997) evaluated the potential effects of ethylene inhalation on male and female rat reproduction, growth and development using OECD Guideline 421

(Reproduction/ Development Toxicity Screening Test). Administration of ethylene at nominal concentrations of 200, 1000, or 5000 ppm showed no evidence of toxicity. There were no adverse effects on male or female reproductive performance, fertility, pregnancy, maternal and suckling behavior, or growth and development of the offspring from conception to Day 4 post-partum. The general toxicity NOEL was 5000 ppm and the reproductive/developmental toxicity NOEL was 5000 ppm.

The Panel believes that OEHHA should derive the ethylene REL from the chronic rat study, as follows:

Study	Hamm et al. (1984)
Study population	Fischer 344 Rats (120/sex/group)
Exposure Method	Inhalation exposure at 300, 1000 or 3000 ppm
Critical effects	None
Exposure continuity	6 hr/d, 5 d/wk
Exposure duration	24 months
NOEL	3000 ppm
Average experimental exposure	535 ppm
Human equivalent conc.	535 ppm (gas with no extrathoracic effects, based on RGDR = 1.0 using default assumption that lambda (a) = lambda (h))
Subchronic uncertainty factor	1
LOAEL uncertainty factor	1
Interspecies uncertainty factor	10
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	100
Inhalation reference exposure level (REL) for ethylene	5.4 ppm (6.2 mg/m ^{3})

Response. OEHHA staff agree that this is an acceptable approach to a REL and is considering basing the chronic REL for ethylene on the Hamm et al. report. However, since an HEC calculation has been made, an interspecies uncertainty factor of 3 can be used instead of 10. Unfortunately, no critical effect can be assigned from the study by Hamm et al. In the workplace ethylene is considered to be a “simple” asphyxiant. Thus its target organ could be considered to be the respiratory system and/or the blood since asphyxiants prevent oxygen from getting to hemoglobin. However ethylene has been used as an anesthetic in people (for example: Brumbaugh JD. 1928. Effects of ethylene-oxygen anesthesia on the normal human being. JAMA 91:462-465). Such use indicates effects other than asphyxiation. In addition ethylene can be metabolized to ethylene oxide which is a neurotoxicant. Thus, in humans there is evidence to consider ethylene as a gas with systemic effects.

Comment 7. The Panel notes that, given the fact that no effects have been detected in any studies of ethylene, even at very high air concentrations (1% ethylene), this REL is very conservative. The Occupational Safety and Health Administration (OSHA) does not regulate inhalation exposure to ethylene. The American Conference of Governmental and Industrial

Hygienists (ACGIH) has determined ethylene is essentially toxicologically inert. It has not set a threshold limit value (TLV) for ethylene, but has classified it as a "simple asphyxiant," defined as follows:

> Simple Asphyxiants -- "Inert" Gases or Vapors. A number of gases and vapors, when present in high concentrations in air, act primarily as simple asphyxiants without other significant physiologic effects. A TLV may not be recommended for each simple asphyxiant because the limiting factor is the available oxygen.

Response: Ethylene is included because it is listed as a Hot Spots chemical. OEHHA admits that it is difficult to develop a reference exposure level for a simple asphyxiant. However several reports, which are cited in the revised chronic toxicity summary for ethylene, have indicated that ethylene has been used as an anesthetic. This implies that ethylene has neurotoxic effects and is not just a simple asphyxiant.

Comment 8: OEHHA's REL discussion should emphasize the lack of effects observed for ethylene, even at concentrations as high as 10,000 ppm in a subchronic study.

Response: The chronic REL summary states that "The available data indicate that ethylene has a low potential for non-cancer chronic toxicity in experimental animals." Also it states that no effects were seen in the 13 week study where 10,000 ppm were studied.

II. Comments regarding the 1,3-butadiene REL. OEHHA developed a chronic inhalation REL of 8 $\mu g/m^3$ for 1,3-butadiene based on ovarian atrophy in mice exposed by inhalation.

Comment 9. OEHHA should base the butadiene REL on rat data, because human metabolism of butadiene is more similar to the rat than the mouse. Ovarian atrophy in the mouse is not an appropriate endpoint for derivation of the REL. OEHHA notes in the draft Technical Support Document that "the animal species most sensitive to a substance is not necessarily the most similar to humans in developing adverse effects from a particular exposure." In the case of butadiene, use of the most sensitive species - the mouse - is not appropriate, because compelling evidence indicates that the rat is a more appropriate model for estimating risks to humans. The ovarian atrophy observed in the mouse has not been observed in the rat, even when exposed to butadiene at concentrations as high as 8000 ppm. This is due to differences in the metabolism of butadiene by the mouse and the rat. Studies show that human metabolism of butadiene is similar to that of the rat, and not of the mouse. Therefore, direct extrapolation from the mouse ovarian effects is inappropriate to derive a health effect level for human protection.

The Panel previously has submitted comments to OEHHA concerning the potential reproductive toxicity of 1,3-butadiene. For example, in December 1996 the Panel submitted comments on OEHHA's "Draft Prioritized Candidate Chemicals Under Consideration for

Developmental/Reproductive Toxicity Evaluation," dated October 4, 1996. [Note: Letter from Langley A. Spurlock, Vice President, CHEMSTAR, to Cynthia Oshita, Senior Hazardous Materials Specialist, OEHHA, re: Draft Prioritized Candidate Chemicals Under Consideration for Developmental/Reproductive Toxicity Evaluation, October 4, 1996 (Dec. 2, 1996)] In October 1997, the Panel submitted comments in response to OEHHA's request for relevant information on chemicals under consideration for Proposition 65 listing via administrative mechanisms. [Note: *Comments of the Chemical Manufacturers Association Olefins Panel on the Possible Listing of 1,3-Butadiene as a Reproductive Toxicant Via Administrative Mechanisms,* submitted to Cynthia Oshita, OEHHA (Oct. 21, 1997)] Attachments to these comments include relevant excerpts from Panel comments to OSHA and testimony to OSHA by Dr. Mildred Christian, a leading authority on developmental and reproductive toxicity. The Panel urges OEHHA to review these comments and their attachments with respect to developing an REL for butadiene. Upon request, we will submit additional copies of the comments and attachments.

As explained in the previous comments to OEHHA, the mouse is unique in its sensitivity to butadiene. Ovarian atrophy or other reproductive effects have not been observed in the rat at butadiene exposure levels up to 8000 ppm administered by inhalation for two years (Owen *et* al., 1987). In addition, no histopathologic changes were detected in the ovaries of rats, guinea pigs, rabbits, or dogs exposed to butadiene at concentrations up to 6700 ppm for eight months (Carpenter *et al.*, 1944, as discussed in Christian, 1996).

Dr. Glenn Sipes and his colleagues, of the University of Arizona, have developed data that explain the mechanism by which butadiene causes ovarian atrophy in the mouse (Doerr *et al.*, 1996). Their work shows that the monoepoxide metabolite of butadiene causes some ovarian effects in the mouse, but not in the rat. The diepoxide metabolite causes ovarian effects in both the mouse and rat, but is more potent in the mouse and is far more potent in the mouse than is the monoepoxide. In other words, the primary cause of the ovarian atrophy observed in mouse (and not observed in the rat) appears to be the diepoxide metabolite of butadiene.

Rats are much less efficient at metabolizing butadiene to monoepoxide than are mice, and primates - including humans - convert even less butadiene to the monoepoxide than do rats (Csanady, *et* al., 1992; Schmidt and Loeser, 1986; Himmelstein, *et al., 1994;* Himmelstein, *et al.*, 1995; Dahl, *et al*., 1991). Workers exposed to butadiene showed at least 25-fold lower levels of the monoepoxide hemoglobin adduct per ppm-hour than rats, and more than 100-fold lower adduct levels than mice (Osterman-Golkar, *et al*., 1993). Furthermore, the metabolism of the monoepoxide in the mouse proceeds largely by further epoxidation to the diepoxide (Himmelstein, *et al.*, 1997). In contrast, rats form very little diepoxide (Csanady, *et al.*, 1992; Thorton-Manning, *et al.*, 1995), and primates hydrolyze most of the monoepoxide, rather than convert it to diepoxide (Csanady, *et al.*, 1992; Dahl, *et al.*, 1991). Thus, diepoxide levels are much higher in mice than in rats or primates (Thornton-Manning, *et al.*, 1995; Sweeney, *et al.*, 1997; Seaton, *et* al., 1995).

In summary, the diepoxide metabolite of butadiene appears to be responsible for the ovarian atrophy observed in the mouse. Very little diepoxide, if any, is produced through

metabolism in rats, and no atrophy is observed in rats exposed to butadiene. Even less diepoxide is produced in human tissues. Therefore, the data in mice are not relevant to assessment reproductive effects in humans, and the mouse ovarian atrophy is an inappropriate basis for the establishment of an REL.

Response. OEHHA staff agree that the mouse ovary may be more (or much more) sensitive to butadiene due to butadiene's metabolism to the diepoxide and that people are more like the rat in their formation of epoxides from butadiene. The diepoxide could be much more rapidly destroyed in rats than in mice. (In a somewhat analogous situation both mice and rats form a reactive carcinogenic epoxide from aflatoxin. Mice metabolize the aflatoxin epoxide via glutathione much more rapidly than rats, so that the rat is about 1000x as sensitive as the mouse to aflatoxin-induced carcinogenesis.)

Unique may not be an appropriate term in the case of butadiene if mice are really at one end of the spectrum in sensitivity to butadiene. Unique is probably better applied to situations such as male rat kidney tumors due to accumulation of alpha2u globulin which only accumulates in the kidneys of male rats. OEHHA staff still propose using an interspecies uncertainty factor of 3 for this endpoint with butadiene because we believe that pharmacodynamic differences between mice and men are still not adequately counted for.

Comment 10. OEHHA should develop an REL based on rat data. Apart from reproductive toxicity, the mouse NTP study relied upon by OEHHA gave a NOAEL of 200 ppm, based on nonneoplastic hematotoxic effects (NTP, 1993). As for ovarian atrophy, however, these effects in the mouse do not appear applicable to other species. In the chronic study of Sprague-Dawley rats, blood was evaluated from 20 animals of each sex per group after 3, 6, 12, and 18 months of exposure to 0, 1000, or 8000 ppm of butadiene (IISRP, 1981; Owen *et al.*, 1987). Any changes of hematological parameters that occurred were within normal values for the strain and laboratory, and the study authors did not consider them to be toxicologically significant.

Cowles *et al.* (1994) conducted retrospective mortality, prospective morbidity, and hematological analyses of male workers employed in butadiene monomer production from 1948 to 1989. Hematology data was available for 429 of these workers. No hematological differences were seen for any butadiene-exposed employees, including a group exposed to an estimated time-weighted average of 10 ppm, as compared to employees not exposed to butadiene. This is consistent with Checkoway and Williams (1982), who reported minimal changes in the hematology of a subgroup of 8 workers in a styrene-butadiene rubber manufacturing plant, exposed to 20 ppm butadiene, versus 145 workers exposed to less than 2 ppm butadiene. The statistical significance of the changes is questionable due to the very small population and the failure to account for confounding factors such as race, smoking, body size, exercise, and ethanol intake. Checkoway, *et al.* (1984) concluded that the hematologic parameter values for the subgroup of 8 were within the normal range. Both Checkoway, *et al.*, (1984) and IARC (1992) concluded that the changes could not be interpreted as an effect on the bone marrow.

This difference in the hematological effects seen in the mouse study versus rat and human studies is in keeping with the metabolic differences discussed above. *In vitro* and *in vivo* evidence indicates that hematopoietic effects such as macrocytic megaloblastic anemia induced in mice by butadiene exposure are due to the epoxide metabolites, especially the monoepoxide (Colagiovanni, et al., 1993; Irons, et al., 1995). Mice, but not rats or humans, have a subpopulation of primitive hematopoietic progenitor cells which are very sensitive to the monoepoxide metabolite. Species differences in the metabolism of butadiene to the epoxides, as well as the different susceptibility of the hematopoietic system, indicate that the mouse is not the most appropriate species for deriving a chronic REL.

Because human metabolism of butadiene is more similar to that of the rat than that of the mouse, the Panel believes that the REL is more appropriately based on rat data than on mouse data. A suitable study is the two-year chronic inhalation study (IISRP, 1981; Owen, *et al*., 1987). That study provided a NOEL of 1000 ppm, which can be converted to an REL as follows:

Study	IISRP, 1981; Owen, *et al.*, 1987
Study population	Sprague-Dawley rats (100/sex/group)
Exposure method	Discontinuous whole body inhalation exposure (0, 1000, or 8000 ppm)
Critical effects	Minor clinical effects (eye and nose excretions, slight ataxia); increased liver and kidney weights; nephrosis.
LOAEL	8,000 ppm
NOEL	1,000 ppm
Exposure continuity	6 hr/d, 5 d/wk
Exposure duration	2 years
Average experimental exposure	178.6 ppm
Human equivalent concentration	178.6 ppm (gas with no extrathoracic effects, based on RGDR = 1.0 using default assumption that lambda (a) = lambda (h))
LOAEL uncertainty factor	1
Subchronic uncertainty factor	1
Interspecies uncertainty factor	10
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	100
Inhalation reference exposure level	1.8 ppm (4 mg/m^3)

Response. The commentator has provided a plausible alternative to the chronic REL calculated by OEHHA. However, since there is a 200 ppm NOAEL in mice for a hematological toxicity, the use of the rat 1000 ppm NOAEL may not be appropriate. Yet since no hematologic effects were seen in 2 epidemiologic studies at 10 and 20 ppm butadiene, the use of the hematologic endpoint may also not be appropriate. As stated below, OEHHA prefer to use the mouse data because of the sensitivity of the endpoint.

Comment 11. If OEHHA uses mouse data, it should apply a pharmacokinetic adjustment. For the reasons discussed above, the Panel believes the rat provides a better model for conducting a human health risk assessment of butadiene than does the mouse. If OEHHA nevertheless chooses to base the REL on mouse data, it should use a physiologically-based pharmacokinetic (PBPK) model to adjust that data, due to the great differences in mouse metabolism of butadiene from that of rats and humans. Use of the 200 ppm NOAEL for hematological effects and applying OEHHA's standard adjustments would result in an REL of 0.36 ppm. Without adjustment for the metabolic differences between mice and humans, however, that REL would be extremely conservative.

Extensive work has been done and is continuing to develop and refine PBPK models for butadiene (Himmelstein, *et al.*, 1997; ECETOC, 1997). Upon request, the Panel would be pleased to provide technical support to OEHHA to apply appropriate PBPK adjustments to mouse data for the development of a REL, if OEHHA declines to use rat data for the REL.

Response. OEHHA appreciates the offer of technical support by the commentator. OEHHA staff have some experience in pharmacokinetic modeling of butadiene (Brown, J.P., and Collins, J.F.: Use of microcomputers to apply butadiene metabolic data to public health risk assessment. FASEB J. 7:A1130, 1993). A credible approach might be to use an interspecies uncertainty factor less than the default of 10 (or 3 after an HEC adjustment) for mouse to man since in the case of butadiene humans are not up to (3 to) 10 times more sensitive than mice. Pharmacokinetic information indicates that mice are not less sensitive than people to 1,3-butadiene. However we still need to account for pharmacodynamic differences. Thus we use an interspecies UF of 3 after the HEC adjustment.

OEHHA staff note that USEPA has used a benchmark dose approach to develop a (proposed) reproductive/developmental RfC for butadiene of 0.15 ppb (0.3 $\mu g/m^3$) based on the dominant lethal effect of decreased litter size in mice at birth.

Chemical Manufacturers Association – Phthalate Ester Panel

Comments on the chronic RELs for **phthalic anhydride** were made by the Phthalate Ester Panel of the Chemical Manufacturers Association in a letter dated January 29, 1998. OEHHA proposed a chronic REL for phthalic anhydride of 10 $\mu g/m^3$ based on eye and respiratory irritation, asthma, and bronchitis in 23 workers occupationally exposed for a mean of 13.3 years (Neilsen *et al.* (1988; 1991)). (Comments of the Panel on DEHP were dealt with previously.)

Comment 1: *Phthalic anhydride*. OEHHA should base an interim REL for phthalic anhydride on the ACGIH TLV, and should emphasize in its discussion phthalic anhydride's solid nature and its low oral toxicity.

Response: OEHHA has not based chronic RELs on ACGIH TLVs. USEPA, OEHHA, and even ACGIH have all determined ACGIH TLVs should not be used in developing health-based exposure guidance for general populations including the elderly and children. TLVs lack a consistent basis and are intended to protect only healthy workers from discontinuous exposures, rather than the public from continuous exposures. Many TLVs are not health-based and/or are intended to reduce rather than eliminate the occurrence of adverse health effects.

Comment 2: OEHHA should emphasize in the REL discussion the fact that phthalic anydride is a solid at ambient temperatures, and that it has very low systemic toxicity when ingested.

Response: OEHHA noted the crystalline form of phthalic anhydride at ambient temperatures and its low vapor pressure. Mass concentration units ($\mu g/m^3$) were not converted to volume concentration units (ppb) in the Chronic Toxicity Summary. However as noted above for DEHP, particulate air contaminants may exist at levels hazardous to human health. The particulate nature of phthalic anhydride in inhalation exposure studies in animals administered by Sarlo and Clark (1992) and Sarlo and associates (1994) was clearly presented. Text is being added at several locations in the document to emphasize the particulate nature of DEHP in human and animal exposure studies.

Comment 3: OEHHA based the proposed REL for phthalic anhydride on a pair of studies by Nielsen et al. (1988; 1991). Those studies do not support a correlation between phthalic anhydride exposure and the purported critical effects. The reported effects were minimally adverse and reversible, are commonly reported by workers, and could have been due to colds, allergies, or exposure to other chemicals.

Response: Several categories of response were significantly increased in heavily exposed workers compared with those with limited exposures. The effects noted (asthma, chronic bronchitis, conjunctivitis, and rhinitis) were consistent with a hypersensitization response among repeatedly exposed workers. A similar hypersensitization response was noted in animals exposed to phthalic anhydride dust (Sarlo *et al.*, 1994). The induction of asthma and

bronchitis would not be categorized as a "minimally adverse" response. Reversibility of adverse effects is not a sufficient reason to ignore the finding; among other reasons, the RELs are intended to protect the public from continuous lifetime exposure. That effects noted in occupationally exposed workers may be due, in least in part, to exposure to other substances is a reasonable concern. However, as noted above, the immunologically-based effects noted are consistent with those noted among rats exposed only to phthalic anhydride. As for the contention that effects noted among the heavily exposed workers might be due to colds or allergies, there is no reason to anticipate the heavily exposed workers should be more affected than lightly exposed workers.

Comment 4: No existing chronic or subchronic inhalation studies of phthalic anhydride are appropriate for the derivation of an REL, so OEHHA should not establish a final REL for phthalic anhydride.

Response: As described in the response to comment 8, OEHHA still concludes that the data of Nielsen et al. (1988; 1991) are adequate for the purposes of deriving a chronic REL. As is the case for all chemicals reviewed, additional data would be desirable and will be considered if such data should become available in the future.

Comment 5: As an interim measure, OEHHA should base an interim REL on the ACGIH TLV, adjusted for continuous exposure and variation in sensitivity.

Response: OEHHA has not based chronic RELs on ACGIH TLVs. USEPA, OEHHA, and even ACGIH have all determined ACGIH TLVs should not be used in developing health-based exposure guidance for general populations including the elderly and children. TLVs lack a consistent basis and are intended to protect only healthy workers from discontinuous exposures rather than the public from continuous exposures. Many TLVs are based on feasible control technology, not health, and are intended to reduce rather than eliminate the occurrence of adverse health effects.

Chloropicrin Manufacturers' Task Force (CMTF)

The Chloropicrin Manufacturers' Task Force (CMTF) submitted comments on January 29, 1998 regarding the draft chronic reference exposure level for **chloropicrin** presented in the OEHHA *Air Toxics "Hot Spots" Risk Assessment Guidelines Part II. Technical Support Document for Determining Chronic Reference Exposure Levels*. The members are Ashta Chemicals, Holtrachem Manufacturing, Niklor Chemical, Trinity Manufacturing, Agrevo Canada, Angus Chemical, Dow AgroSciences, Great Lakes Chemical Corp. and Trical Products. OEHHA developed a chronic REL of 4 $\mu g/m^3$ based on respiratory system effects (nasal rhinitis) in rats.

Comment 1. OEHHA's proposed REL for chloropicrin is based on a chronic inhalation oncogenicity study performed by whole-body exposure to rats (Burleigh-Flayer and Benson, 1995). OEHHA identified increased mortality, increased lung and liver weights and rhinitis as effects of chloropicrin inhalation exposure in their summary of the Burleigh-Flayer and Benson study. CMTF disagrees that liver weights were affected by chloropicrin treatment in the chronic rat study. Tables 17-22 of the study final report (Burleigh-Flayer and Benson, 1995) present organ weight data that show male rat liver weights, both absolute and relative to body and brain weight, were unaffected by exposure to chloropicrin. The absolute liver weight of female rats was statistically-significantly depressed in the mid-dose group (as was this group's body weight) but not in the low or high-dose groups. The liver weight of the female animals as compared to their body or their brain weight, i.e., relative liver weight, was not affected by chloropicrin treatment in any dose level in the study. The decrement in absolute liver weight but not relative liver weight observed in the mid-dose female rats is a reflection of the body weight diminution experienced by these animals and is not indicative of a toxic effect in the liver. The study director concluded this, and on page 19 of the study report writes: "Some statistically-significant changes in absolute kidney and liver weight for female animals from the low and/or mid groups were believed to be the result of their lower final body weight and were not believed to be exposure related."

Response. OEHHA reexamined this issue and accepts the commentator's correction that the liver findings involve decreased liver and body weights in the mid-dose female rats, lack a monotonic dose-response relationship, and are not evidence of a direct toxic effect to this organ. Therefore the identification of liver effects as an endpoint is being removed.

Comment 2. OEHHA adjusted the No Observed Adverse Effect Level (NOAEL) from the Burleigh-Flayer and Benson study for continuous exposure (to 0.018ppm) and applied an uncertainty factor of 3 for interspecies uncertainty and an additional factor of 10 for intraspecies uncertainty. The CMTF believes that, because the critical effects that support the derivation of the OEHHA REL are limited to respiratory system irritation and are not progressive, there is no need for an interspecies uncertainty factor. The nonspecific irritation effects seen at the portal of entry and target organ following overexposure to chloropicrin are equivalent across all species tested (Chun and Kintigh, 1993; Yoshida, 1987; Schardein, 1994; Schardein, 1993a and 1993b; Burleigh-Flayer, 1994; NCI, 1978; Wisler, 1995; Ulrich, 1995). 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.

Response. The available data do indicate that chloropicrin is highly reactive and causes effects at the immediate sites of contact. But the effects noted can be more severe than irritation. Kane and associates (1979) noted exfoliation, erosion, ulceration, and necrosis of respiratory and olfactory epithelium of mice exposed to 7.9 ppm chloropicrin for 6 hours per day for 5 days. Fibrosing peribronchitis and peribronchiolitis were noted in the lower respiratory tract. Furthermore there is no evidence comparing the relative toxicity of chloropicrin between rodents and humans. Most notably, increased mortality was observed in the Burleigh-Flayer and Benson study. Secondly, similar effects are commonly noted among different species exposed to the same chemical but the magnitude of exposures causing equivalent response may differ substantially.

Comment 3. Likewise, there is no basis to presume that human respiratory tissue will be differentially susceptible to chloropicrin irritation. Therefore, a 10-fold factor for intraspecies uncertainty is not justified for chloropicrin.

Response. The intraspecies factor is intended to protect sensitive subgroups, such as the elderly and children, and those with preexisting medical conditions that may increase the susceptibility to adverse effects following exposure to chloropicrin. Variability in response among individuals to the same toxic stimuli has been noted in virtually all toxicity studies, although the degree of variability may differ for different chemicals and different endpoints. On the basis of currently available data, OEHHA believes a 10-fold intraspecies uncertainty factor is warranted.

Comment 4. Because the respiratory effects of chloropicrin are concentration and not dose-dependent, duration of exposure is not a factor in producing effects, nor in preventing effects. Accordingly, the OEHHA adjustment of the Burleigh-Flayer exposure to a continuous exposure is unnecessary. According to the American Conference of Governmental Industrial Hygienist (ACGIH), exposure to chloropicrin at a concentration of 0.1 ppm will not result in eye or respiratory irritation, but irritation does occur at concentrations of 0.3 to 0.37 ppm (ACGIH, 1991). Concentration-dependent chemicals are defined as fast-acting chemicals whose toxic effects are immediate, and correlate more closely to concentration than dose. Included in this category are sensory irritants, and chemicals that are corrosive or vesicant in their action. In contrast, the effects of dose-dependent chemicals are a function of both concentration and duration of exposure" (Craig, 1995). Chloropicrin at low levels (0.15-0.3 ppm) produces a clear warning of exposure. At higher exposure levels (1 ppm or more), chloropicrin produces a consistent pattern of pulmonary injury in humans and test animals. The protective warning properties of chloropicrin occur at airborne concentrations of 0.15 ppm. Exposure to chloropicrin below this concentration has no effect and an application of safety, or uncertainty, factors is without rationale. Because the short-term effects, i.e. sensory irritation, are the overriding effects from chloropicrin exposure, chronic toxicity data from animal studies should not be used to establish chloropicrin exposure criteria.

Response. The commentator did not provide any direct evidence to support the contention that effects following chloropicrin exposure are completely independent of exposure duration. Were a large subchronic uncertainty factor applied, the commentator's point might have greater relevance. But in this case no subchronic uncertainty factor was used. Thus the degree to which exposure duration may have lesser importance for this chemical is already reflected in the data collected in the chronic exposure study. The commentator's main point may be thus directed at the approximately 5.6-fold adjustment used to account for the discontinuous (6 hr/day, 5/day per week) exposures. There are no data demonstrating that there would be no difference between continuous and discontinuous exposures in this case, so some adjustment is warranted. In the Kane study, recovery was observed three days after the completion of a 5 day exposure period, indicating that continuous exposure may result in more severe effects than discontinuous exposure (where some recovery will be taking place).

Comment 5. In response to the statement in the draft REL indicating that adequate reproductive toxicity data is a major area of uncertainty in the chloropicrin data base, the CMTF would like to point out the existence of a chloropicrin multi-generation reproductive toxicity study (Schardein, 1994).

Response. OEHHA thanks the commentator for providing information about this unpublished study. As of June 1999 it has not appeared in the peer-reviewed literature. However, OEHHA would like to obtain a copy for review.

Elementis Chromium

Comments on the chronic REL for **chromium VI** were made by R.J. Barnhart, Ph.D., Vice President-Technical, of Elementis Chromium, Corpus Christi, Texas in a letter dated January 27,1998. OEHHA proposed a chronic REL of 0.0008 $\mu g/m^3$ for respiratory effects based on a study by Lindberg and Hedenstierna (1983) of workers exposed to chromic acid.

Comment 1. Page A-161. The table listing specific compounds. The chemical formulas for potassium chromate, sodium chromate, potassium dichromate and sodium dichromate are wrong. Hydrogen atoms should not be included in these formulas.

Response. Comment noted. The hydrogen atoms will be removed. OEHHA regrets the error.

Comment 2. Page A-162. Physical and Chemical Properties. The properties listed are not valid for all the compounds identified on page A-161. These properties are reasonably accurate for chromic acid but not for the other compounds.

Response. The title will be changed to reflect this comment.

Comment 3. Page A-162. Section Ill. Second paragraph. Chromates are no longer used in cooling towers or automobiles to inhibit corrosion in recirculating water.

Response. Chromates have been phased out over the last several years. The reference cited was published in 1988. The California Air Resources Board banned this use in 1989. We will revise the text accordingly.

Comment 4. Page A-162. Section IV. First two paragraphs. In both of these studies the effects of poor personal hygiene practices are probably significant. This is noted in Lucas and Kramkowski (1975). Although personal hygiene practices were not specifically discussed in the Lindberg and Hedenstierna (1983) publication, another study done on chrome plating workers by the same group (Lindberg and Vesterberg, 1983) noted that more than a third of the workers studied (33/91) had "yellow hands" or chrome sores. These are obvious signs of very poor personal hygiene practices that can easily result in the direct transfer of chromic acid to the outer nasal passages and septum. Also, in electroplating the normal operations involve putting objects to be plated in the baths, removing these objects from the baths and adjusting the operating conditions of the bath. These procedures usually require short periods where the operator is directly above the bath subjected to high exposures and long periods away from the bath at much lower exposure. This would produce high peak exposures even though average exposures would be much lower. In fact in Lindberg and Hedenstierna (1983) the following statement is made:

> *The observation that damage to the nasal septum correlated better with short-term peak exposure than with 8-hr mean concentrations of chromic acid clearly underscores the detrimental effects of high peak concentrations of chromic acid.*

Consequently, many of the effects reported are very likely the result of poor personal hygiene or high peak exposures rather than the reported average exposures. When studies of electroplating workers are used for regulatory purposes, these limitations should be recognized.

Response. The poor hygiene practices of the workers in the Lindberg and Hedenstierna (1983) study is unfortunate, both for the workers and for the use of the study as the basis of the chronic REL. Epidemiological studies usually have many complicating factors. However, epidemiological studies of chromium VI workers in other industries exposed to species other than chromic acid have also reported toxicity of the upper respiratory system. Other lung symptoms reported in the key study, such as a diminished forced expiratory flow between Monday morning and Thursday afternoon, are not likely to have resulted from poor personal hygiene.

OEHHA staff attempt to use the best study of a chemical that it can find in the peer-reviewed literature to develop a chronic REL. When a Hazard Index exceeds 1, air district staff consult with OEHHA staff on a case-by-case, chemical-by-chemical basis about the likelihood of adverse health effects. Risk management is an important part of the Air Toxics Hot Spots program.

Comment 5. Page A-163. Section VI. The use of Lindberg and Hedenstierna (1983) for the derivation of a Chronic Reference Exposure Level (REL) for all hexavalent chromium compounds is not appropriate. This study involves workplace exposure to chromic acid. Although chromic acid is a hexavalent chromium compound, it is very unlikely to be a significant component of the hexavalent chromium content of ambient air. Chromic acid is very acidic and highly oxidizing and therefore has very low stability in the environment (Barnhart, 1997). When exposed to the environment it will either react and be chemically reduced to the trivalent chromium state or be neutralized to a dichromate or chromate salt. Under certain conditions these chromate salts can be stable in the environment and therefore regulatory levels for ambient air should be based on these compounds (Finley *et al.*, 1993).

Response. Neither OEHHA nor US EPA agrees that the study of Lindberg and Hedenstierna (1983) is not appropriate. Hexavalent chromium is toxic. It is preferable from the point-of-view of protecting public health to use the data available on the most toxic species present. It would be helpful to know the half-life of the chromium VI ion in the air if that is what the comment about the very low stability of chromic acid in the environment implies. OEHHA's REL is for all chromium VI ions, not just those from chromic acid. In the Air Toxics Hot Spots Program, facilities do not speciate their chromium VI emissions. A 1988 report by the Research Triangle Institute (The fate of hexavalent chromium in the atmosphere. ARB Contract A6-096-32) indicated an average experimental half-life of 13 hours. Since emissions are continuous, there is the potential for continuous exposure. Reports of high percentages of

chromium VI above abandoned hazardous waste sites, as well as notable measurements of CrVI in ambient air and soil near chrome plating facilities, also seem inconsistent with a short half-life for chromium VI.

Comment 6. Page A-164. First paragraph. Both the principal author of the cited study (Lindberg, 1986) and the USEPA (USEPA, 1990) concluded that at average exposures to chromic acid of < 1 $\mu g/m^3$ no effect in the respiratory tract was seen. Therefore, even if this study is considered, the use of an average exposure level of 0.24 $\mu g/m^3$ Cr (VI) and a LOAEL uncertainty factor of 10 is not justified.

Response. Lindberg's conclusion might be applicable for healthy workers, not for sensitive individuals. Workers that were exceptionally sensitive to respiratory irritation might choose to work in a different setting. Despite its 1990 conclusion, US EPA developed a RfC for chromic acid mists and Cr VI aerosols based on the Lindberg and Hedenstierna (1983) report. A LOAEL factor of 10 (or possibly greater) is certainly justified by the nasal ulceration and/or perforation seen in 11 of 24 workers exposed to levels above 2 $\mu g/m^3$ (Table 3 below). The subjective irritation (reported by 4 of 19 workers exposed to levels below 2 $\mu g/m^3$) could justify a UF of 3. However, the atrophy of the nasal mucosa seen below 2 $\mu g/m^3$ in 4 in of 19 workers is considered by OEHHA staff to be a serious adverse effect.

Table 3 (from Lindberg and Hedenstierna, 1983). – Conditions of the Nose and Subjective Symptoms in Groups with Different Mean Values of Exposure and with Different Highest Exposure Values Measured Near the Baths where the Exposed Worker had worked During Some Part of the Day

	8-hr Mean Value of Exposure		Highest Exposure Value		
CR(VI) $\mu g/m^3$	≤1.9	2-20	0.2-1.2	2.5-11	20-46
N	19	24	10	12	14
Subjective irritation	4	11	0	8	4
Atrophy	4	8	1	8	0
Ulceration	0	8*	0	0	7#
Perforation only	0	3	0	0	3

* Two of 8 also had a perforation.
\# Two of 7 also had a perforation.

Comment 8. Based on these comments I recommend that the REL of 0.0008 $\mu g/m^3$ proposed for hexavalent chromium in this draft not be accepted and that all relevant information including animal studies be considered in developing an appropriate REL. Additionally the use of the benchmark dose method (Malsch, *et al.*, 1994) should be considered since it allows the use of a larger database in deriving this value.

Response: OEHHA thanks the commentator for his comments. We have considered relevant information, including animal studies. In the Hot Spots program facilities do not speciate their emissions of chromium VI into aerosols, mists, and particulates. Thus to protect public health OEHHA concentrates on the most toxic species.

US EPA developed 2 RfCs for chromium VI. Neither RfC was based on a benchmark dose approach. The first RfC was 0.008 $\mu g/m^3$ for chromic acid mists and chromium VI aerosols based on the study by Lindberg and Hedenstierna (1983). OEHHA has reviewed the documentation on IRIS for that RfC and disagrees with some of the interpretations made by USEPA, including whether or not nasal atrophy is a severe effect (OEHHA believes that it is) and the exposure concentration selected as the basis of the REL. In addition, for this RfC USEPA decided that the multiplication of 2 intermediate UFs of 3 (which is actually the square root of 10) resulted in 9, not 10.

The second RfC, with the higher value of 0.1 $\mu g/m^3$ for chromium VI particulates, was based on the same studies in rats (Glaser et al., 1985; 1990), which were used by Malsch et al. to develop their value of 0.34 $\mu g/m^3$ by the benchmark approach, a value close to the value USEPA derived using the NOAEL/UF approach. The BC derived by Malsch et al. used the 95% lower confidence limit of the EC_{10} (designated a Maximum Likelihood Estimate) rather than of the EC_{05} preferred by OEHHA. Use of the LCL on an EC_{05} would result in a value even closer to the US EPA value of 0.1.

References cited by commentator**:**

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Finley, B. L., D. M. Proctor, and D. J. Paustenbach (1992). An Alternative to the USEPA's Proposed Inhalation Reference Concentrations for Hexavalent and Trivalent Chromium. *Regulatory Toxicology and Pharmacology* 16:161-176.

Lindberg, E. (1986). *Health Hazards in Chrome Plating.* Department of Environmental Hygiene, Karolinska Institute, Stockholm.

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Malsch, P. A., D. M. Proctor, and B. L. Finley (1994). Estimation of a Chromium Inhalation Reference Concentration Using the Benchmark Dose Method: A Case Study. *Regulatory Toxicology and Pharmacology* 20: 58-82.

United States Environmental Protection Agency (1990). Noncarcinogenic Effects of Chromium. Update to Health Assessment Document. Publ. No. EPA/600/8-87/048F. Office A Research and Development, U.S. Environmental Protection Agency, Washington, DC.

Union Carbide Corporation - Isophorone

Comments on the **isophorone** chronic REL were made by J. M. Cleverdon, Project Safety Manager for Union Carbide Corporation, in a letter dated December 17, 1997. The proposed chronic REL for isophorone (1,1,3-trimethyl-3-cyclohexene-5-one) was based on a probe and final study of inhalation teratology conducted by Bio/dynamics for Exxon Biomedical Sciences in 1983 and 1984. Mice and rats were exposed for 6 hours per day during gestation. Reduced crown-rump length were noted in female rat fetuses at 115 ppm, but not at 50 ppm. Thus a time-weighted gestational exposure NOAEL of 12.5 ppm, an interspecies uncertainty factor of 3, and an intraspecies uncertainty factor of 10 were used to derive a REL of 0.4 ppm (2,000 $\mu g/m^3$). Exencephaly was noted in 4 fetuses of animals exposed to 150 ppm in the probe study (a finding not reproduced in the final study) and this effect was also cited in the summary of critical endpoints observed.

Comment 1. Union Carbide Corporation would like to thank you and your group for allowing us to comment on the draft document Air Toxics Hot Spots Program Risk Assessment Guidelines Part III: Technical Support Document for the Determination of Noncancer Chronic Toxicity Reference Exposure Levels, and specifically on Appendix A.69, Chronic Toxicity Summary - Isophorone. In general, we feel that the Air Toxicology and Epidemiology Section has done a credible job in developing methodologies for determining RELs and that the application of this methodology has been used appropriately in deriving a value of 2,000 $\mu g/m^3$ for isophorone.

We would, however, take exception with the characterization of isophorone as "teratogenic". In the Chronic Toxicity Summary document, it is correctly pointed out on page A-424 (lst full paragraph, 10th sentence) that in a probe study a malformation, exencephaly, was observed in a late resorption in one rat litter from the high exposure concentration group (150 ppm), and in two litters of mice exposed to the high concentration group (in one late resorption from 1 litter, and in two live fetuses from a second litter). The document goes on to state on page A-425, sentence 10: "However, exencephaly is included as a critical effect in this summary because it is considered a serious teratogenic effect that was present at a dose only slightly higher than the LOAEL of the primary study (115 ppm)." We take exception to that statement because it fails to take into consideration the unconventional design of this teratology probe study and the outcome of the definitive developmental toxicology study.

Response. OEHHA has revisited the data bearing on the teratogenicity of isophorone. In this case, as in many other cases examined for this document, there remains considerable uncertainty, and substantial arguments can be made on both sides of the issue. This debate will only be adequately resolved with the acquisition of better data. The number of animals tested, on which the issue rests, is small but the effect observed, exencephaly, is of great concern. The authors of the original report suggested that the exencephaly was likely unrelated to isophorone exposures, but the data are inadequate to obviate concern.

Comment 2. It is very important to keep in mind that this probe study (copy attached) did not employ the typical design of a Segment II developmental toxicity study. Normally, such

studies involve sacrifice shortly before birth. There is a considerable historical database on developmental effects observed shortly before birth, by which time organogenesis is complete. That procedure was not followed in this case, however. Here, the probe study was conducted by exposing female rats and mice on days 6 through 15 of gestation. The mothers were sacrificed on gestation day 16 and the fetuses weighed, measured and examined for external malformations. This examination took place on approximately 4 days (mice) and 6 days (rats) prior to parturition and a critical time period of organogenesis. There is no historical database on which to evaluate the results observed in this probe study at gestation day 16. Thus, it is very difficult to evaluate the biological significance of the findings on day 16.

Response. While there may be limited comparable historical data, the probe study had a 12 member control group, which in any case are the best data on which to compare the exposed groups. In addition, it is unlikely that the results of the exencephaly would be different if the fetuses had been examined at day 20 or 22 of gestation.

Comment 3. This difficulty is compounded by the fact that the definitive study, conducted using substantially more females than in the probe study (22 per group for versus 12 per group in the probe study), found no exencephaly and no significant differences from controls in internal or external malformations at gestation day 20 (rats) and gestation day 18 (mice). If the effect observed in the probe study had been of biological significance, it would likely have appeared in the definitive study; but it did not.

Response. The definitive study, like the probe study, had relatively few exposed individuals. Assuming for the sake of argument that the exencephaly was actually induced by isophorone, the fact that such an endpoint affecting only a minority of individuals would be observed clustered in only one of a series of two small studies is not particularly surprising. The exencephaly may have been a chance occurrence unrelated to isophorone exposure or it may be an effect that occurs with a low incidence rate. Only additional study can resolve this issue.

Comment 4. In addition, in any developmental toxicity study (and in particular in this probe study) there is uncertainty in the exact timing of conception to within a twelve to twenty-four hour period (based upon vaginal smears and/or discovery of a plug). Hours and even minutes are critical in these early stages of embryo development. Observed landmark events can very well be dependent on the precise time of conception relative to terminal sacrifice. The stage of development in the late resorptions is even more uncertain since the exact time of death in these embryos could not be determined.

Response: The experimental control group was subject to the same uncertainties and yet no exencephaly was noted in those animals. Presumably, the initiating events producing exencephaly occur in the early stages of neural tube development. The comment does not seem to consider the irreversible course of events leading to exencephaly.

Comment 5. Considering the arguments above, it is not unreasonable to anticipate that various malformations, including exencephaly, might be observed in a probe study of this design. However, such findings should not be construed to indicate that the material is a teratogenic substance, particularly given the fact that exencephaly was not seen in the definitive study conducted by a more appropriate design where fetal examinations were conducted at term. Indeed, in the definitive study no significant differences from controls were seen for any malformations. The study authors concluded that the exencephaly found in the probe study was not related to the test material in light of the results of the definitive study.

Response: The studies raise a serious concern that can not be discounted on the basis of the issues raised by the commentator. The commentator does raises the legitimate argument that the effects noted could be unrelated to isophorone exposure. Again, this debate will only be resolved with better data relevant to this issue.

Comment 6. The fact that the malformations observed in the probe study were isolated to the high concentration group may be related to the evidence of delays in development identified in the definitive study.

Response: The clustering of malformations in the high-dose group would also be consistent with a dose-response effect by an agent causing the endpoint.

Comment 7. We do not contest the fact that fetal toxicity and delays in development were noted in that study. This finding in the definitive study is consistent with fetal toxicity and delayed development observed in many Segment II developmental toxicity studies conducted with solvents and other chemicals and seen in association with mild maternal toxicity.

Response: The chronic REL document for isophorone cited these effects as the primary finding used to derive the REL. Since there are uncertainties involved in the interpretation of the exencephaly noted in the probe study, the reference to teratogenicity will be removed from Sections I and VI. However, the discussion of the concern that this effect could be related to isophorone exposure will remain as a point of discussion in the document.

Comment 8. In addition to this specific comment on the isophorone, your letter of October 31, 1997 requested comments on a proposal to limit the degree of accuracy of chronic inhalation reference exposure levels to one significant figure. We feel that when significant figures are used in a real sense, accuracy is probably reasonably good to two significant digits, e.g., 95. mg/m^3, 9.5 mg/m^3, 0.095 mg/m^3, but not, for instance, to four significant digits 95.25 mg/m^3, 9.525 mg/m^3 or 0.09525 mg/m^3. We believe that expressing values to one significant digit would not necessarily reflect the accuracy of some measurements in this discipline.

Response: Uncertainty factors as used by OEHHA and USEPA for the development of chronic reference exposure levels are generally based on estimates of the most appropriate

value to the nearest order-of-magnitude (10-fold difference) or at best a 3-fold difference. While we may have more precise information on some components of the risk assessment, the final REL can be no more certain than the weakest link in the chain of data used to derive it. Thus, for example, we can not place any greater confidence in a REL estimate of 9.5 or 9.9 mg/m^3. OEHHA is still considering whether to use one or two significant figures.

Vinyl Acetate Toxicology Group

Comments on the chronic REL for **vinyl acetate** were made by Robert J. Fensterheim, Executive Director of the Vinyl Acetate Toxicology Group, Inc. ("VATG"). The VATG represents all of the North American manufacturers of vinyl acetate and some of the major users of vinyl acetate which include: AT Plastics, Inc.; Borden, Inc.; Celanese Limited; E. I. Du Pont de Nemours and Company; Exxon Biomedical Sciences, Inc.; Millennium Petrochemicals; Rohm and Haas Company; and Union Carbide Corporation. OEHHA proposed use of the US EPA RfC of 200 $\mu g/m^3$ as the chronic REL for vinyl acetate.

Comment 1: OEHHA has proposed an inhalation reference exposure level of based on a two year bioassay by Owen 1988. That study was sponsored by the vinyl acetate industry. In proposing the REL for vinyl acetate, OEHHA elected to make use of the Reference Concentration (RfC) developed by U.S. EPA which is presented in their Integrated Information Risk System (IRIS) database. The VATG support OEHHA's determination to rely on the EPA Reference Concentrations for purposes of establishing RELs, but the RfC must be based on the latest science and be up-to-date. In order to ensure continued consistency, we believe that OEHHA should adopt a provision for presumptive and automatic updating of the REL whenever the EPA RfC is revised. Vinyl acetate, like several other compounds involved in active research and risk assessment activities, will be reevaluated in the near future. On January 2, 1998 (63 FR 75), EPA announced their decision to update the IRIS databases for several compounds including vinyl acetate. This update, which will include a reevaluation of the RfC, is scheduled to start in FY 1998. That update will be partially based on the considerable mechanistic research that the VATG has sponsored. We suggest that in developing the RELs that OEHHA make reference to the IRIS database so that updates to the EPA RfCs can be readily incorporated into the OEHHA RELs program.

Response: The USEPA RfC for vinyl acetate has been in place since 1990. All USEPA Reference Concentrations (RfCs), available when the Technical Support Document (TSD) on Chronic Reference Exposure Levels was drafted in October 1997, are being used as chronic RELs. Use of RfCs as chronic RELs was one action that OEHHA took to implement Governor's Executive Order W-137-96, which concerned the enhancement of consistency and uniformity in risk assessment between Cal EPA and USEPA. RfCs released after October 1997, including ones that are revisions of those in the October 1997 draft, will be evaluated for use in the Hot Spots program by reviewing the scientific basis of each RfC when it becomes available and by determining whether the scientific literature cited in the RfC is appropriate. Appropriate RfCs will be submitted yearly to the SRP for review and possible endorsement. OEHHA intends to harmonize with USEPA as much as possible, but not uncritically and not automatically.