CHRONIC TOXICITY SUMMARY

1,4-DICHLOROBENZENE

(p-dichlorobenzene; di-chloricide; p-dichlorobenzol; Paradow; Paramoth; Parazene; p-chlorophenyl chloride)

CAS Registry Number: 106-46-7

I. Chronic Toxicity Summary

Inhalation reference exposure level	**800 µg/m^3** (100 ppb)
Critical effect(s)	General effects (reduced body weights and food consumption) in rats CNS effects (tremors) in rats Respiratory/dermal effects (nasal and ocular discharge) in rats Liver effects (increased liver weight) in rats, and Kidney effects (increased kidney weight) in rats.
Hazard index target(s)	Nervous system; respiratory system; alimentary system; kidney

II. Chemical Property Summary (HSDB, 1997; CRC, 1994)

Description	White crystals, monoclinic prisms
Molecular formula	$C_6H_4Cl_2$
Molecular weight	147.01 g/mol
Boiling point	174^{o}C
Melting point	52.7^{o}C
Vapor pressure	10 torr @ 54.8^{o}C
Solubility	Soluble in chloroform, carbon disulfide, alcohol, ether, acetone, benzene
Conversion factor	1 ppm = 6.0 mg/m^3 at 25ºC

III. Major Uses and Sources

Commercial grade 1,4-dichlorobenzene (1,4-DCB) is available in the USA as a technical grade liquid, typically containing a small percentage (>0.1% by weight) of meta (1,3-DCB) and ortho (1,2-DCB) isomers; as a solution in solvent or oil suspension; or as crystalline material pressed into various forms (HSDB, 1997). Besides its role as an intermediate in the synthesis of various organics, dyes and pharmaceuticals, 1,4-dichlorobenzene is used as a space or garbage deodorizer for odor control. The insecticidal and germicidal properties of 1,4-dichlorobenzene are used to control fruit borers and ants, moths, blue mold in tobacco seed beds, and mildew and mold on leather or fabrics. In 1996, the latest year tabulated, the statewide mean outdoor monitored concentration of 1,4-DCB was approximately 0.15 ppb

(CARB, 1999). The annual statewide industrial emissions from facilities reporting under the Air Toxics Hot Spots Act in California based on the most recent inventory were estimated to be 30,577 pounds of dichlorobenzene (CARB, 2000).

IV. Effects of Human Exposure

Case reports of human exposure to 1,4-DCB include malaise, nausea, hepatic manifestations (yellow atrophy and cirrhosis), proteinuria, bilirubinuria, hematuria, and anemia. A woman exposed to 1,4-DCB for 6 years developed central nervous system effects, including severe cerebellar ataxia, dysarthria, weakness in all limbs, and hyporeflexia (U.S. EPA, 1985).

No epidemiologic studies of 1,4-DCB exposures were located.

V. Effects of Animal Exposure

Rats, rabbits and guinea pigs were exposed to 0, 96, 158, 341 or 798 ppm (0, 577, 950, 2050 or 4800 mg/m^3) 1,4-DCB by inhalation 7 hours/day, 5 days/week for 6-7 months (Hollingsworth *et al.*, 1956). High dose animals showed marked tremors, weakness, loss of weight, eye irritation and unconsciousness. Liver and kidney changes included cloudy swelling and centrilobular cellular degeneration (liver). In another inhalation study in rats animals were exposed to 0, 75 or 500 ppm (0, 451 or 3006 mg/m^3) for 5 hours/day, 5 days/week for 76 weeks (Riley *et al.*, 1980). The authors found increased kidney and liver weights in the high dose group. Thus 75 ppm was a NOAEL. Studies with oral exposure to 1,4-DCB, including the NTP (1987) chronic bioassay study (maximum dose of 300 mg/kg-day), have also found an increased incidence of renal and hepatic lesions (cellular degeneration and focal necrosis).

Three inhalation reproductive studies, one in rabbits (Hayes *et al.*, 1985), one in mice (Anderson and Hodge, 1976), and one in rats (Chlorobenzene Producers Assn., 1986), found minimal reproductive effects. In rabbits exposed on days 6-18 of gestation to 100, 300, and 800 ppm 1,4-DCB, only the differences in percentage of implantations resorbed and in percentage of litters with resorptions were significantly increased and only in the 300 ppm group (Hayes *et al.*, 1985). No reduction in reproductive performance was observed in mice exposed to 0, 75, 225, or 450 ppm 1,4-DCB for 6 hours/day for 5 days (Anderson and Hodge, 1976).

In a two-generation reproductive study (Chlorobenzene Producers Association, 1986), Sprague-Dawley rats P1 (28/sex/group) were exposed to 0, 50, 150 or 450 ppm (0, 301, 902, or 2705 mg/m^3) of 1,4-DCB vapor, 6 hours/day, 7 days/week for 10 weeks, and then mated for 3 weeks. The second generation F1 weanlings were exposed to 1,4-DCB for 11 weeks and then mated. No developmental abnormalities were observed in pups examined. At 450 ppm significant decreases in live births, pup weights, and pup survival were seen in both the F1 and F2 generations. Non-reproductive effects observed in the parental males in the 150 and 450 ppm groups included significantly increased liver and kidney weights. All dose

levels caused hyaline droplet nephrosis in post-pubescent males; but this change was associated with the formation of alpha-2u-globulin, an abnormality considered specific for male rats with no relative human significance (U.S. EPA, 1991). The Chlorobenzene Producers Association reproductive study was chosen by the U.S. EPA to derive the RfC.

VI. Derivation of Chronic Reference Exposure Level

Study	Chlorobenzene Producers Association, 1986
Study population	Sprague-Dawley rats (28 rats/sex/group)
Exposure method	Discontinuous whole-body inhalation exposures (0, 50, 150 or 450 ppm)
Critical effects	Reduced body weights and food consumption; tremors; nasal and ocular discharge; increased liver and kidney weights
LOAEL	150 ppm
NOAEL	50 ppm
Exposure continuity	6 hr/day for 7 days/week
Average experimental exposure	13 ppm for NOAEL group (50 x 6/24)
Human equivalent concentration	13 ppm for NOAEL group (gas with systemic effects, based on RGDR = 1.0 using default assumption that lambda (a) = lambda (h))
Exposure duration	10 weeks
LOAEL uncertainty factor	1
Subchronic uncertainty factor	3
Interspecies uncertainty factor	3
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	100
Inhalation reference exposure level	0.1 ppm (100 ppb, 0.8 mg/m^3, 800 µg/m^3)

The chronic REL for 1,4-dichlorochlorobenzene is also the U.S. EPA RfC. OEHHA agrees with the U.S.EPA analysis. A 3-fold subchronic uncertainty factor (instead of 10) was used by U.S. EPA because of data suggesting limited progression of hepatic lesions (Riley *et al.*, 1980). Ten weeks are also greater than 8% of a rat's two-year lifetime and thus in accord with OEHHA's use of a subchronic UF of 3 (OEHHA, 2000).

For comparison, Riley *et al*. (1980) found a chronic NOAEL of 75 ppm for kidney and liver effects in rats, which is equivalent to 11.2 ppm continuous exposure. Use of an RGDR of 1 and a total UF of 30 (3 for interspecies and 10 for intraspecies) results in a REL estimate of 0.4 ppm.

VII. Data Strengths and Limitations for Development of the REL

The major strengths of the REL for 1,4-dichlorochlorobenzene are the observation of a NOAEL and the demonstration of a dose-response relationship. The major uncertainties are the lack of human data and the lack of chronic, multiple-species health effects data.

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CHRONIC TOXICITY SUMMARY

1,1-DICHLOROETHYLENE

(DCE; 1,1-dichloroethene; VDC; vinylidene chloride)

CAS Registry Number: 73-35-4

I. Chronic Toxicity Summary

Inhalation reference exposure level	**70** m**g/m^3** (20 ppb)
Critical effect(s)	Increased mortality; hepatic effects (mottled livers and increases in liver enzymes) in guinea pigs
Hazard index target(s)	Alimentary system

II. Physical and Chemical Properties (HSDB, 1994; CRC, 1994)

Description	Colorless liquid
Molecular formula	$C_2H_2Cl_2$
Molecular weight	96.95 g/mol
Boiling point	31.7°C
Melting point	–122.5°C
Vapor pressure	500 torr @ 20°C
Solubility	Soluble in water (2.5 g/L); miscible in organic solvents
Conversion factor	3.97 µg/m^3 per ppb at 25 °C

III. Major Uses and Sources

1,1-Dichloroethylene (1,1-DCE) is used in the production of polyvinylidene chloride copolymers (HSDB, 1994). 1,1-DCE containing copolymers include other compounds such as acrylonitrile, vinyl chloride, methacrylonitrile, and methacrylate. These copolymers are used in flexible packaging materials; as flame retardant coatings for fiber, carpet backing, and piping; as coating for steel pipes; and in adhesive applications. Flexible films for food packaging, such as SARAN and VELON wraps, use such polyvinylidene chloride copolymers. The annual statewide industrial emissions from facilities reporting under the Air Toxics Hot Spots Act in California based on the most recent inventory were estimated to be 2458 pounds of vinylidene chloride (CARB, 2000).

IV. Effects of Human Exposure

Limited information exists regarding the human health effects following exposure to 1,1-DCE. A few case reports and mortality studies have reported hepatotoxicity and

nephrotoxicity after repeated, low-level exposures (USEPA, 1976; Ott *et al.*, 1976). However, these investigations were conducted in industrial settings with the possibility of mixed chemical exposures. In preliminary clinical findings reported by the EPA (1976), workers exposed to 1,1-DCE for 6 years or less had a high incidence of hepatotoxicity, with liver scans and measurements of liver enzymes revealing 50% or greater loss in liver function in 27 of 46 exposed workers. Unfortunately, no follow-up study was reported.

V. Effects of Animal Exposure

Several studies have reported on the subchronic or chronic toxicity of 1,1-DCE in laboratory animals exposed either via oral or inhalation routes. The liver is the primary target organ of 1,1-DCE toxicity following acute or chronic inhalation exposure. Such exposure is marked by both biochemical changes (alterations in serum enzyme levels) and histological changes (e.g., midzonal and centrilobular swelling, degeneration, and necrosis) (Gage, 1970; Lee *et al.*, 1977; Plummer *et al.*, 1990; Quast, 1976; Quast *et al.*, 1986). Unfortunately, these longer-term studies used only one or two doses or a limited number of animals.

Male and female rats exposed intermittently (6 hours/day, 5 days/week) to 125 or 200 ppm 1,1-DCE over 30 days exhibited centrilobular fatty degeneration or hepatocellular necrosis (Quast 1976, as cited by USDHHS, 1994). Two other studies identified hepatic changes in rats at lower concentrations of 1,1-DCE (6 hours/day, 5 days/week): cytoplasmic vacuolation after 30- or 90-day exposure to 25 or 75 ppm 1,1-DCE (Balmer *et al.*, 1976, as cited by USDHHS, 1994), and fatty changes after 6 months at 25 ppm 1,1-DCE (Quast *et al.*, 1986).

Laboratory animals appear less tolerant of continuous exposure (23-24 hours per day) than intermittent exposure. Beagle dogs exposed to 100 ppm 1,1-DCE for 8 hours/day, 5 days/week for 42 days had no evidence of hepatotoxicity, but continuous exposure to 48 ppm for 90 days caused liver changes (Prendergast *et al.*, 1967). Similarly, monkeys continuously exposed to 48 ppm for 90 days exhibited focal necrosis and hemosiderin deposition, while no liver toxicity was apparent following 42 days of intermittent exposure to 100 ppm 1,1-DCE (Prendergast *et al.*, 1967). Guinea pigs exposed to 1,1-DCE for 24 hours per day for 90 days (0, 5, 15, 25, or 48 ppm) displayed mottled livers at 15 ppm, and increased liver enzyme levels (serum glutamic-pyruvic transaminase (SGPT) and alkaline phosphatase (AP)) at 48 ppm. A NOAEL of 5 ppm based on liver changes (Prendergast *et al.*, 1967) is indicated by the results.

Data on continuously exposed guinea pigs from Prendergast *et al*. (1967)

ppm 1,1-DCE (mg/m^3)	*Survival*	*Body weight change*	*Liver AP*	*SGPT*
0	312/314	+69.0%	0.08±0.03	10±5
5 (20)	43/45	+58.6%	0.08±0.03	11±3
15 (61)	12/15	+55.3%	Not reported	Not reported
25 (101)	12/15	+74.0%	Not reported	Not reported
48 (191)	8/15	+50.3%	0.19±0.04	>70

Additional adverse effects observed to a lesser extent in laboratory animals include respiratory and renal toxicity. Nephrotoxicity observed following chronic 1,1-DCE exposure included gross organ (increases in kidney weight) (Klimisch *et al.*, 1979; Quast *et al.*, 1986) and histological changes (tubular swelling, degeneration, and necrosis) (Klimisch *et al.*, 1979; Lee *et al.*, 1977; Prendergast *et al.*, 1967). Continuous exposure of rats to 48 ppm 1,1-DCE for 90 days caused nuclear hypertrophy of the renal tubular epithelium (Prendergast *et al.*, 1976). Mice exposed to 25 ppm 1,1-DCE 4 hours/day, 4 or 5 days/week, for 52 weeks displayed severe tubular nephrotoxicity (Maltoni *et al.*, 1985 as cited by USDHHS, 1994). Nasal irritation was observed in rats exposed to 200 ppm for 4 weeks (Gage 1970). But no respiratory effects were attributed to 1,1-DCE exposure in rats, monkeys, dogs, rabbits, or guinea pigs exposed to 100 ppm intermittently for 6 weeks (Prendergast *et al.*, 1967) or in rats exposed to 75 ppm for 18 months (Quast *et al.*, 1986).

Toxicokinetic studies in laboratory animals have demonstrated that 1,1-DCE is readily absorbed and rapidly distributed following inhalation exposure (Dallas *et al.*, 1983; McKenna *et al.*, 1978b). Following inhalation exposure to radioactively labeled 1,1-DCE, rats preferentially accumulate radioactivity in the kidney and liver (McKenna *et al.*, 1978b; Jaeger *et al.*, 1977). Glutathione (GSH) conjugation appears to be the major detoxification route for 1,1-DCE intermediates, and GSH-depleting experimental states, such as drugs and fasting, may tend to increase 1,1-DCE toxicity (Jaeger *et al.*, 1977; McKenna *et al.*, 1978; Reichert *et al.*, 1978). One study greatly increased 1,1-DCE induced lethality and hepatotoxicity in rats by pretreatment with acetaminophen (Wright and Moore, 1991).

VI. Derivation of Chronic Reference Exposure Level (REL)

Study	Prendergast *et al.* (1967)
Study population	Guinea pigs (15 per group, except 45 animals in 20 mg/m^3 group)
Exposure method	Continuous whole body inhalation (0, 20, 61, 101, or 189 mg/m^3)
Critical effects	Increased mortality at 61, 101, and 189 mg/m^3; hepatic effects (mottled livers and increases in SGPT and AP enzymes) noted at 189 mg/m^3
LOAEL	61 mg/m^3 (15 ppm)
NOAEL	20 mg/m^3 (5 ppm)
Exposure continuity	Continuous
Exposure duration	90 days
Average experimental exposure	20 mg/m^3 for NOAEL group
Human equivalent concentration	20 mg/m^3 for NOAEL group (gas with systemic effects, based on default assumption that RGDR = 1 using default assumption that lambda (a) = lambda (h))
LOAEL uncertainty factor	1
Subchronic uncertainty factor	10 (since guinea pig life-span is approx. 6 years)
Interspecies uncertainty factor	3
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	300
Inhalation reference exposure level	0.07 mg/m^3 (70 $\mu g/m^3$; 0.02 ppm; 20 ppb)

The principal study (Prendergast *et al.*, 1967) identified adverse hepatic and/or renal effects in rats (15 or 45/group), guinea pigs (15 or 45/group), dogs (2 or 6/group), and monkeys (3, 9, or 21/group) exposed to inhaled 1,1-DCE. Continuous exposure to 1,1-DCE, 24 hours/day over 90 days, demonstrated more severe effects than intermittent exposure, 6 hours/day, 5 days/week for 6 weeks, in the species tested. Unlike the other available subchronic and chronic studies, this principal study included multiple exposure levels of 0, 5, 15, 25 and 48 ppm (0, 20, 61, 101, and 189 mg/m^3). Mortality, hematologic and body weight data were well tabulated and presented in this study. Histopathologic evaluation was conducted on the heart, lung, liver, spleen and kidneys. Following continuous exposure, adverse hepatic effects included focal necrosis in monkeys (LOAEL = 189 mg/m^3, NOAEL = 101 mg/m^3), in dogs (LOAEL = 189 mg/m^3, NOAEL = 101 mg/m^3), and in rats (LOAEL = 189 mg/m^3, NOAEL = 101 mg/m^3); and altered lipid content and increases in SGPT and alkaline phosphatase in guinea pigs (LOAEL = 189 mg/m^3, NOAEL = 20 mg/m^3). Additionally, renal alterations were observed in rats as nuclear hypertrophy in the tubular epithelium (LOAEL = 189 mg/m^3, NOAEL = 61 mg/m^3). Monkeys exposed to 1,1-DCE also displayed a greater than 25% decrease in body weight (LOAEL 189 mg/m^3, NOAEL 20 mg/m^3). The subchronic study by Prendergast *et al.* (1967) was chosen over the chronic studies because of its better design, its use of continuous exposure, and its exhibition of toxic effects below the LOAELs reported in the other studies.

Although limited in number, the other chronic and subchronic studies available consistently demonstrate adverse hepatic effects following 1,1-DCE exposure (Lee *et al.*, 1977; Maltoni *et al.*, 1985; Plummer *et al.*, 1990; Quast *et al.*, 1986). Hepatocellular fatty change was observed in rats exposed to 25 ppm or 75 ppm 1,1-DCE intermittently (6 hrs/d, 5 d/wk) for 18 months. This mid-zonal fatty change was also observed at the 12-month interim sacrifice, but did not appear to progress in severity or incidence over time (Quast *et al.*, 1986). A more severe hepatocellular necrosis and renal tubular necrosis were observed in mice exposed to 55 ppm 1,1-DCE 6 hr/d, 5 d/week for 1 year (Lee *et al.*, 1977).

For comparison, Quast *et al.* (1986) determined a LOAEL of 25 ppm for liver effects of minimal severity in rats after 18 months exposure. Use of continuous time adjustment to 4.5 ppm, multiplication by an RGDR of 1, and division by a total UF of 100 (3 for LOAEL to NOAEL, 3 for interspecies, and 10 for intraspecies) results in an estimate of 45 ppb (200 $\mu g/m^3$).

VII. Data Strengths and Limitations for Development of the REL

Uncertainty factors are appropriate due to the limited number of subchronic and chronic inhalation studies (greater than 1 year duration) in laboratory animals. In addition, few industrial surveys and epidemiological studies are available on the adverse effects of 1,1-DCE in humans; these are limited by small sample size, short follow-up, and/or brief exposure periods. But this limited evidence does suggest an association between repeated exposure to 1,1-DCE and liver damage in humans (EPA, 1976), and the key study is an animal study which found adverse hepatic effects. No toxicokinetic data regarding the absorption, distribution, metabolism or excretion of 1,1-DCE in humans are available.

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CHRONIC TOXICITY SUMMARY

N,N-DIMETHYLFORMAMIDE

(N-formyldimethylamine)

CAS Registry Number: 68-12-2

I. Chronic Toxicity Summary

Inhalation reference exposure level	**80 µg/m^3** (30 ppb)
Critical effect(s)	Liver dysfunction and respiratory irritation in humans
Hazard index target(s)	Alimentary system, respiratory system

II. Chemical Property Summary (HSDB, 1994)

Description	Colorless to very slightly yellow liquid
Molecular formula	C_3H_7NO
Molecular weight	73.09 g/mol
Boiling point	153°C
Melting point	–61°C
Vapor pressure	3.7 torr @ 25°C
Solubility	Soluble in alcohol, ether, acetone, benzene, and chloroform; miscible with water
Conversion factor	2.99 µg/m^3 per ppb at 25ºC

III. Major Uses and Sources

Dimethylformamide (DMF) is primarily used as a solvent in the production of polyurethane products and acrylic fibers. It is also used in the pharmaceutical industry, in the formulation of pesticides, and in the manufacture of synthetic leathers, fibers, films, and surface coatings (Howard, 1993; Gescher, 1993; Redlich *et al.*, 1988). DMF may be emitted to the environment as a result of its use in a variety of petrochemical industries (Howard, 1993). The annual statewide industrial emissions from facilities reporting under the Air Toxics Hot Spots Act in California based on the most recent inventory were estimated to be 18,249 pounds of DMF (CARB, 2000).

IV. Effects of Human Exposure

Among 100 workers occupationally exposed to DMF for at least one year (mean exposure of 5 years; range = 1-15 years), a statistically significant incidence of hepatic impairment, as indicated by elevated gamma-glutamyl transpeptidase levels and digestive disturbances, was noted (Cirla *et al.*, 1984). Other changes, that were not statistically significant, included

increased SGOT and SGPT and enlarged livers. The mean time-weighted average concentration of DMF was 22 mg/m^3 (range = 8-58 mg/m^3). Symptoms of irritation occurring only during work at statistically significantly higher incidences included watery eyes, dry throat, and coughing. Also, the exposed workers reported a reduced sense of smell and dry coughs at home with a statistically significant difference as compared to controls. Several of the DMF exposed workers also reported alcohol intolerance characterized by a disulfiram-type reaction (facial flushing and palpitations following alcohol ingestion). Alcohol consumption, a potential confounder, was controlled for in the study design.

A similar study was conducted on workers who had been employed in an acrylic acid fiber plant for more than 5 years (Cantenacci *et al.*, 1984). Concentrations to which the workers were exposed were characterized as either an 8-hour TWA of 18 mg/m^3 or an 8-hour TWA of 3 mg/m^3. Measures of liver function including SGOT, SGPT, gamma-glutamyl transferase, and alkaline phosphatase levels were not significantly different between exposed and unexposed workers. However, the U.S. EPA cautions that because only 54 matched pairs of workers were examined, the power of this study was not high enough to reliably detect a difference in enzyme levels.

Redlich *et al*. (1988) characterized a plant-wide outbreak of liver disease among workers in a factory coating fabric with polyurethane. Fifty-eight of 66 (88%) workers participated and each had standard liver screening function tests done at least once. At the work site DMF was being used in poorly ventilated areas without appropriate skin protection. No other major known hepatotoxic exposure was identified. Overall, 36 of 58 (62%) workers tested had elevations of either aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels. Enzyme abnormalities occurred almost exclusively in production workers (35 out of 46 abnormal). Only 1 of 12 non-production workers showed elevations in enzyme levels ($p < 0.0001$). Serologic tests excluded known infectious causes of hepatitis in all but 2 workers. Changes, characteristic of liver injury, were confirmed by histologic examination of biopsy specimens from 4 workers. Improvement in liver enzyme abnormalities and symptoms in most patients were seen, after modification of work practices and removal of workers most severely affected from exposure. However, some patients showed persistent elevations of enzyme levels. No measurements or estimates of DMF exposure levels were reported.

Wang *et al*. (1991) investigated the prevalence of liver injury associated with DMF exposure in 183 of 204 (76%) employees of a synthetic leather factory by performing medical examinations, liver function tests, and creatine phosphokinase (CPK) determinations. Air concentrations were measured with personal samplers and gas chromatography. The concentration of DMF in air to which each worker was exposed was categorized as high (DMF exposure index 2: 25-60 ppm; 75-180 mg/m^3), medium (index 1: 10-40 ppm), and low (index 0: <10 ppm). High exposure concentrations were significantly associated with elevated alanine aminotransferase (ALT) levels (i.e., greater than or equal to 35 International Units/liter), a result that did not change after stratification by hepatitis B carrier status. Logistic regression analysis indicated that exposure to high DMF levels was associated with elevated ALT ($p = 0.01$), whereas hepatitis B surface antigen (HBsAg) was slightly but independently associated with elevated ALT ($p = .07$). Workers with normal ALT values had significantly higher mean ALT and aspartate aminotransferase (AST) activities, especially

among those who were not HBsAg carriers. A significant association existed between elevated CPK levels and exposure to DMF. However, an analysis of the CPK isoenzyme among 143 workers did not reveal any specific damage to muscles. Thus the authors ascribed the liver injury to DMF.

U.S. EPA (1994) states that subjective evidence of liver toxicity, such as digestive impairment and alcohol intolerance, is often observed at exposures below those that cause clinical changes in liver enzymes. Thus, the symptoms may be more sensitive indicators of hepatic impairment.

Three unexplained cases of small-for-date third trimester intrauterine deaths were observed in a group of women working as quality control analysts in the pharmaceutical industry (Farquhason *et al.*, 1983). This represented a 30% stillbirth rate as compared with the average for the general population of about 0.26%. While the authors concluded that the occurrence of stillbirth in these women was not likely due to chance, the effects cannot be solely attributed to DMF because the women were exposed to other agents in addition to DMF.

V. Effects of Animal Exposure

Malley *et al*. (1994) exposed male and female Crl:CD rats and mice to 0, 25, 100, or 400 ppm DMF for 6 hr/day, 5 days/week for 18 months (mice) or 2 years (rats). No compound-related effects on clinical observations or survival were observed. Body weights of rats exposed to 100 (males only) and 400 ppm were reduced, while body weights were increased in 400 ppm mice. No hematologic changes were observed in either species. Serum sorbitol dehydrogenase activity was increased in rats exposed to 100 or 400 ppm. DMF-related morphological changes were observed only in liver. Exposure of rats to 100 and 400 ppm produced increased relative liver weights, centrilobular hepatocellular hypertrophy, lipofuscin/hemosiderin accumulation in Kupffer cells, and centrilobular single cell necrosis (400 ppm only). In mice, increased liver weights (100 ppm males, 400 ppm both sexes), centrilobular hepatocellular hypertrophy, accumulation of lipofuscin/hemosiderin in Kupffer cells, and centrilobular single cell necrosis were observed in all exposure groups. These observations occurred in a dose-response fashion and were minimal at 25 ppm. No increase in hepatic cell proliferation was seen in mice or female rats. Slightly higher proliferation was seen in male rats exposed to 400 ppm at 2 weeks and 3 months but not at 12 months. Thus 25 ppm was a chronic NOAEL for both rats and mice.

A developmental toxicity study using three species (mice, rabbits, and rats) and four routes of administration (oral, inhalation, dermal, and intraperitoneal) identified the rabbit as the most sensitive of the three species. Groups of 15 pregnant rabbits were exposed for 6 hours per day on days 8-20 of gestation to 50, 150, or 450 ppm (150, 449, or 1350 mg/m^3) DMF (Hellwig *et al.*, 1991). Slight maternal toxicity, as indicated by non-statistically significant decreases in maternal body weight gain, was observed in the 450 ppm exposure group. An increased number of total malformations per litter was observed in the 450 ppm exposure group. Malformations observed at statistically higher incidences compared to controls included hernia umbilicalis, external variations, pseudoankylosis of the forelimbs, and skeletal

variation and retardation. The authors conclude that there was a clear teratogenic effect in rabbits following maternal exposure to 450 ppm DMF and a marginal effect following exposure to 150 ppm DMF. A NOAEL of 50 ppm for fetal and maternal effects was reported. Inhalation exposure to 150 ppm was calculated by the authors to approximate a daily dose of 45 mg/kg/day, which coincides with previous work on this compound in this species.

VI. Derivation of Chronic Reference Exposure Level

Study	Cirla *et al.*, 1984; Catenacci *et al.*, 1984
Study population	Occupationally exposed workers
Exposure method	Discontinuous inhalation exposures
Critical effects	Digestive disturbances and slight hepatic changes
LOAEL	22 mg/m^3
NOAEL	Not observed
Exposure continuity	8 hr/day (10 m^3/day), 5 days/week (assumed)
Average occupational exposure	7.9 mg/m^3 for LOAEL group (22 x 10/20 x 5/7)
Human equivalent concentration	7.9 mg/m^3
Exposure duration	5 years (mean exposure duration)
LOAEL uncertainty factor	3
Subchronic uncertainty factor	3
Interspecies uncertainty factor	1
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	100
Inhalation reference exposure level	0.08 mg/m^3 (80 $\mu g/m^3$, 0.03 ppm, 30 ppb)

The U.S. EPA (1994) based its RfC of 30 $\mu g/m^3$ on the same study but included a Modifying Factor (MF) of 3 due to lack of reproductive toxicity data in the DMF database. The criteria for use of modifying factors are not well specified by U.S. EPA. Such modifying factors were not used by OEHHA. Intermediate uncertainty factors were used for LOAEL to NOAEL and subchronic to chronic extrapolation because of the mild nature of the effects observed and the less than chronic exposure duration.

For comparison Hellwig *et al*. (1991) found a developmental NOAEL of 50 ppm in rabbits exposed 6 hours per day on gestation days 8-20, equivalent to continuous exposure of 12.5 ppm. Multiplication by an RGDR of 1 and division by a UF of 30 (3 for interspecies and 10 for intraspecies) results in a REL estimate of 400 ppb. The NOAEL of 25 ppm for rats and mice in the chronic study of Malley *et al*. (1994) leads to a REL estimate of 150 ppb.

VII. Data Strengths and Limitations for Development of the REL

The major strength of the REL for N,N-dimethylformamide is the availability of human health effects data over several years of exposure. The major uncertainties are the difficulty

in estimating exposure patterns and magnitude, the lack of a NOAEL observation, and the lack of complete reproductive and developmental toxicity data.

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CHRONIC TOXICITY SUMMARY

EPICHLOROHYDRIN

(1-chloro-2,3-epoxy-propane)

CAS Registry Number: 106-89-8

I. Chronic Toxicity Summary

Inhalation reference exposure level	**3 µg/m^3** (0.8 ppb)
Critical effects	Histological changes in nasal turbinates in rats
Hazard index target(s)	Respiratory system; eyes

II. Physical and Chemical Properties (HSDB, 1997; CRC, 1994)

Description	Colorless liquid
Molecular formula	C_3H_5ClO
Molecular weight	92.52 g/mol
Density	1.181 g/cm^3 @ 20° C
Boiling point	117° C
Melting point	–26°C
Vapor pressure	13 torr @ 20° C
Solubility	Slightly soluble in water, soluble in most organic solvents
Conversion factor	1 ppm = 3.78 mg/m^3 @ 25° C

III. Major Uses and Sources

Epichlorohydrin is a major raw material used in the manufacture of epoxy and phenoxy resins. It is also used as a solvent and in the synthesis of glycerol. Other uses include that of insect fumigation and as a chemical intermediate for the formation of glycidyl acrylate derivatives such as those used in the formation of eyeglass lenses (HSDB, 1994). The annual statewide industrial emissions from facilities reporting under the Air Toxics Hot Spots Act in California based on the most recent inventory were estimated to be 4841 pounds of epichlorohydrin (CARB, 2000).

IV. Effects of Exposures to Humans

Studies of male reproductive function have shown no evidence of decreased sperm counts in populations occupationally exposed to epichlorohydrin (Milby *et al.*, 1981).

V. Effects of Exposures in Animals

Rats were exposed for 136 weeks (6 hours/day, 5 days/week) to 0, 10, 30, or 100 ppm (0, 38, 113, or 380 mg/m^3) epichlorohydrin (Laskin *et al.*, 1980). Kidney damage in the form of renal tubular degeneration and dilatation was observed in rats exposed to 30 ppm or greater. The observation of severe inflammation in the nasal passages of 90% of the control animals, as well as in the treated animals, prevented comparison of this effect between the two groups.

A subchronic exposure of rats to 9, 17, 27, 56, or 120 ppm (34, 64, 102, 212, or 454 mg/m^3) for 6 hours/day, 5 days/week for 11-19 exposures showed evidence of extrarespiratory effects. These included liver congestion and necrosis and tubular atrophy in the kidneys at the highest concentration (Gage, 1959). Lethargy and weight loss were observed at 56 ppm.

A study on the effects of epichlorohydrin exposure for 10 weeks (6 hours/day, 5 days/week) on male and female fertility in rats and rabbits showed that male rats, exposed to 50 ppm (189 mg/m^3), were significantly less fertile than controls, as measured by successful matings to unexposed females (John *et al.*, 1979; 1983a). No histological changes were observed in the testes of the male rats at the end of exposure. No significant effects on fertility occurred in the exposed female rats. Degenerative changes in the nasal epithelium were observed in the female rats exposed to 25 ppm (94.5 mg/m^3), and in both sexes at 50 ppm.

A teratology study was carried out in rats and rabbits exposed to 0, 2.5, or 25 ppm (0, 9.5, or 95 mg/m^3) epichlorohydrin 7 hours/day during the critical days of gestation. There were no significant differences between controls and treated animals in the incidence of developmental defects, in maternal toxicity, or in histopathology of the lungs, nasal turbinates, or trachea (John *et al.*, 1983b).

Mice and rats (10/sex/concentration/strain) were exposed to 0, 5, 25, or 50 ppm (0, 19, 95, or 190 mg/m^3) epichlorohydrin for 6 hours/day, 5 days/week for 90 days (Quast *et al.*, 1979). Animals were observed for clinical signs of toxicity and were measured biweekly for body weight changes. Body weight measurements, clinical chemistry, hematology, and urinalysis were conducted. Gross and histopathological examinations were performed at the end of the experiment. Exposures of rats to 25 and 50 ppm epichlorohydrin resulted in inflammation, focal erosions, hyperplasia, and metaplasia in the nasal turbinates. No adverse effects were observed in rats exposed to 5 ppm (19 mg/m^3). Mice similarly showed focal erosion, hyperplasia and metaplasia in the epithelium of the nasal turbinates when exposed to 25 ppm epichlorohydrin or greater.

VI. Derivation of Chronic Reference Exposure Level

Study	Quast *et al.* (1979)
Study population	Rats and mice (10 per sex per concentration)
Exposure method	Discontinuous whole-body inhalation
Critical effects	Inflammation, focal erosions, hyperplasia, and metaplasia in the nasal turbinates
LOAEL	25 ppm (94.5 mg/m^3)
NOAEL	5 ppm (19 mg/m^3)
Exposure continuity	6 hours/day, 5 days/week
Exposure duration	90 days
Average experimental exposure	0.89 ppm (5 x 6/24 x 5/7)
Human equivalent concentration	0.083 ppm (gas with extrathoracic respiratory effects, RGDR = 0.093, based on MVa = 0.14 m^3/day , MVh = 20 m^3/day, SAa(ET) = 15 cm^2), SAh(ET) = 200 cm^2
LOAEL uncertainty factor	1
Subchronic uncertainty factor	3
Interspecies uncertainty factor	3
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	100
Inhalation reference exposure level	0.0008 ppm (0.8 ppb; 0.003 mg/m^3; 3 $\mu g/m^3$)

The U.S. EPA (1994) based its RfC of 1 $\mu g/m^3$ on the same study but used a subchronic UF of 10 for a 90 day study instead of 3 (OEHHA, 2000).

VII. Data Strengths and Limitations for Development of the REL

The strengths of the inhalation REL for epichlorohydrin include the availability of controlled exposure inhalation studies in multiple species at multiple exposure concentrations and with adequate histopathogical analysis and the observation of a NOAEL. Major areas of uncertainty are the lack of adequate human exposure data, the lack of chronic inhalation exposure studies, the limited reproductive toxicity data, and the small groups tested in the study.

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CHRONIC TOXICITY SUMMARY

1,2-EPOXYBUTANE

(1-butene oxide; 1,2-butene oxide; 1,2-butylene oxide; 1,2-epoxybutane; 2-ethyloxirane; ethylethylene oxide; NCI-C55527)

CAS Registry Number: 106-88-7

I. Chronic Toxicity Summary

Inhalation reference exposure level	**20** μ**g/m^3** (6 ppb)
Critical effect(s)	Degenerative lesions of the nasal cavity in mice
Hazard index target(s)	Respiratory system; cardiovascular system

II. Physical and Chemical Properties (HSDB, 1997)

Description	Colorless liquid with disagreeable odor
Molecular formula	C_4H_8O
Molecular weight	72.12 g/mol
Density	0.837 g/cm^3 @ 17°C
Boiling point	63.3°C
Melting point	Not available (CRC, 1994)
Vapor pressure	176 torr @ 25°C
Solubility	Soluble in ethanol, ether, acetone, water
Odor threshold	Unknown
Conversion factor	1 ppm = 2.95 mg/m^3

III. Major Uses or Sources

1,2-Epoxybutane is used as a chemical intermediate, acid scavenger, and stabilizer for chlorinated solvents (Reprotext, 1994). It is highly reactive, flammable, and undergoes exothermic polymerization reactions in the presence of acids, bases, and some salts. It is less volatile than ethylene oxide or propylene oxide (Reprotext, 1994). The annual statewide industrial emissions from facilities reporting under the Air Toxics Hot Spots Act in California based on the most recent inventory were estimated to be 6105 pounds of 1,2-epoxybutane (CARB, 2000).

IV. Effects of Human Exposure

No human toxicological data were found for 1,2-epoxybutane.

V. Effects of Animal Exposure

F344/N rats (50/sex) were exposed to 0, 200, or 400 ppm EBU for 6 hours/day, 5 days/week for 2 years (NTP, 1988). Survival was impaired and concentration-related increases of inflammation, respiratory epithelial hyperplasia, olfactory sensory epithelial atrophy, and hyperostosis of the nasal turbinate bone cavity were observed in male and female rats exposed to either concentration.

B6C3F1 mice (50/sex) were exposed to 0, 50, or 100 ppm EBU for 6 hours/day, 5 days/week for 2 years (NTP, 1988). Survival and body weight gain were reduced significantly at 100 ppm in both sexes. Significant concentration-related increases in incidence of chronic inflammation, epithelial hyperplasia, and erosion of the nasal cavity were noted in both sexes at either concentration. Increases in granulocytic hyperplasia and splenic hematopoiesis were noted at both concentrations in female mice.

Number of mice with lesions in the nasal cavity and olfactory sensory epithelium (NTP, 1988)

Sex		*Males*			*Females*	
EBU concentration	0 ppm	50 ppm	100 ppm	0 ppm	50 ppm	100 ppm
Number of mice studied	49	49	50	50	50	48
Nasal cavity						
Chronic inflammation	0	33	40	0	39	44
Erosion	0	7	17	0	16	24
Regeneration	0	15	17	0	14	15
Epithelial hyperplasia	0	32	45	1	34	35
Squamous metaplasia	1	24	41	0	34	41
Squam. cell papilloma	0	0	1	0	0	0
Olfactory sensory epithelium – atrophy	0	13	32	0	25	35

Male and female mice exposed to 800 ppm (2360 mg/m^3) EBU for 6 hours/day, 5 days/week, for 13 weeks were listless after the first exposure (NTP, 1988). Animals from this group all died by the end of the 13-week exposure. Renal tubular necrosis, and thymic and splenic atrophy were seen in mice exposed to 800 ppm; decreased liver weights were observed following exposure of mice to 400 ppm (1180 mg/m^3) or more. Inflammation of the nasal turbinates was seen in female mice exposed to 100 ppm (295 mg/m^3) or more. No inflammation was observed in controls.

Miller *et al.* (1981) exposed rats and mice of either sex to 0, 75, 150, or 600 ppm (0, 221, 442, or 1770 mg/m^3) EBU 6 hours/day, 5 days/week, for 13 weeks. In this study, no treatment-related effects were noted except for histological lesions in the nasal mucosal epithelium and reduced specific gravity in the urine of rats treated with 600 ppm.

Wolf (1961) observed increased lung weights in rats exposed to 800 ppm of a mixture of epoxybutane isomers. No increase in lung weight was seen at 400 ppm.

Sikov *et al.* (1981) conducted experiments to determine the reproductive toxicity of EBU in rats and rabbits. Rats were exposed to 0, 250, or 1000 ppm (0, 738, or 2950 mg/m^3) 1,2-epoxybutane for 7 hours/day, 5 days/week for 3 weeks prior to gestation, or for 7 hours/day on days 1-19 of gestation. Maternal toxicity in the form of 10% weight loss was observed in rats exposed to 1000 ppm. One death out of 42 occurred in the dams exposed to 1000 ppm. No adverse histological, reproductive, or developmental effects were seen at any concentration. Exposure of rabbits on days 1-24 of gestation to the same concentrations as in the rat experiment showed more severe effects at lower concentrations than those observed in rats. In the rabbits, 6 out of 48 dams died during exposure to 250 ppm, and 14 out of 24 died at 1000 ppm. Extensive maternal mortality in this study prevented evaluation of the reproductive and developmental effects.

VI. Derivation of Chronic Reference Exposure Level

Study	National Toxicology Program (NTP, 1988)
Study population	Rats and mice
Exposure method	Discontinuous inhalation to 0, 50, or 100 ppm EBU
Critical effects	Damage to the upper respiratory epithelium was observed in both species at all concentrations. Mice also showed an increased incidence of granulocytic hyperplasia and splenic hematopoiesis at both concentrations, possibly due to inflammation in the upper respiratory tract.
LOAEL	50 ppm (mice)
NOAEL	Not observed
Exposure continuity	6 hours/day, 5 days/week
Exposure duration	2 years
Average experimental exposure	8.9 ppm for LOAEL group (50 x 6/24 x 5/7)
Human equivalent concentration	1.8 ppm for LOAEL group (gas with extrathoracic respiratory effects, RGDR = 0.20, based on MVa = 0.06 m^3/day, MVh = 20 m^3/day, SAa(ET) = 3.0 cm^2, SAh(ET) = 200 cm^2)
LOAEL uncertainty factor	10 (high incidence of adverse effects)
Subchronic uncertainty factor	1
Interspecies uncertainty factor	3
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	300
Inhalation reference exposure level	0.006 ppm (6 ppb; 0.02 mg/m^3; 20 µg/m^3)

The chronic REL is also the U.S. EPA RfC (U.S. EPA, 1994). OEHHA staff reviewed and agreed with U.S. EPA's analysis of the data.

VII. Data Strengths and Limitations for Development of the REL

The strengths of the inhalation REL for 1,2-epoxybutane include the availability of controlled exposure inhalation studies in multiple species at multiple exposure concentrations and with adequate histopathological analysis. Major areas of uncertainty are the lack of adequate human exposure data and the lack of observation of a NOAEL in the key study.

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CHRONIC TOXICITY SUMMARY

ETHYLENE DICHLORIDE

(1,2-dichloroethane)

CAS Registry Number: 107-06-2

I. Chronic Toxicity Summary

Inhalation reference exposure level	**400 µg/m^3** (100 ppb)
Critical effect(s)	Hepatotoxicity; elevated liver enzyme levels in serum of rats.
Hazard index target(s)	Liver

II. Physical and Chemical Properties (HSDB, 2000; CRC, 1994)

Description	Clear, colorless, oily liquid
Molecular formula	$C_2H_4Cl_2$
Molecular weight	98.97 g/mol
Density	1.2351 g/cm^3 @ 20ºC
Boiling point	57.4ºC
Melting point	–96.9ºC
Vapor pressure	64 torr @ 20ºC
Solubility	Slightly soluble in water (0.869 g/100 ml at 20ºC); miscible with alcohol; soluble in ordinary organic solvents
Conversion factor	1 ppm = 4.05 mg/m^3

III. Major Uses or Sources

Ethylene dichloride (EDC) is used primarily in the production of vinyl chloride monomer (HSDB, 2000). It is also an intermediate in the manufacture of trichloroethane and fluorocarbons and is used as a solvent. In California, EDC is also used as a reactant carrier in the production of solid fuel (CARB, 1997). EDC was commonly used as a gasoline additive to scavenge inorganic lead compounds. The transition to the use of lead-free gasoline has essentially eliminated the use of EDC as a fuel additive in this country. EDC was also used as a soil fumigant but is no longer registered for this use on agricultural products in the United States. The annual statewide industrial emissions from facilities reporting under the Air Toxics Hot Spots Act in California based on the most recent inventory were estimated to be 24,935 pounds of ethylene dichloride (CARB, 2000).

IV. Effects of Human Exposure

Toxicological data resulting solely from long-term exposure to EDC in humans are lacking. Nausea, vomiting, dizziness, and unspecified blood changes were reported in a study of workers exposed to levels of 10-37 ppm EDC (Brzozowski *et al.*, 1954). Kozik (1957) reported adverse central nervous system and liver effects in workers occupationally exposed to concentrations of 16 ppm EDC and below. Rosenbaum (1947) also reported nervous system effects in a study of 100 Russian workers exposed for less than 5 years to concentrations of EDC less than 25 ppm.

Immediately following a 30-minute exposure to an unknown concentration of EDC, a 51 year-old male was somnolent and experienced vomiting (Nouchi *et al.*, 1984). Delirious and trembling, the worker was admitted to the hospital 20 hours post-exposure. The liver was palpable, but serum liver enzymes were normal. The patient lapsed into a coma 3.5 hours following admission to the hospital. A marked elevation in serum liver enzymes was noted on the second day of hospitalization, 35 hours post-exposure. Multiple organ failure occurred on the fourth day of hospitalization and the patient died of arrhythmia. At autopsy, the lungs were congested and edematous. Diffuse degenerative changes were observed in the myocardium. Extensive centrilobular necrosis was observed in the liver, and acute centrilobular necrosis was observed in the kidney. Nerve cells in the brain, including Purkinje cells, appeared shrunken with pyknotic nuclei. The latency period for hepatotoxicity of approximately 20 hours suggests that metabolism of the compound yields the reactive agent (see below).

V. Effects of Animal Exposure

As with humans, the absorption and distribution of EDC in rats following ingestion or inhalation is rapid and complete (IARC, 1999). Metabolism in rats and mice is extensive with 85% of the metabolites appearing in urine. Metabolism occurs predominantly via two pathways, one catalyzed by cytochrome P450 and one by glutathione S-transferase. The direct conjugation with glutathione catalyzed by glutathione S-transferase may ultimately result in the putative alkyating agent (episulfonium ion) primarily responsible for toxicity and carcinogenicity. Evidence for DNA-damaging metabolites resulting via the P450 pathway exists (IARC, 1999). However, this pathway appears to be a minor route for toxic metabolite formation.

Acute exposure in mice resulted in toxic effects similar to those seen in the human case study presented above, including liver and kidney damage (Francovitch *et al*., 1986). Acute EDC exposure exhibits a steep dose-response curve with respect to mortality. However, the long-term exposure studies were notable for the limited organ toxicity and mortality observed in comparison to acute studies (IARC, 1999).

Male and female rats (50 per sex) were exposed to 50 ppm EDC 7 hours per day, 5 days per week for 2 years (Cheever *et al.*, 1990). Absolute and relative liver weights were not significantly different from controls. Daily observations, gross pathology, and extensive

histopathology revealed no differences from controls other than a slight increase in unspecified testicular lesions in the EDC group. Additional rats were exposed to 50 ppm EDC with 0.05% disulfiram (a non-carcinogen used extensively in the rubber industry and as a treatment (Antabuse) for alcoholism) in the diet. Disulfiram treatment resulted in increased number of tumors, increased blood levels of EDC, and increased liver (primarily bile duct cysts) and kidney (chronic nephropathy) lesions. It was concluded that some pathways responsible for metabolism of EDC were inhibited by disulfiram, resulting in increased EDC blood levels and bioactivation to toxic metabolites via other metabolic pathways.

Rats (8-10 per sex per group) were exposed to 0, 5, 10, 50, and 150-250 ppm EDC 7 hours per day, 5 days per week for up to 18 months (Spreafico *et al.*, 1980). Serum chemistry measurements were taken after 3, 6, 12, and 18 months of exposure. Rats to be examined after 3, 6 and 18 months of exposure were 3 months of age at the beginning of the experiment, and rats to be examined after 12 months of exposure were 14 months of age at the beginning of the experiment. Complete histological exams were conducted but non-cancer effects were not discussed. No consistent treatment-related changes in serum chemistry parameters were observed at 3, 6, or 18 months of exposure. However, rats exposed to higher levels of EDC for 12 months exhibited changes in serum chemistry indicative of chronic liver damage, primarily increased alanine aminotransferase (ALT) levels at the two highest exposures. Lactate dehydrogenase (LDH) and aspartate aminotransferase (AST) levels were significantly decreased, but did not appear to be dose-related. γ-Glutamyl transpeptidase levels were elevated but at non-significant levels. Indicators of kidney toxicity included increased blood urea nitrogen levels in the 150 ppm group and increased uric acid levels at the two highest exposures. However, the control values for both of these parameters were significantly lower than that seen in rats tested at other times in this study. Thus, the toxicological significance is questionable. Cholesterol was reduced significantly at the higher exposure levels but the toxicological significance of this finding was unknown. The marked difference between serum chemistry parameters following 12 months of exposure, compared to those following 3, 6, and 18 months of exposure, may be due to the considerable difference in the age of the rats at the start of exposure. This study identifies a 12-month LOAEL of 50 ppm and a NOAEL of 10 ppm in rats.

A study examining the interaction between 1,2-dichloroethane and disulfiram (DSF) exposed rats to EDC concentrations of 150, 300, or 450 ppm 5 days per week for 30 days (Igwe *et al.*, 1986a; Igwe *et al.*, 1986b). Increased liver weights and increased 5-nucleotidase (5-NT) activity were observed in rats following exposure to 450 ppm EDC (the LOAEL for this study). This study also determined that the interaction between DSF and EDC greatly increased the toxicity of EDC (i.e., increased serum activities of SDH, APT, and 5-NT, bilateral testicular atrophy, periportal necrosis and cytoplasmic swelling of hepatocytes, and bile duct proliferation). Therefore, any person exposed to DSF either occupationally or therapeutically is likely to be more susceptible to the effects of EDC toxicity.

Rats, rabbits, guinea pigs, dogs, cats, and monkeys were used in exposures ranging from approximately 100 to 1000 ppm EDC (Heppel *et al.*, 1946). At the highest experimental concentration of 963 ppm, high mortality was observed in rats, rabbits, and guinea pigs following exposure 7 hours per day, 5 days per week for two weeks or less. At 963 ppm

guinea pigs exhibited lacrimation and inactivity during exposure; pulmonary congestion was noted at autopsy. Rats exposed to this concentration exhibited degenerative proliferative changes in the renal tubular epithelium and splenitis. Pulmonary congestion and focal hemorrhage were also noted in 2 of 4 rats examined. While 4 of 6 cats exposed to this concentration survived until sacrifice 11 weeks following termination of exposure, congestion and fatty infiltration of the liver were observed at necropsy. Due to high mortality in the rodents at the higher concentration, a subsequent experiment exposed rats and guinea pigs 7 hours per day, 5 days per week to 100 ppm EDC for four months. No increase in mortality or effects on growth was observed in rats exposed to this concentration. The rats were successfully bred and their pups were exposed with the dams. No significant findings were observed upon gross and histological examinations of 10/39 exposed and 10 control rats. This study is severely limited by the methods used to determine the exposure concentration and by the lack of quantitative measurements of toxicity other than death. This study does, however, indicate that fatty infiltration of the liver is one indication of toxicity following multiple exposures to EDC.

In developmental toxicity studies summarized by Zhao *et al.* (1997), rats were exposed to 0, 24.8, and 207.6 mg/m^3 (equivalent to 0, 6, and 51 ppm) EDC for 6 hr/day from two weeks before mating and throughout gestation. Statistically significant increases in pre-implantation loss and decreased male pup weights were observed at the highest dose. Gross skeletal and visceral malformations were not found.

In a developmental study by Payan *et al.* (1995), Sprague-Dawley rats were exposed to 150, 200, 250, or 300 ppm EDC for 6 hrs/day from day 6 to 20 of gestation. Maternal toxicity (reduced body weight gain; death of two females) was observed at the highest exposure. Statistically significant evidence of altered growth and teratogenic effects were not observed at any concentration.

Rao *et al*. (1980) exposed rats and rabbits to 100 or 300 ppm EDC for 7 hr/day on days 6 through 15 (rats) or 6 through 18 (rabbits) of gestation. Maternal toxicity (mortality) was observed in rabbits at 100 ppm, and both species at 300 ppm. One rat exhibited resorption of all implantations at the maternally-toxic dose. Otherwise, no fetotoxic or teratogenic effects were observed in either species. In a reproduction study, rats were exposed to 25, 75, or 150 ppm EDC 6 hr/day, 5 days/week for 60 days before breeding. Exposure following this period was 6 hr/day, 7 days/week. Maternal animals were not exposed to EDC from gestational day 21 through day 4 postpartum. EDC had no effect on reproduction over one generation within two litters.

In a two-generation study conducted by Lane *et al.* (1982), ICR Swiss mice were administered 30, 90, or 290 mg/L EDC in drinking water (equivalent to about 5, 15, or 50 mg/kg bw/day) starting five weeks before mating of the F_0 generation. No treatment-related effects on fertility, gestation, viability, weight gain, or lactation indices were noted. EDC exposure did not result in teratogenic or dominant lethal effects.

No gross or histopathological indications of hepato- or nephrotoxicity were observed in Osborn-Mendel rats (47 or 95 mg/kg bw/day, 5 days/week for both sexes) or B6C3F1 mice

(97 or 195 mg/kg bw/day, 5 days/week for males; 149 or 299 mg/kg bw/day, 5 days/week for females), which were given EDC via gavage for 78 weeks (NCI, 1978). However, rats of each sex and female mice had significantly reduced survival at the highest dose.

In a comparative study of the toxicity of EDC, Morgan *et al.* (1990) administered 0, 500, 1000, 2000, 4000, and 8000 ppm in drinking water to several species of rats for 13 weeks. A statistically significant increase in kidney weight was observed in male and female Fischer 344/N rats administered 1000 ppm or greater in drinking water. However, minimal histological damage was observed only in the kidney of female Fischer 344/N rats. A statistically significant decrease in body weight was observed in rats administered 8000 ppm. Significant decreases in absolute and relative kidney weight were observed in male and female rats administered concentrations of 1000 ppm EDC. A significant increase in relative liver weight was observed in male rats administered 2000 ppm EDC and greater and female rats administered 4000 ppm EDC and greater. Similar but less marked toxicity was observed in the Sprague-Dawley and Osborne-Mendel rats administered 1000 ppm. Additionally, rats were administered EDC in corn oil by gavage at doses of 0, 30, 60, 120, 240, and 480 mg/kg for 13 weeks (Morgan *et al.*, 1990). Rats administered EDC by gavage exhibited high mortality in the higher dose groups. Statistically significant increases in kidney weights were observed in surviving male rats administered EDC and in female rats administered 120 or 240 mg/kg. However, no histological damage to the liver or kidney was observed.

VI. Derivation of Chronic Reference Exposure Level (REL)

Study	Spreafico *et al.*, 1980.
Study population	Rats (8-10 per sex/group)
Exposure method	Discontinuous whole-body inhalation exposures (0, 5, 10, 50, or 150-250 ppm)
Critical effects	Significant elevation in liver enzymes
Exposure duration	12 months
Exposure continuity	7 hours/day, 5 days/week
LOAEL	50 ppm
NOAEL	10 ppm
Average experimental exposure	2.1 ppm for NOAEL group (10 x 7/24 x 5/7)
Human equivalent concentration	3.2 ppm for NOAEL group (gas with systemic effects, based on RGDR = 1.5 for lambda (a) : lambda (h)) (Gargas *et al*., 1989)
LOAEL uncertainty factor	1
Subchronic uncertainty factor	1
Interspecies uncertainty factor	3
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	30
Inhalation reference exposure level	0.1 ppm (100 ppb; 0.4 mg/m^3; 400 μg/m^3)

Cheever *et al*. (1990) and Spreafico *et al.* (1980) were the only chronic inhalation exposure studies found in the literature that presented non-cancer effects. No reproductive and

developmental effects were observed in studies published in peer-reviewed journals. The study by Spreafico *et al*. (1980) was chosen for REL development based on the utilization of multiple exposure levels and the observation of a NOAEL and a LOAEL for liver effects.

The Agency for Toxic Substances and Disease Registry (ATSDR) calculated a chronic inhalation minimal risk level (MRL) for EDC of 0.2 ppm (ATSDR, 1994). The calculation was based on the study by Cheever *et al*. (1990), which determined a free-standing NOAEL of 50 ppm for lack of liver effects. A LOAEL was not determined. To derive the MRL, the ATSDR applied uncertainty factors (UFs) of 10 each for intraspecies and interspecies variability, and a modifying factor of 3 to account for database deficiencies, to the NOAEL of 50 ppm. The criteria for use of modifying factors are not well specified by ATSDR. Such modifying factors were not used by OEHHA. A continuity correction for discontinuous exposure was not applied. The resulting MRL was 0.2 ppm (0.7 mg/m^3).

For comparison to the proposed REL, a REL developed by OEHHA based on the free-standing NOAEL of 50 ppm determined in rats by Cheever *et al*. (1990) would include a continuity correction (50 ppm x 7/24 x 5/7) resulting in an equivalent continuous level of 10.42 ppm.. Application of an RGDR = 1.5 and UFs of 3 for interspecies and 10 for intraspecies differences result in a REL of 0.5 ppm (2 mg/m^3).

VII. Data Strengths and Limitations for Development of the REL

The strengths of the inhalation REL for ethylene dichloride include the availability of chronic inhalation exposure data, the relatively large number of exposure levels at lower concentrations (allowing for better elucidation of the dose-response relationship for hepatotoxicity), and the observation of a NOAEL. Major areas of uncertainty are the lack of adequate human exposure data, the small groups tested in the key study, and the lack of health effects data from multiple species.

The small number of animals per group and the relatively modest clinical chemistry findings observed in the Spreafico *et al.* (1980) study may have resulted in false-positives, false-negatives, and lack of clear dose-response relationships. Repeating the study in one or more experimental animal species with full histopathological examination of organs and a greater number of animals/dose would significantly enhance the chronic toxicity database for EDC.

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CHRONIC TOXICITY SUMMARY

ETHYLENE OXIDE

(oxirane, dimethylene oxide, epoxyethane)

CAS Registry Number: 75-21-8

I. Chronic Toxicity Summary

Inhalation reference exposure level	**30** m**g/m^3** (18 ppb)
Critical effect(s)	Neurotoxicity in rats
Hazard index target(s)	Nervous system

II. Physical and Chemical Properties (HSDB, 1995; CRC, 1994)

Description	Colorless gas
Molecular formula	C_2H_4O
Molecular weight	44.06 g/mol
Density	1.80 g/L @ 25ºC
Boiling point	10.6ºC
Melting point	–111.6ºC
Vapor pressure	1095 torr @ 20ºC
Conversion factor	1 ppm = 1.80 mg/m^3

III. Major Uses or Sources

The majority of all ethylene oxide (EtO) produced is used as a chemical intermediate in the production of various compounds including ethylene glycol, glycol ethers, and non-ionic surfactants (ATSDR, 1990). EtO is also used as a fumigant for food and cosmetics, and in hospital sterilization of surgical equipment and heat sensitive materials such as plastics. The annual statewide industrial emissions from facilities reporting under the Air Toxics Hot Spots Act in California based on the most recent inventory were estimated to be 43,972 pounds of ethylene oxide (CARB, 2000).

IV. Effects of Human Exposure

Ten hospital sterilizer workers were matched with controls and examined for physical and neuropsychological health (Estrin *et al.*, 1990). The workers had operated sterilizers using 12% EtO and 88% Freon for an average of 5 years (range 0.5-10 years). Regular monitoring of workroom air had not been done. Measurements at the time of the study indicated concentrations of 15 ppm EtO or less. However, a second measurement showed an air concentration of 250 ppm EtO. A significantly greater percent of exposed workers exhibited

a bilateral reflex reduction in the ankle compared to controls. Nerve conduction tests did not identify significant differences between control and exposed workers, but a highly significant reduction ($p = 0.009$) in finger tapping speed was observed in exposed workers. The exposed group also performed more poorly on tests of spatial and visual abilities, and on tests of visual motor function. The results extended previous work by the same group (Estrin *et al*., 1987).

Cognitive impairment and personality dysfunction were observed more frequently in hospital workers chronically exposed to EtO, compared to a control group (Klees *et al.*, 1990). 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. Neuropsychological function in the workers was classified as either normal or impaired on the basis of the questionnaires and of 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." Disagreement 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) ($\chi^2 = 6.0861$; $p<0.05$). The Klees *et al*. (1990) study cites several earlier case reports of EtO neurotoxicity.

Recent studies have identified hemoglobin adducts, sister chromatid exchanges, and other hematological effects as indicators of ethylene oxide exposure (Ribeiro *et al.*, 1994; Sarto *et al.*, 1991). However, a recent study of 68 female workers from 9 hospitals in the U.S. and one in Mexico not only reports biological indicators of ethylene oxide exposure, but also provides a complete blood count with differential (Schulte *et al.*, 1995). The workers were classified as low- or high-exposure based on a mean 8-hour time weighted average of 0.08 or 0.17 ppm EtO. The mean length of employment for workers from U.S. hospitals was 5.5 and 10 years for low- and high-exposure workers, respectively. The mean length of employment in low- and high-exposure workers from the hospital in Mexico was 5.9 and 4.2 years, respectively. In workers from U.S. hospitals only, statistically significant decreases in hematocrit and hemoglobin were observed in high-exposure workers compared to low-exposure workers. Also, a statistically significant increase in lymphocytes and a significant decrease in neutrophils were observed in high-exposure workers compared to controls. In the workers from the hospital in Mexico, a significant relationship of EtO exposure and elevated neutrophil count was observed using regression.

At least 2 epidemiological reports indicate a possible association of EtO exposure and spontaneous abortion. Hemminki *et al.* (1982) analyzed spontaneous abortions in Finnish hospital sterilizing staff using data from a postal questionnaire and from a hospital discharge register. The study included all sterilizing staff employed in Finnish hospitals in 1980; the controls were nursing auxiliaries. When the women were involved in sterilizing procedures during their pregnancies, the frequency of spontaneous abortion was 16.7% versus 5.6% for the non-exposed pregnancies. The independent analysis of spontaneous abortions using the hospital discharge register confirmed the findings. Thus two analyses suggested that EtO exposure may carry a risk of spontaneous abortion among sterilizing staff.

More recently Rowland *et al*. (1996) sent questionnaires to 7,000 dental assistants (ages 18-39 years) registered in California in 1987. Of these, 4,856 responded (69%). They analyzed

1,320 women whose most recent pregnancy was conceived while working full-time. Thirty-two reported exposure to EtO; unexposed dental assistants comprised the comparison group. Among exposed women, the age-adjusted relative risk (RR) of spontaneous abortion was 2.5 [95% (CI) = 1.0-6.3]. The RR for pre-term birth was 2.7 (95% CI = 0.8-8.8) and the RR for post-term birth was 2.1 (95% CI = 0.7-5.9). The RR of any of these adverse outcomes among exposed women was estimated to be 2.5 (95% CI = 1.0-6.1). These results also indicate a possible relationship of EtO and spontaneous abortion.

V. Effects of Animal Exposure

A 2 year inhalation bioassay exposed groups of 80 male rats to 0, 50, or 100 ppm EtO 7 hours per day, 5 days per week for 104 weeks (Lynch *et al.*, 1984). Mean body weights were significantly lower and mortality was significantly higher in both exposure groups. Inflammatory lesions of the lung, nasal cavity, trachea, and inner ear were observed more frequently in EtO exposed rats. Skeletal muscle myopathy, consisting of atrophy and degeneration of skeletal muscle fibers, was observed more frequently in rats exposed to 100 ppm EtO compared to controls. Neoplastic changes were also observed in EtO exposed rats.

Mice (30 per sex) were exposed to 0, 10, 50, 100, or 250 ppm EtO for 6 hours per day, 5 days per week, for 10 weeks (males) or 11 weeks (females) (Snellings *et al.*, 1984). Neuromuscular screening was conducted, and samples of urine and blood were collected. A significantly greater percent of exposed mice exhibited abnormal posture during gait and reduced locomotor activity. A dose-response was observed for these effects, with significant changes at 50 ppm and greater. An abnormal righting reflex was observed in a significantly greater percent of mice exposed to 100 ppm and above. Reduced or absent toe and tail pinch reflexes were observed in a significantly greater percent of mice exposed to 250 ppm EtO. Hematological changes observed in mice exposed to 250 ppm include slight, yet significant, decreases in red blood cell count, packed cell volume, and hemoglobin concentration. Absolute and relative spleen weights were significantly decreased in female mice exposed to 100 and 250 ppm and in male mice exposed to 250 ppm EtO. A significant increase in relative liver weight was observed in female mice exposed to 250 ppm EtO. Male mice exhibited a significant decrease in body weight at 10, 50, and 250 ppm and a significant decrease in absolute testes weights at 50, 100, or 250 ppm EtO. This study indicates a subchronic NOAEL for neurological effects of 10 ppm EtO.

In a study of the testicular effects of EtO, male rats were exposed to 500 ppm EtO 6 hours per day, 3 days per week for 2, 4, 6, or 13 weeks (Kaido *et al.*, 1992). An awkward gait was observed in rats after 6-9 weeks of exposure. Although no significant changes in body weight were observed, a statistically significant dose-related decrease in testes weight was observed at 4, 6, and 13 weeks of exposure. Progressive degeneration and loss of germ cells were also observed during the 13 week exposure. While severe loss of germ cells and marked morphological changes in remaining germ cells were observed at 6 weeks of exposure, some intact spermatids were observed at 13 weeks of exposure. This suggests that recovery of spermatogenesis occurred.

Saillenfait *et al*. (1996) studied the developmental toxicity of EtO in pregnant Sprague-Dawley rats using inhalation exposure during gestation days 6 to 15. Two protocols were used: (1) exposure for 0.5 hr once a day to 0, 400, 800, or 1200 ppm EtO; or (2) exposure for 0.5 hr three times a day to 0, 200, or 400 ppm EtO or to 0, 800, or 1200 ppm EtO. The second protocol caused fetal toxicity as indicated by reduced fetal weight at 800 ppm (the LOAEL for this endpoint) and at 1200 ppm, and overt maternal toxicity manifested as reduced body weight gain at 1200 ppm. No embryolethality or teratogenicity occurred in either exposure protocol.

VI. Derivation of Chronic Reference Exposure Level (REL)

Study	Snellings *et al*., 1984
Study population	Male and female B6C3F1 mice
Exposure method	Inhalation chamber exposure to 0, 10, 50, 100, or 250 ppm ethylene oxide
Critical effects	Impaired neurological function
LOAEL	50 ppm
NOAEL	10 ppm
Exposure continuity	6-hours/day, 5 days/week
Exposure duration	10 weeks (males), or 11 weeks (females)
Average experimental exposure	1.79 ppm (10 x 8/24 x 5/7)
Human equivalent concentration	1.79 ppm ((gas with systemic effects, based on RGDR = 1.0 using default assumption that lambda (a) = lambda (h)))
LOAEL uncertainty factor	1
Subchronic uncertainty factor	3
Interspecies uncertainty factor	3
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	100
Inhalation reference exposure level	18 ppb (30 $\mu g/m^3$)

Snellings *et al*. (1984) found a subchronic NOAEL of 10 ppm for neurological effects in mice. A neuromuscular screening test indicated that certain reflex responses and locomotor activities were altered in EtO-exposed animals. Human studies have also indicated neurological impairment in ethylene oxide exposed workers.

VII. Data Strengths and Limitations for Development of the REL

The strengths of the inhalation REL for ethylene oxide include the use of an animal study with both a LOAEL and a NOAEL and the use of an endpoint seen in both animals and humans.

Major areas of uncertainty are the short time-frame of the key study, the lack of an appropriate human study, and the limited number of developmental toxicity studies.

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CHRONIC TOXICITY SUMMARY

GLUTARALDEHYDE

(1,5-pentanedial; 1,5-pentanedione; glutaric dialdehyde; Aldesen; Cidex; Sonacide)

CAS Registry Number: 111-30-8

I. Chronic Toxicity Summary

Inhalation reference exposure level	**0.08 µg/m^3** (0.02 ppb)
Critical effect(s)	Squamous metaplasia of the respiratory epithelium in the nose of male and female mice
Hazard index target(s)	Respiratory system

II. Chemical Property Summary (HSDB, 1996; CRC, 1994; Chemfinder, 2000)

Description	Colorless liquid/oil
Molecular formula	$C_5H_8O_2$
Molecular weight	100.12 g/mol
Boiling point	188°C (decomposes) (CRC, 1994)
Melting point	–6°C (Chemfinder, 2000)
Solubility	Soluble in water, alcohol, benzene
Conversion factor	4.1 µg/m^3 per ppb at 25ºC

III. Major Uses and Sources

Glutaraldehyde is a chemical frequently used as a disinfectant and sterilizing agent against bacteria and viruses (2% solution), an embalming fluid and tissue fixative, a component of leather tanning solutions, and an intermediate in the production of certain sealants, resins, dyes, and electrical products (HSDB, 1996). For commercial purposes, solutions of 99%, 50%, and 20% are available. Glutaraldehyde is also an atmospheric reaction product of cyclohexene. The annual statewide industrial emissions from facilities reporting under the Air Toxics Hot Spots Act in California based on the most recent inventory were estimated to be 29,603 pounds of glutaraldehyde (CARB, 2000).

IV. Effects of Human Exposure

Evidence of the toxicity of glutaraldehyde to humans is limited to reports of occupational exposure from its use as a disinfectant and sterilizing agent. Frequently observed effects from exposure include skin sensitivity resulting in dermatitis, and irritation of the eyes and nose with accompanying rhinitis (Jordan *et al.*, 1972; Corrado *et al.*, 1986; Hansen, 1983; Wiggins *et al.*, 1989). Occupational asthma has also been reported among workers repeatedly exposed

to glutaraldehyde, particularly respiratory technologists who use glutaraldehyde as a sterilizing agent for endoscopes (Chan-Yeung *et al.*, 1993; Stenton *et al.*, 1994; Gannon *et al.*, 1995). Quantitation of the exposure levels that led to glutaraldehyde sensitization was not available from the studies.

V. Effects of Animal Exposure

The histopathology of the respiratory tract in rats and mice exposed to glutaraldehyde by inhalation was examined (Gross *et al.*, 1994). F344 rats and B6C3F1 mice (20 animals of each sex and of each species at each exposure level for a total of 480 rodents) were continuously exposed to glutaraldehyde in recirculating exposure chambers at concentrations of 0, 62.5, 125, 250, 500, or 1000 ppb glutaraldehyde for one day, 4 days, 6 weeks, or 13 weeks. At termination, respiratory tract tissue as well as duodenum and any gross lesions were collected and formalin fixed. Animals were treated with tritiated thymidine two hours before termination to evaluate cell replication in certain respiratory tract tissues. Respiratory tract tissue sections were made as follows: transverse sections of the nose and trachea, frontal section of the carina, and longitudinal section of the lung. Ten male and 10 female mice exposed to 1000 ppb and one female mouse exposed to 500 ppb group died during the course of the study. Two male and 3 female rats exposed to 1000 ppb died during the course of the study. Histopathological examination of animals surviving to the end of the study entailed scoring the severity of the finding from “no response” to “very severe” response on a 0 to 5 scale. Unit length labeling index, the indicator of cell proliferation, was evaluated by autoradiography at two sites: the nasal vestibule and the dorsal atrioturbinate.

Lesions in animals treated with glutaraldehyde appeared primarily in the anterior third of the nose. Lesions were apparently more increased in mice compared to rats due to some level of “background” non-suppurative lesions in the rats. Mice were considered devoid of background lesions. In the 13-week study, female mice were the most sensitive, with lesions averaging a score of 2 (mild and clear, but of limited extent and/or severity). The lesions were characterized as neutrophilic infiltration primarily in the squamous epithelium of the vestibule, with thickening of the epithelium leading to loss of the characteristic surface grooves. Both cell size and number were reported to be increased. Lesions were generally found to increase in nature and severity with increased time and level of exposure. Obstruction of the nasal vestibule was thought to account for the mortality of animals in the higher dose groups. In female mice at 13 weeks, all glutaraldehyde dose groups showed the accumulation of eosinophilic proteinaceous deposits in the respiratory epithelium of the maxilloturbinate margin. Examination of unit length labeling indices as a measure of growth showed significant increases in all treated groups of female mice. No evidence of exposure related lesions was found in the respiratory tract in the trachea, carina, bronchi, or lungs.

Mean Subjective Pathology Scores for Nasal Lesions in Female Mice at 13 Weeks

	Glutaraldehyde	*Intraepithelial neutrophils*	*Subepithelial neutrophils*	*Squamous metaplasia*
	0 ppb	0	0.4	0
	62.5 ppb	2.0	2.0	0
	125 ppb	2.4	2.8	0
	250 ppb	3.2	3.2	0
	500 ppb	2.8	2.8	0.5
	1000 ppb*	--	--	--

*Animals exposed to 1000 ppb died early in the experiment.

Greenspan *et al.* (1985) exposed male and female F-344 rats to 0, 0.3, 1.1 and 3.1 ppm glutaraldehyde and 0, 0.2, 0.63, and 2.1 ppm glutaraldehyde, respectively, in a 9-day study, and both sexes to 0, 21, 49, and 194 ppb glutaraldehyde in a 14 week study. Animal numbers were not specified. Exposures were conducted for 6 hours per day, 5 days per week. In the 9-day study, observations in the high and intermediate dose level groups included reduced body weight gain, inflammation of the nasal and olfactory mucosa, and sensory irritation. In the two highest doses of the 14-week study, statistically significant differences in body weight gain were observed as well as perinasal wetness. No histopathological indication of inflammation in olfactory or nasal mucosa was observed.

Mice were exposed to 0, 0.3, 1.0, and 2.6 ppm glutaraldehyde vapors for 6 hours/day for 4, 9, or 14 days (Zissu *et al.*, 1994). These mice were killed immediately after the exposure period. Other groups exposed to 1.0 ppm for 14 days were killed after recovery periods of 1, 2, and 4 weeks. After 4 days of exposure to the lowest dose, mice showed lesions in the respiratory epithelium of the septum, and the naso- and maxilloturbinates. After exposure to 1.0 ppm glutaraldehyde, lesions were still judged as severe after 2 weeks of recovery.

A study comparing the effects of intra-nasally instilled glutaraldehyde and formaldehyde on rat nasal epithelium found inflammation, epithelial degeneration, respiratory epithelial hypertrophy, and squamous metaplasia in treated animals (St. Clair *et al.*, 1990). Acute inhalation exposure to formaldehyde produced identical lesions. Ten-fold higher concentrations of instilled formaldehyde were required to produce the same effect as instilled glutaraldehyde.

In a chronic study, NTP (1998, 1999) exposed groups of 50 male and 50 female F344/N rats to 0, 250, 500, or 750 ppb glutaraldehyde vapor by inhalation for 6 h/day, 5 days/week, for 104 weeks. Survival of 500 and 750 ppb female rats was less than that of the chamber controls. Mean body weights of all exposed groups of male rats and 500 and 750 ppb female rats were generally less than those of the chamber controls. Increased incidences of nonneoplastic nasal lesions occurred primarily within the anterior section of the nose in 500 and 750 ppb rats and to a lesser extent in 250 ppb rats. The more significant lesions included hyperplasia and inflammation of the squamous and respiratory epithelia and squamous metaplasia of the respiratory epithelium. Thus 250 ppb (1000 $\mu g/m^3$) is a chronic LOAEL for rats.

In the same study NTP (1998, 1999) exposed groups of 50 male and 50 female B6C3F1 mice to 0, 62.5, 125, or 250 ppb glutaraldehyde vapor by inhalation for 6 h/day, 5 days/week, for 104 weeks. Survival of exposed mice was similar to that of the chamber controls. Mean body weights of female mice exposed to 250 ppb were generally less than those of the controls. The incidence of inflammation of the nose was marginally increased in 250 ppb females. Incidences of squamous metaplasia of the respiratory epithelium were increased in 250 ppb males and females and 125 ppb females. Incidences of hyaline degeneration of the respiratory epithelium were increased in all exposed groups of females. Thus 62.5 ppb was a chronic LOAEL for female mice.

Incidence of Nasal Lesions in Female Mice exposed for 104 weeks

	Glutaraldehyde	*Inflammation*	*Respiratory epithelium hyaline degeneration*	*Respiratory epithelium squamous metaplasia*
	0 ppb	6/50	16/50	7/50
	62.5 ppb	7/49	35/49	11/49
	125 ppb	13/50	32/50	16/50
	250 ppb	14/50	30/50	21/50

VI. Derivation of Chronic Reference Exposure Level (REL)

Study	NTP 1998, 1999
Study population	Male and female F344 rats and B6C3F1 mice (50/sex/group)
Exposure method	Continuous inhalation exposure (0, 62.5, 125, and 250 ppb in mice; 0, 250, 500, or 750 ppb in rats)
Critical effects	Respiratory epithelium squamous metaplasia
LOAEL	62.5 ppb (female mice)
NOAEL	Not observed
BMC_{05}	20.5 ppb
Exposure continuity	6 hr/day, 5 days/week
Exposure duration	104 weeks
Equivalent continuous exposure	3.7 ppb (20.5 x 6/24 x 5/7)
Human equivalent concentration	0.62 ppb (gas with extrathoracic respiratory effects, RGDR = 0.17, BW = 28 g, MV = 0.032 L/min, SA = 3 cm^2)
LOAEL uncertainty factor	not needed in BMC approach
Subchronic uncertainty factor	1
Interspecies uncertainty factor	3
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	30
Inhalation reference exposure level	0.02 ppb (0.08 µg/m^3)

Several studies indicate that the upper respiratory tract is a target for the toxicity of glutaraldehyde from inhalation exposure. Reports of toxicity to humans show that exposure can lead to occupational asthma as well as cause irritation of the eyes and nose with accompanying rhinitis. Likewise, animals exposed to glutaraldehyde by the inhalation route show evidence of respiratory irritation with the induction of lesions of the anterior nasal cavities upon long-term exposure (Gross *et al.*, 1994; Greenspan *et al.*, 1985; NTP, 1998, 1999). The NTP (1998, 1999) study yielded a chronic LOAEL for female mice of 62.5 ppb. Gross *et al.* (1994) showed neutrophilic infiltration in the olfactory epithelium in the lowest dose exposure group. (Female mice exposed to 62.5 ppb also showed subepithelial neutrophilic infiltration.) This level was taken to be the subchronic LOAEL. This effect on the nasal epithelium was demonstrated to be both concentration- and exposure duration-dependent.

A benchmark concentration was determined using EPA's version 1.20 BMC software and the dose-response data on respiratory epithelium squamous metaplasia in female mice. The quantal-linear model gave an MLE_{05} of 31.24 ppb, a BMC_{05} of 20.51 ppb, and a p value of 0.9471. With the benchmark approach no LOAEL UF is needed. The study was a lifetime study so the subchronic UF is 1. An interspecies UF of 3 rather than 10 was used since an RGDR adjustment had been made. The default intraspecies UF of 10 was used so that the total UF was 30. The resulting chronic REL for glutaraldehyde is 0.02 ppb (0.08 $\mu g/m^3$).

For comparison with the proposed REL, the study of Gross *et al*. (1994) used 62.5 ppb continuous exposure. Multiplying by the RGDR of 0.17 and dividing by a cumulative uncertainty factor of 300 (3 for a LOAEL, 3 for subchronic, 3 for interspecies, and 10 for intraspecies) results in a REL of 0.035 ppb (0.1 $\mu g/m^3$).

VII. Data Strengths and Limitations for Development of the REL

The major strength of the inhalation REL for glutaraldehyde is the availability of controlled exposure inhalation studies in multiple species at multiple exposure concentrations and with adequate histopathogical analysis. Major areas of uncertainty are the lack of human data, the lack of reproductive and developmental toxicity studies, the lack of dermal sensitization studies, and the lack of observation of a NOAEL.

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CHRONIC TOXICITY SUMMARY

HYDRAZINE

(diamine; diamide; nitrogen hydride; levoxine)

CAS Registry Number: 302-01-2

I. Chronic Toxicity Summary

Inhalation reference exposure level	**0.2 µg/m^3** (0.1 ppb)
Critical effect(s)	Amyloidosis of the liver and thyroid in hamsters
Hazard index target(s)	Alimentary system; endocrine system

II. Chemical Property Summary (HSDB, 1995; CRC, 1994)

Description	Colorless, oily liquid or white crystals
Molecular formula	N_2H_4
Molecular weight	32.05 g/mol
Boiling point	113.5°C (Merck, 1983; CRC, 1994)
Melting point	2.0°C
Vapor pressure	14.4 torr @ 25°C
Solubility	Miscible with water, methyl-, ethyl-, isobutyl alcohols; slightly miscible with hydrocarbons; insoluble in chloroform, ether
Conversion factor	1.31 µg/m^3 per ppb at 25ºC

III. Major Uses and Sources

Hydrazine is a highly reactive base and reducing agent. Its primary uses are as a high-energy rocket propellant, as a reactant in military fuel cells, in nickel plating, in the polymerization of urethane, for removal of halogens from wastewater, as an oxygen scavenger in boiler feedwater to inhibit corrosion, and in photographic development (Von Burg and Stout, 1991). Hydrazine was historically used experimentally as a therapeutic agent in the treatment of tuberculosis, sickle cell anemia, and non-specific chronic illnesses (Von Burg and Stout, 1991; Gold, 1987). The annual statewide industrial emissions from facilities reporting under the Air Toxics Hot Spots Act in California based on the most recent inventory were estimated to be 1664 pounds of hydrazine (CARB, 2000).

IV. Effects of Human Exposure

One person was occupationally exposed to hydrazine at unknown levels once per week for a period of 6 months (Sotaniemi *et al.*, 1971). The worker showed symptoms of conjunctivitis, tremors, and lethargy for 1-2 days following each exposure. Vomiting, fever, and diarrhea developed on the last day of exposure and progressed to abdominal pain and incoherence. The previously healthy 59-year old individual died three weeks after the last exposure. Evidence of tracheitis, bronchitis, heart muscle degeneration, and liver and kidney damage was found at autopsy. A single case report can not prove a cause and effect relationship between hydrazine exposures and the noted symptoms and death, but the repeated association between exposures and symptoms is highly suspicious. Liver toxicity is also associated with acute exposure to hydrazine.

The only epidemiological studies of human hydrazine exposures found involve workers in a hydrazine manufacturing plant (Wald *et al.*, 1984; Wald, 1985; Morris *et al.*, 1995). Workers were exposed to various durations of at least 6 months between 1945 and 1972 and have been followed through 1992. The studies are based on a review of medical records. Only 78 of 427 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, these small studies have little power to detect increased mortality, and age of death was not examined. The authors reported that relative risks up to 3.5 could have gone undetected.

Dermal sensitization has also been reported from repeated contact with hydrazine (Van Ketal, 1964; Von Keilig and Speer, 1983; Wrangsjo and Martensson, 1986).

V. Effects of Animal Exposure

An inhalation study of the toxicity and carcinogenicity of hydrazine was conducted in cats, mice, hamsters, and dogs (Vernot *et al.*, 1985). Various animal groups were exposed 6 hours/day, 5 days/weeks for one year to concentrations of 0.05, 0.25, 1.0, and 5.0 ppm anhydrous hydrazine base. Exposed and controls groups were made up of the following animals: 100 Fischer 344 rats/sex at 0.05, 0.25, 1.0, and 5.0 ppm hydrazine plus 150 rats/sex as controls; 400 female C57BL/6 mice at 0.05, 0.25, and 1.0 ppm hydrazine plus 800 female mice as controls; 200 male Golden Syrian hamsters at 0.25, 1.0, and 5.0 ppm hydrazine plus 200 male hamsters as controls; 4 beagle dogs/sex at 0.25 and 1.0 ppm hydrazine plus 4 dogs/sex as controls. Animals were observed post-exposure for the following periods: 18 months for rats, 15 months for mice, 12 months for hamsters, and 38 months for dogs. Animals were observed hourly during the exposure period and daily in the post-exposure period.

No non-cancer toxic effects were observed in mice or dogs, with the exception of a single dog, exposed to 1.0 ppm hydrazine, which showed cyclic elevations in serum glutamic-pyruvic transaminase levels and, upon necropsy at 36 months post-exposure, showed liver

effects described as "clusters of swollen hepatocytes that had highly vacuolated cytoplasm." Of the other species examined, hamsters showed toxicity at the lowest dose levels, particularly amyloidosis in various organs including liver, spleen, kidney, thyroid, and adrenal glands. An increased incidence of amyloidosis was seen at the lowest exposure level (0.25 ppm hydrazine) in the liver and thyroid (67/160 exposed vs. 42/180 control for the liver and 20/117 exposed vs. 9/155 control in the thyroid; $p \leq 0.01$ by Fisher's exact test). This effect was found to be dose related. The incidence of hemosiderosis of the liver was also significantly increased in all exposed groups. Significantly increased incidences of toxic effects observed in the 1.0 and 5.0 ppm hydrazine groups include amyloidosis of the spleen, kidney glomerulus, and adrenals glands, and lymphadenitis of the lymph nodes. Significantly increased toxic effects observed only in the highest dose group include amyloidosis of the kidney interstitium and thyroid, and senile atrophy of the testis. The authors note these effects appear to reflect accelerated changes commonly associated with aging in hamsters.

Incidence of Nonneoplastic Lesions in Male Hamsters (from Table 3 of Vernot *et al*.)

Lesion	*Control*	*0.25 ppm*	*1.0 ppm*	*5.0 ppm*
Liver				
Amyloidosis	42/180 (23)*	67/160 (42)[a]	68/148 (46)[a]	79/159 (50)[a]
Hemosiderosis	42/180 (23)	63/160 (39)[a]	77/148 (52)[a]	94/159 (59)[a]
Bile duct hyperplasia	14/180 (8)	31/160 (19)[a]	28/148 (19)[a]	44/159 (28)[a]
Biliary cyst	45/180 (25)	45/160 (28)	42/148 (28)	55/159 (35)[b]
Thyroid				
Amyloidosis	9/155 (6)	20/117 (17)[a]	11/127 (9)	22/137 (16)[a]
Adrenal				
Amyloidosis	38/177 (22)	49/199 (32)[b]	52/141 (37)[a]	76/153 (50)[a]

* Incidence of lesion (% of animals with lesion)
[a] Incidence significantly greater than control, $p \leq 0.01$
[b] Incidence significantly greater than control, $0.01 < p \leq 0.05$

In the hydrazine exposed rats, effects were observed in the respiratory tract of exposed animals. Specifically, squamous metaplasia of the larynx, trachea, and nasal epithelium (males only) was observed in the highest dose group (5.0 ppm hydrazine). Inflammation was also observed in the larynx and trachea of rats exposed to 5.0 ppm hydrazine. Increased incidence of focal cellular change of the liver was observed in female mice at 1.0 and 5.0 ppm hydrazine. Other effects with increased incidence only in the high dose group include hyperplastic lymph nodes in females, endometriosis, and inflammation of the uterine tube.

The toxic effects from inhalation of hydrazine over a six month period from both intermittent and continuous exposure scenarios were examined (Haun and Kinkead, 1973). Groups of 8 male beagle dogs, 4 female rhesus monkeys, 50 male Sprague-Dawley rats, and 40 female ICR rats per dose group were continuously exposed to 0.2 or 1.0 ppm hydrazine or intermittently (6 hours/day, 5 days/week) to 1.0 or 5.0 ppm hydrazine. A control group consisted of equal numbers of animals. The experimental design was such that each intermittent exposure group had a time-weighted-average matching continuous exposure group. Dose-related body weight reductions were observed in all treated groups as well as

evidence of hepatic degeneration, fatty deposition in the liver, central nervous system depression and lethargy, eye irritation, and anemia.

Toxic effects from the exposure of rats, mice, and dogs to airborne hydrazine at levels of 0, 4.6, or 14 ppm intermittently for 6 months were reported (Comstock *et al.*, 1954). Observed adverse effects included anorexia, irregular breathing, vomiting, fatigue, and emphysema in dogs; pulmonary congestion and emphysema in rats and mice; and lung and liver damage in rats.

Lymphoid bronchial hyperplasia was observed in guinea pigs exposed to 2-6 ppm hydrazine for 5 days/week for 19-47 days (Weatherby and Yard, 1955).

VI. Derivation of Chronic Reference Exposure Level (REL)

Study	Vernot *et al.*, 1985
Study population	Hamster
Exposure method	Inhalation of 0, 0.25, 1, and 5 ppm
Critical effects	Amyloidosis and hemosiderosis of the liver; thyroid amyloidosis
LOAEL	0.25 ppm
NOAEL	Not observed
Exposure continuity	6 hour/day, 5 days/week
Exposure duration	1 year
Average experimental exposure	0.045 ppm for LOAEL group (0.25 x 6/24 x 5/7)
Human equivalent concentration	0.045 ppm for LOAEL group (gas with systemic effects, based on RGDR = 1.0 using default assumption that lambda (a) = lambda (h))
LOAEL uncertainty factor	10 (low incidence above controls but serious adverse effects)
Subchronic uncertainty factor	1
Interspecies uncertainty factor	3
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	300
Inhalation reference exposure level	0.0001 ppm (0.1 ppb, 0.0002 mg/m^3, 0.2 µg/m^3)

Vernot *et al.*(1985) present a thorough examination of chronic health effects from inhalation exposure to hydrazine. This study was chosen for the development of the chronic reference exposure level because (1) it was conducted with an adequate number of animals, (2) the critical/sensitive adverse effect (degenerative change in the liver in hamsters) showed a dose-response relationship, and (3) the findings of this study support data found in studies by other groups.

This study shows a dose-related increase in the incidence of amyloidosis and hemosiderosis in hamsters intermittently exposed by inhalation to levels of hydrazine greater than 0.25 ppm. Other effects noted at 0.25 ppm included weight depression during exposure, mineralization

of the kidney, and amyloidosis of the thyroid. Haun and Kinkead (1973) have also noted lesions of the liver in dogs, monkeys, and mice exposed continuously to 0.2 ppm hydrazine for 6 months by inhalation. Comstock *et al.* (1954) observed liver damage in groups of rats exposed to hydrazine vapors. The single case report of hydrazine inhalation toxicity in humans showed necrosis and degeneration of the liver (Sotaniemi *et al.*, 1971).

VII. Data Strengths and Limitations for Development of the REL

The strengths of the inhalation REL for hydrazine include the availability of chronic inhalation exposure data from a well-conducted study with histopathological analysis. Major areas of uncertainty are the lack of adequate human exposure data, the lack of reproductive and developmental toxicity studies, and the lack of observation of a NOAEL in the key study.

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CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT

NOTICE TO INTERESTED PARTIES

NOTICE OF PUBLIC COMMENT PERIOD

ON

AIR TOXICS "HOT SPOTS" PROGRAM RISK ASSESSMENT GUIDELINES

SEPTEMBER 17, 1999

The Office of Environmental Health Hazard Assessment (OEHHA) is releasing the second part of a revised draft document, *Air Toxics Hot Spots Program Risk Assessment Guidelines Part III: Technical Support Document for the Determination of Noncancer Chronic Reference Exposure Levels* to solicit public comment on the revision and to obtain review by the ARB's Scientific Review Panel. This draft document is part of a series of Risk Assessment Guidelines that are being developed by OEHHA for use in implementing the Air Toxics "Hot Spots" Program mandated by the Air Toxics Hot Spots Information and Assessment Act of 1987, as amended. The original draft document was released in October 1997. More than forty sets of comments were received from the public. Staff have reviewed the comments, responded to the comments in writing, and revised the draft document.

The original 1997 document contained a description of the methodology and toxicity summaries and Reference Exposure Levels for 120 compounds. To facilitate review, OEHHA decided to release the chemical toxicity summaries in batches of 40. In June 1999 a revised draft document including the methodology (Introduction), toxicity summaries for the first 40 chemicals (based primarily on their emissions in California), and public comments with staff responses to the methodology and these 40 chemicals were distributed for review. This notice pertains to the toxicity summaries for the second set of 40 chemicals, which will be distributed for public review (along with the responses to comments received during the first public comment period) by September 27, 1999. The document will be available on the OEHHA Home Page at **http://www.oehha.ca.gov**. The distribution of the document will commence a 30-day public review period that will end on October 27, 1999. We are soliciting public input on the second batch of toxicity summaries and Reference Exposure Levels during this public comment period.

Please direct any inquiries concerning technical matters or availability of the document to Dr. James Collins at (510) 622-3146. Please direct your written comments regarding the revised draft document to Dr. Melanie A. Marty, Chronic RELs, 1515 Clay St., 16th Floor, Oakland, CA 94612. Information about dates and agenda for meetings of the Scientific Review Panel can be obtained from the ARB web page at http://www.arb.ca.gov/srp/srp.htm.

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 Sprague Dawley 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 μg/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 *2*4 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.

Response to Comments on the Scientific Review Panel Draft of the

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

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

Comment 1: In regard to physical and chemical properties, a more complete description of the metabolites would be that chloropicrin photodegrades into phosgene, which is hydrolyzed to CO_2, HCl, NO_x, and monatomic chlorine.

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

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

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

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

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

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

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

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

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

Comment 6: Although the draft suggests that acute exposures to airborne toxicants follow a graded response (OEHHA, 1998), exceptions are known and acknowledged by OEHHA. Airborne exposures to chloropicrin stimulate the trigeminal nerve in the nose. This system is protective and responds on an all-or-none basis to chemicals such as CO_2, acetic acid, and H_2S in addition to chloropicrin. Human data for chloropicrin exposure are cited by OEHHA and support the position that an UF for interspecies differences in chloropicrin responsiveness is not justified. Likewise a 10-fold factor for intraspecies variability is not justified.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Comments from Elizabeth Margosches, Ph.D.,

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

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

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

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

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

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

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

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

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

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

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

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

Response: Comment is noted and appreciated.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Response: Comment noted. As stated above, the lowering of the UF because a BC approach has been used is not entirely blind since to use the BC approach one must first have better data than one would have in the worst case of a free-standing NOAEL or LOAEL, and more of the data is being used in the BC approach thus addressing the uncertainty of using only a NOAEL or LOAEL (free-standing or otherwise). OEHHA has considered the body of evidence for each chemical before deciding on which UF to use. Staff agree that there could be cases in which the UF used with the BC_{05} might be greater than 3, but it seems less likely when enough subjects have been exposed such that the BC approach can be used. Of course there is always the possibility that there are people with severe idiosyncratic reactions at low levels in the population.

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

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

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

Response: Comment noted.

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

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

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

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

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

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

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

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

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

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

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

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

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

Response: Comment noted.

Comments from Chemical Manufacturer's Association Isopropanol Panel

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

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

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

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

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

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

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

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

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

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

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

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

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

Response: OEHHA has utilized information from two studies in rats, Gill *et al*. (1995) and Burleigh-Flayer *et al*. 1994, which examined effects on motor activity of exposure to up to 10,000 ppm isopropanol. The Gill *et al* study identified a NOAEL of 500 ppm for CNS effects (as decreased motor activity). An uncertainty factor of 10 was applied for interspecies extrapolation and another factor of 10 was applied for intraspecies extrapolation. A time adjustment based on modified Haber's Law with n=2 brings the REL to 12 ppm (about 31 mg/m^3). Effects on the CNS are considered serious effects.

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

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

Comment 1: OEHHA proposes a REL of 1 ppm (3.9 mg/m^3) for methyl bromide. If accepted, this REL would be based on a NOAEL of 103 ppm from a study in beagle dogs exposed to methyl bromide for 23-24 days (Pharmaco-LSR, 1994). Dogs exposed to 103 ppm showed minimal evidence of neurotoxicity, primarily characterized by decreased activity on Day 9 of the study. OEHHA declines to use the standard lognormal time extrapolation because the limited number and size of the distinct dose groups in the study was deemed insufficient for analysis using this model. Rather than using the NOAEL derived from the acute exposure study, OEHHA inappropriately proposes to apply a 100-fold safety factor to the NOAEL observed after a 7-hour/day exposure for 8 days. This approach is inconsistent with OEHHA's standard procedure.

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

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

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

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

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

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

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

Concentration x MW conversion (ppm to mg/m^3) x inhalation volume/hour x hours = Total Dose to animal

Animal total dose x MW conversion (mg/m^3 to ppm) x 1/human inhalation volume/hour = human equivalent ppm

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

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

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

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

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

Comment 1: OEHHA calculated the acute REL for Ni and Ni compounds on the basis of Cirla *et al*. (1985) in which a sensitive population of metal platers with occupational asthma were exposed to nickel sulfate hexahydrate, a soluble nickel compound, and evaluated for atopy and pulmonary function challenge. The critical effect was an FEV_1 decrement > 15%, a mild adverse effect that is reversible following removal from exposure. Because the Cirla *et al*. (1985) study involved a sensitive human population, there was no need to apply an interspecies or an intraspecies uncertainty factor. However, since the critical endpoint was a LOAEL (33 μg as extrapolated to a one-hour concentration), OEHHA's calculation reflects application of a LOAEL uncertainty factor of 3, which produced a 1-hour acute REL of 11 μg Ni/m^3.

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

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

Comment 2: We also agree with OEHHA's application of a LOAEL uncertainty factor of 3 rather than 10, since the adverse effect in the study by Cirla *et al*. -- a small reversible decrement in airway function as evidenced by FEV_1 measurements -- is caused by mild irritation of the respiratory tract. Accordingly, we support the Acute 1-hour REL of 11 μg Ni/m^3 that OEHHA has calculated for soluble nickel sulfate. We believe, however, that its application should be limited to nickel compounds and that it should be identified as a "worst-case" value when applied to insoluble or sparingly soluble nickel species.

Response: As indicated above, we are not aware of sufficient data to draw the distinction between soluble and insoluble compounds as suggested by the comment. Further while we have classified the effects as mild, it is on the borderline of severe and mild. The study documents FEV_1 changes >15%. We generally categorized effects < 20% as mild. Thus, some of the subjects may have responded in the severe range. Further as suggested by the Scientific Review Panel, the UF for mild effects was changed to 6 from 3 based on available data and analyses of the LOAEL to NOAEL ratios. Consequently, the REL has decreased by 50%.

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

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

Comment 4: In addition, OEHHA should correct one confusing entry in the Acute Toxicity Summary. Section I of that Summary shows the Acute REL to be 11 μg Ni/m^3, as does the derivation calculation in Section VII of the Summary. But the initial line in Section VII shows the REL to be 3.3 μg Ni/m^3. That entry should be corrected.

Response: The value of 3.3 μg Ni/m^3 was incorrectly listed on the initial line of Section VII. The value of 11 μg Ni/m^3 was based on the use of 3 for the LOAEL to NOAEL uncertainty factor when the effect is mild irritation. Based on a comment by the Scientific Review Panel at the December2, 1998 meeting we are changing the LOAEL to NOAEL uncertainty factor to 6 and the nickel REL to 6 μg Ni/m^3.

Comment from Dr. Kathy Norlein, Minnesota Department of Health

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

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

Comments from Mr. Ted Holcombe, Pacific Gas and Electric

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

References used in the response:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Comment 1: There is an ambient air quality standard for H_2S that was adopted which has been reviewed formally and informally on several occasions over nearly thirty years of existence. The latest formal review that I am aware of occurred in 1984. The standard is presently set at 0.03 ppm which is utilized by all air districts. This standard is considerably lower than the proposed REL forwarded to you by OEHHA staff for your consideration of adoption. CAPCOA guidelines set the original acute REL and AAQS at 42 $\mu g/m^3$. OEHHHA staff proposes a value of 142 $\mu g/m^3$, but in Table A-1 of the referenced report a value of 100 $\mu g/m^3$ is indicated.

Field observations and review of public complaints historically received by the Air Districts would indicate a "no observed effects level" (NOEL) at or below the AAQS. The public has complaints on record to the air districts of both nausea and headaches at or below the AAQS of 35 $\mu g/m^3$. These are the same symptoms reported in the laboratory study utilized to adjust a reported "lowest observed effects level" (LOEL) to the proposed 142 $\mu g/m^3$ REL. There is no scientific data to refute the argument of a NOEL that is lower than that proposed and there is valid data in the AAQS H_2S review record to indicate a lower value.

Response: OEHHA is revisiting the H_2S REL and has obtained records of complaint and air concentration from the Air District. OEHHA intends to revise the REL back to the AAQS based on the physiological responses of headache and nausea at levels substantially above the detection of H_2S odor.

Comment: The referenced human exposure studies were for 30 minute exposures and adjusted for a one-hour exposure by dividing the identified LOEL by two. There is no scientific evidence to indicate a linear time exposure relationship, or that a one-hour averaged exposure that allows markedly higher peaks than the hourly REL value is appropriate. From field responses and other exposure studies it appears that H_2S is unique in that a few minutes of exposure may induce a noted effect such as nausea. In the 1984 review of the AAQS it was noted that some districts had adopted a shorter term standard (i.e., 3 minutes) in addition to the state AAQS. A shorter than one-hour AAQS was recommended by our District. It was further noted that ambient air monitoring documented peak values as high as 22.5 times the hourly value, and peaks several fold the hourly average were common.

Response: Comments noted. OEHHA agrees with the commentator and is revising the proposed REL for H_2S to base it on the AAQS.

Comment: The OEHHA utilized study was performed on a sensitive population and no safety factor for a more sensitive population was used for this reason. There is no indication that the noted effect is the most sensitive health effect, nor that other sub-populations found in the general population such as asthmatic children, pregnant women, infants, or the respiratory impaired are not more sensitive to H_2S. I would suggest that the frequently noted effects judged

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

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

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

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

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

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

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

Response: The comment is noted and much appreciated.

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

Response: We will add the citation.

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

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

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

Response: Comment noted and appreciated.

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

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

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

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

Comment 7: Page 31, paragraph 4, line 5-7 – Table 7 indicates that these criteria correspond to severe effects in a methacholine challenge test, not as a response to inhalation of an airborne chemical. Please clarify. Would the criteria in Table 7 for a methacholine challenge apply to a histamine challenge as well?
The criterion for the FEV_1/FVC ratio should be added to Table 7 also.

Response: Table 7 categorizes the adverse effects on pulmonary function into severity categories using methacholine challenge as the example in row 2. When evaluating the effects of a chemical, for instance SO_2, it is the effects of the inhalation challenge with the chemical that we are rating in comparison to Table 7 using methacholine challenge results. We would have to research the histamine challenge question, but the point of the table is really how much of an effect on the various pulmonary function measures is mild, severe, or life-threatening.

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

Response: We have added it to the reference section.

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

Response: Comment noted.

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

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

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

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

Comments from Western Independent Refiners Association

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

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

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

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

Comment 3: Uncertainty factors used to derive sensory irritants concentrations should be smaller than those used to establish safe exposure levels for systemic toxicity. Most irritant gases act directly on the mucous membranes or on the lungs and the intensity of effect is usually

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

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

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

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

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

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

December 10, 1998

Comments from ChemRisk on behalf of the Western States Petroleum Association

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

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

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

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

those responses above 20% should be considered is not substantiated in the comment or in the paper by Paustenbach *et al*. (1997) referred to later in these comments.

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

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

Comment 4: At times, OEHHA selected a critical endpoint in animals when other quality human data were available that reported a dose-response relationship for the most sensitive adverse effect. We suggest that OEHHA set RELs primarily on appropriate human studies. Otherwise, RELs will quite often be overly stringent due to the repeated, and unnecessary application of uncertainty factors. For example, OEHHA selected a decrease in fetal body weight as the critical adverse effect for developing a one-hour limit for toluene to protect against severe adverse effects. Human data were available that demonstrate neurological impairment following acute exposure to toluene. While our recommended NOAEL of 1,875 mg/m^3 toluene is the same as OEHHA's selected NOAEL based on animal weights, OEHHA's ultimate "severe adverse effects level" represents an overly conservative estimate because an additional uncertainty factor of 10 for animal to human extrapolation is incorporated. We have reviewed the published papers regarding developmental effects and find that toluene is only a developmental risk at doses that produce frank toxicity. These doses are much greater than those recommended here, and they also illustrate the inappropriateness of using studies that use repeated daily exposures for setting acute exposure limits.

Response: The chemical toluene is a reproductive and developmental toxicant under Proposition 65. Animals studies show clear evidence of developmental and reproductive toxicity. We used human studies of the CNS effects of toluene to develop the REL and have used reproductive/developmental effects as the basis of the level protective against severe adverse

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

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

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

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

Response: OEHHA evaluated TLVs in our examination of existing guidelines during the REL development process. However, these values lack a consistent basis for derivation, are not designed for use with the general public and in fact are not recommended for use for the general public by ACGIH. In addition, in many cases, they do not prevent adverse health effects among workers (Roach and Rappoport, 1990). ACGIH documentation has been consulted to identify potentially relevant studies.

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

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

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

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

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

Response: It is unclear why the commentator recommends against combining individual datasets in the benchmark concentration approach. One of the advantages of the benchmark approach in that you can use information from multiple appropriate studies available on that endpoint. This same commentator in comment number one suggests using the methodology of Guth *et al*., 1992, which develops a dose-response curve based on an aggregate of all of the

various high quality studies. The categorical regression analysis recommended in comment # 1 combines datasets and conducts a regression analysis on the combined data points.

Comment on Arsenic: OEHHA used the Nagymajtenyi *et al*., 1985, study on developmental toxicity of arsenic oxide in mice as the basis for their REL. The ATSDR (1997) interpreted the Nagymajtenyi study to show that high levels of arsenic can cause developmental effects, but does not provide a clear basis for estimating a level of concern in humans. In addition, Ide and Bullough (1988) and Perry *et al*. (1948) show that no respiratory tract irritation is observed in occupational workers exposed to inorganic arsenic at a concentration of 0.11 mg/m^3 for two months. ATSDR identified 0.11 mg/m^3 as a NOAEL for respiratory irritation, which is the most sensitive adverse endpoint in humans.

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

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

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

data on respiratory irritation as suggested in the comment, we do not think it appropriate to ignore the fact that arsenic compounds are developmental toxicants.

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

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

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

The OEHHA level protective against severe adverse effects for benzene of 3.25 mg/m^3 is based on decreased mean fetal birth weights following repeat exposures. There is insufficient evidence to indicate that benzene is teratogenic or embryotoxic in animals or humans at concentrations of 10 ppm for 8 hr/day (Schwetz, 1983). Instead, we recommend that OEHHA consider more appropriate human data available in the literature involving the health effects of benzene following acute or intermittent exposure. We suggest a one-hour REL of 7.1 ppm, which is below the average odor threshold of 61 ppm to protect against mild transient effects. This is based on a NOAEL of 25 ppm from a human study showing no effects following a single 8-hour exposure (NRC, 1986; Gerarde, 1960). The NOAEL is adjusted with a time extrapolation based on a modified Haber's Law with n = 2 and divided by an uncertainty factor of 10.

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

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

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

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

hour exposure prior to infection in the mouse model would produce the same effect as the 6 hour/day for 5 day exposures. We acknowledge that there are several studies showing adverse impacts on the hematopoietic system in animals after relatively short-term exposures. However, because of the uncertainty in extrapolating for this endpoint from repeated exposures to a one-hour exposure, we are revising the REL and basing it on the studies of Kuna and Kapp (1981), and Coates *et al*. (1984) on reproductive/developmental toxicity in rats. The resultant REL of 0.4 ppm is very close to the original REL of 0.24 ppm.

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

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

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

ACGIH set a ceiling value for formaldehyde of 0.37 mg/m^3 based on irritation. AIHA set an ERPG-1 of 1.23 mg/m^3. We recommend that OEHHA reevaluate the dose-response relationship for formaldehyde and review the paper by Paustenbach *et al*., 1997. OEHHA should omit any additional uncertainty factors accounting for variability of individuals susceptible to formaldehyde since several studies have already established that sensitive individuals such as asthmatics respond no differently than the general population.

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

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

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

results that would be observed if perhaps 100 workers of varying age and health status underwent the same testing. One could take that statement further that a worker population does not provide an adequate population to extrapolate to the general population. Hence, we believe our benchmark concentration analysis is more appropriate for developing a REL applicable to the general population than the occupational exposure limit described in Paustenbach *et al*. (1997).

Comment on Hydrogen Sulfide: OEHHA identified a one-hour REL of 0.14 mg/m^3 (0.1 ppm) to protect against mild adverse effects based on the human study of Jappinen *et al*. (1990). OEHHA based the REL on increased airway resistance in 2 of 10 subjects following a 30-minute exposure to 2 ppm H2S. However, Jappinen reported no statistically significant changes in airway conductance for the entire group. And thus we recommend that OEHHA consider 2 ppm as a NOAEL rather than a LOAEL. This is further supported by Jappinen *et al*., 1990, which demonstrated no significant pulmonary function changes or bronchial responsiveness to histamine in a group of smokers, workers with allergies, and atopic individuals exposed to 1-11 ppm H_2S. Using 2 ppm as a NOAEL, the commentator recommends a REL of 1 ppm (1.4 mg/m^3) to protect against mild adverse effects.

Response: OEHHA has revisited the hydrogen sulfide REL development. Other commentators pointed out that the Ambient Air Quality Standard (AAQS) of 42 $\mu g/m^3$ was not merely an odor threshold. Some individuals experience headache, nausea and even vomiting upon exposure to odorous concentrations of H_2S. There is extensive documentation of this problem from local air pollution control districts. It is hard to argue that headache and nausea are not adverse health effects. While the toxicological mechanism may not be easy to understand or explain, the physiological effects are real. Therefore, OEHHA is proposing to use the one-hour AAQS of 42 $\mu g/m^3$ as the one-hour REL. The toxicological endpoint is thus headache and nausea. The value will not be used in assessing respiratory irritation, which occurs at levels significantly above the AAQS.

Comment on Nickel: OEHHA did not consider the different forms of nickel in the toxicity assessment of a one-hour REL. OEHHA based the REL on pulmonary function changes in workers with occupational asthma exposed to nickel sulfate. The REL was estimated by converting to nickel equivalents. This reduces the observed LOAEL of 0.3 mg/m^3 to 0.067 mg/m^3.

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

Response: OEHHA used a study by Cirla *et al*., 1985 which evaluated changes in lung function of metal plating workers with occupational asthma. The significant effect was >15% decrease in FEV_1. The volunteers were exposed for 30 minutes to 0.3 mg $NiSO_4.6H_2O$. The equivalent concentration of nickel is 67 $\mu g/m^3$. Extrapolating to a one-hour exposure using an exponent, n, set to 1, the resulting nickel concentration is 33 $\mu g/m^3$. This was then divided by an uncertainty factor of 3 for extrapolating from a LOAEL to a NOAEL for mild respiratory effects which results in a REL of 11 $\mu g/m^3$.

The commentator objects to using the nickel equivalents of nickel sulfate hexahydrate as the LOAEL. Nickel is the element that has caused the effect on FEV_1 in the study population, not the sulfate or water moieties of the nickel sulfate hexahydrate. While it may be true that other nickel salts may have different potencies for impacting lung function, in the Hot Spots program, facilities report their emissions as total nickel. Therefore, it is prudent to use a study of soluble nickel compounds as the basis of the REL and apply the nickel proportion of that compound to the derivation of the REL. It may be possible in the future to speciate nickel compounds for the purposes of developing an REL. However, it would then require facilities to speciate their emissions, a potentially costly prospect for most.

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

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

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

Response: OEHHA based the REL on Anderson *et al*. (1983), a study of 16 young healthy subjects evaluating nasal mucus flow, lung function, subjective response, and psychometric performance during 6-hour exposures to clean air, 10, 40 or 100 ppm toluene. No effects were noted at 10 and 40 ppm, but at 100 ppm irritation was experienced in the eyes and nose. The test battery investigated visual perception, vigilance, psychomotor functions, and higher cortical functions. The test battery included five-choice, rotary pursuit, screw-plate, Landolt's rings, Boudon Weisma, multiplication, sentence comprehension, and word memory tests. No statistically significant effects occurred at $p<0.05$. For three tests (multiplication errors, Landolt's rings, and the screw plate test) there was a borderline significance ($0.05<p<0.1$). The subjects reported headache, dizziness, and a feeling of intoxication at 100 ppm. This study was well-controlled and well-conducted. The study was inclusive of irritation and other "subjective" symptoms. The volunteers were asked to rate the following on a continuous scale: their estimate of air temperature, humidity, air movement, light intensity, noise level, air quality, odor level; whether they felt fatigue, sleepiness, work strain, difficulty of work, effort, speed of reaction, irritation of the eyes, nose, throat and lower airway, cough, headache, feeling of intoxication, dizziness, and nausea. Thus, this study was designed to evaluate irritation, contrary to what is implied in the comment. OEHHA believes therefore that this study is useful for developing the REL. It is interesting to note that the authors conclude there is a wide variability in irritation, and that throughout the day there was no adaptation to the irritation. The REL for 6-hours was extrapolated to a one-hour REL using a modified Haber's Law exponent = 2. An uncertainty factor of 10 was applied for interindividual variation in response to derive an REL of 9.8 ppm.

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

The level protective against severe adverse effects is based on a reproductive/developmental toxicity study. Studies of reproductive/developmental toxicity of necessity involve repeated exposures. It is generally not known at what stage in gestation a developmental defect or an

impact on the reproductive capacity of the animal can occur. Thus we have used the one-day exposure concentration (generally 6 or 7 hr/day) in these cases to extrapolate back to a one-hour concentration.

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

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

In the Carpenter (1975) study, 460 mg/m^3 was considered the NOAEL because the number of volunteers that reported irritation was not significantly greater than the control group. In another study, Carpenter *et al*. (1976) found increased observations of eye irritation in all of the volunteers exposed to 930 and 1,800 mg/m^3 xylene for 15 minutes, but only observed irritation in one volunteer (10% of total) at concentrations of 220 and 450 mg/m^3. The NOAEL is identified as 450 mg/m^3 based on eye irritation. Hastings *et al*. (1984) exposed 150 volunteers to 0, 430, 860, and 1,720 mg/m^3 mixed xylenes for 30 minutes and found eye irritation in 56% of controls, 60%, 70% and 90% of the volunteers exposed at 430, 860, and 1730 mg/m^3 respectively. The xylene concentration of 430 mg/m^3 was considered as the NOAEL because reports of eye irritation were the same as controls. This study shows a similar NOAEL to the other studies but uses a 30 minute exposure period. We recommend an REL of 30.4 mg/m^3 to protect against eye irritation based on Nelson *et al*., 1943; Carpenter *et al*., 1975, 1976; Hastings *et al*., 1984. The basis of the REL is a NOAEL of 430 mg/m^3 for eye irritation. The NOAEL was adjusted from the 30 minute exposure to a one-hour REL with a time extrapolation where n=2, and adjusted by an uncertainty factor of 10 to account for human variability in sensitivity to irritation. The one-hour REL (derived by the commentator) is thus 30.4 mg/m^3 for xylene.

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

The comment points out one shortcoming of the study in that exposure durations were quite brief. This does present more uncertainty in extrapolating to an equivalent one-hour concentration, than if the duration were much closer to one-hour. The studies cited by the commentator provide a NOAEL for 15 to 30 minute exposures very similar to the NOAEL for a

3 minute exposure in Nelson *et al*. If OEHHA extrapolates using an exponent of 1 from a 3 minute to a 60 minute concentration, the resulting "equivalent" concentration is 10 fold higher than if the extrapolation runs from 30 minutes to 60 minutes. OEHHA agrees that this other data should be taken into account, but prefers to use an exponent of 1 for extrapolating from exposure durations of less than one hour to a one hour equivalent concentration. Using a NOAEL of 430 mg/m^3 for 30 minute exposure, and extrapolating to a 60 minute exposure results in an equivalent concentration of 50 ppm (220 mg/m^3). Applying an uncertainty factor of 10 for intraspecies variability yields an REL of 5 ppm (22 mg/m^3).