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** (U.S. EPA-RfC) This document summarizes the evaluation of non-cancer health effects by U.S. EPA for the RfC.
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)

Description	White crystals, monoclinic prisms
Molecular formula	$C_6H_4Cl_2$
Molecular weight	147.01
Boiling point	174°C
Melting point	53.1°C (sublimes)
Vapor pressure	10 mm Hg atm @ 54.8 °C
Solubility	Soluble in chloroform, carbon disulfide, alcohol, ether, acetone, benzene
Conversion factor	1 ppm = 6.0 mg/m^3 per ppb 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 and ortho 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.

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

CNS effects have been observed in rats, rabbits and guinea pigs 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: a 16% increase at 26 weeks, 33% at 76 weeks, and 10% at 32 weeks post-exposure. 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 reabsorbed and in percentage of litters with resorptions group 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, 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 for 10 weeks, 6 hours/day, 7 days/week, then mated for 3 weeks. The second generation F1 weanlings were exposed to 1,4-DCB for 11 weeks then mated. No developmental abnormalities were observed in pups examined. At 450 ppm a significant decrease 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 (Chlorobenzene Producers Association, 1986). 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 U.S. EPA Reference Concentration (RfC)

Study	Chlorobenzene Producers Association, 1986 (evaluated by U.S. EPA, 1994)
Study population	Sprague-Dawley rats (28 rats/sex/group)
Exposure method	Discontinuous whole-body inhalation exposures (0, 50, 150 or 450 ppm) over 10 weeks
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
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)

A 3-fold subchronic uncertainty factor was used because of data suggesting limited progression of hepatic lesions (Riley *et al.*, 1980).

The major strengths of the REL 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	**20 μg/m^3**
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)

Description	Colorless liquid
Molecular formula	$C_2H_2Cl_2$
Molecular weight	96.95
Boiling point	31.7°C
Vapor pressure	500 mm Hg @ 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.

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 (SGPT and AP) at 48 ppm. A NOAEL of 5 ppm based on liver changes (Prendergast *et al.*, 1967) is indicated by the results.

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, to 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
NOAEL	20 mg/m^3
Exposure continuity	Continuous
Exposure duration	90 days
Average experimental exposure	20 mg/m^3 for NOAEL group
LOAEL factor	1
Subchronic uncertainty factor	10 (since guinea pig life-span is about 6 years)
Interspecies uncertainty factor	10
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	1000
Inhalation reference exposure level	0.02 mg/m^3 (20 $\mu g/m^3$; 0.005 ppm; 5 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), 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, 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).

Uncertainty factors are appropriate due to the limited number of subchronic and chronic inhalation studies (greater 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). No toxicokinetic data regarding the absorption, distribution, metabolism or excretion of 1,1-DCE in humans is available.

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CHRONIC TOXICITY SUMMARY

DIETHANOLAMINE

(DEA; 2,2'-iminodiethanol; 2,2'-iminobisethanol; diethylolamine; 2,2'-aminodiethanol; 2,2'-dihydroxydiethylamine)

CAS Registry Number: 111-42-2

I. Chronic Toxicity Summary

Inhalation reference exposure level	**20 μg/m^3**
Oral reference exposure level	**0.005 mg/kg-day**
Critical effect(s)	Microcytic anemia, decreased corpuscular hemoglobin and corpuscular volume in rats
Hazard index target(s)	Cardiovascular system; nervous system

II. Physical and Chemical Properties (Melnick and Thomaszewski, 1990; Dow, 1980)

Description	Colorless crystals
Molecular formula	$C_4H_{11}NO_2$
Molecular weight	105.14
Density	1.097 g/cm^3 @ 20°C
Boiling point	268.8°C @ 760 mm Hg
Vapor pressure	0.00014 mm Hg @ 25°C
Solubility	Soluble in alcohol, water, acetone
Conversion factor	1 ppm = 4.3 mg/m^3 @ 25°C

III. Major Uses and Sources

Diethanolamine is used in the formation of soaps, emulsifiers, thickeners, wetting agents, and detergents in cosmetic formulations (Melnick and Thomaszewski, 1990). It is used as a dispersing agent in some agricultural chemicals, as an absorbent for acidic gases, as a humectant, as an intermediate in the synthesis of morpholine, as a corrosion inhibitor, and as a component in textile specialty agents (Beyer *et al.*, 1983). Diethanolamine is permitted in articles intended for use in production, processing, or packaging of food (CFR, 1981; cited in Melnick and Thomaszewski, 1990). It is also found in adhesives, sealants, and cutting fluids (Melnick and Thomaszewski, 1990).

IV. Effects of Chronic Exposures to Humans

There have been no controlled or epidemiological studies of diethanolamine exposure in humans.

V. Effects of Exposures in Animals

Diethanolamine replaces choline in phospholipids (Blum *et al.*, 1972). Systemic toxicity consequently occurs in many tissue types including the nervous system, liver, kidney, and blood system. The direct effects of DEA on the respiratory system are unknown since no subchronic or chronic inhalation studies have been conducted. Effects of DEA on the respiratory system following oral or dermal exposures have also not been examined.

A 13-week drinking water study in rats (10 per sex per group) showed significant dose-dependent hematological changes following exposure to DEA at all concentrations tested: 320, 630, 1250, 2500, and 5000 ppm in males, and 160, 320, 630, 1250, and 2500 ppm in females. Hematological effects included decreased hemoglobin and mean corpuscular volume (Melnick *et al.*, 1994a). Similar hematological changes were observed following daily topical treatment. In addition to the hematological effects, female rats also showed dose-dependent spinal cord and medullary demyelination beginning at a drinking water concentration of 1250 ppm DEA. Male rats displayed demyelination beginning at 2500 ppm. Female rats gained significantly less weight than controls beginning at 63 mg/kg/day topical treatment. In a companion drinking water study (Melnick *et al.*, 1994b), mice (10 per sex per group) were exposed to concentrations of 0, 630, 1250, 2500, 5000, and 10,000 ppm DEA and displayed dose-dependent hepatotoxicity, nephrotoxicity, and cardiac toxicity. Daily topical treatment in a separate study resulted in skin lesions in mice. Significant hepatic toxicity was observed at all drinking water concentrations, and skin lesions were observed at all topical doses.

Barbee and Hartung (1979a) found that repeated treatment of rats with 330 mg DEA/kg/day significantly inhibited formation of phosphatidyl choline and phosphatidyl ethanolamine in the liver as compared with control rats. In a subsequent study, Barbee and Hartung (1979b) noted changes in liver mitochondrial activity in rats (4 per group) following exposure to DEA in drinking water for up to 5 weeks. Mitochondrial changes were observed at 42 mg/kg/day after 2 weeks.

Daily oral treatment of male rats with 0, 250, 500, or 750 mg/kg/day for 5 days, or 100 mg/kg/day for 14 days resulted in reduced activities of the liver enzymes microsomal hydroxylase and N-demethylase activities (Foster *et al.*, 1971).

VI. Derivation of Chronic Reference Exposure Level (REL)

Study	Melnick *et al.* (1994a)
Study population	Rats (female)
Exposure method	Drinking water (*ad libitum*)
Critical effects	Hematological changes (decreased total and mean corpuscular hemoglobin, decreased mean corpuscular volume)
LOAEL	160 mg/L (14 mg/kg/day estimated from water consumption data)
NOAEL	Not observed
Exposure duration	13 weeks
Average exposure concentration	14 mg/kg/day for LOAEL group
LOAEL uncertainty factor	10
Subchronic uncertainty factor	3
Interspecies uncertainty factor	10
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	3,000
Oral reference exposure level	0.005 mg/kg-day
Route-to-route conversion factor	3,500 $\mu g/m^3$ per mg/kg-day
Inhalation reference exposure level	20 $\mu g/m^3$ (4 ppb)

No chronic inhalation studies with diethanolamine were located in the peer-reviewed literature. The study by Melnick *et al.* (1994a) shows dose-dependent adverse hematological and CNS effects in rats exposed to DEA in drinking water. Similar systemic effects were observed following dermal exposure. The Melnick *et al.* subchronic study was of the longest duration and was the most comprehensive report of the systemic effects of DEA in the literature. However, portal-of-entry effects of DEA have not been examined and should be addressed in future studies since this compound has irritant properties. The data from female rats were used since females were more sensitive than males to the hematologic effects of DEA.

The diethanolamine database is relatively weak. Major areas of uncertainty are the lack of adequate human exposure data, the absence of a NOAEL in the major study, the lack of reproductive and developmental toxicity studies, and the lack of chronic inhalation, multiple-species, health effects data.

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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	**30 µg/m^3** (U.S. EPA-RfC) This document summarizes the evaluation of non-cancer health effects by U.S. EPA for the RfC.
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
Boiling point	153° C
Melting point	-61° C
Vapor pressure	3.7 mm Hg @ 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).

IV. Effects of Human Exposure

Among 100 workers occupationally exposed to a DMF for at least one year (mean exposure of 5 years), a statistically significant incidence of hepatic impairment, as indicated by elevated gamma-glutamyl transpeptidase levels and digestive disturbances, were 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. 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.

U.S. EPA (1994) states that subjective evidence of liver toxicity such as digestive impairment and alcohol intolerance, are often observed at exposures below those which 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

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 U.S. EPA Reference Concentration (RfC) (U.S. EPA, 1994)

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
Modifying factors	3 (lack of reproductive toxicity data)
Cumulative uncertainty factor	300
Inhalation reference exposure level	0.03 mg/m^3 (30 $\mu g/m^3$, 0.009 ppm, 9 ppb)

Intermediate uncertainty factors were used for LOAEL and subchronic extrapolation because of the mild nature of the effects observed and the only slightly less than chronic exposure duration.

The major strength of the RfC 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	**1 μg/m^3** (U.S. EPA RfC) This document summarizes the evaluation of non-cancer health effects by U.S. EPA for the RfC
Critical effects	Histological changes in nasal turbinates in rats
Hazard index target(s)	Respiratory system; eyes

II. Physical and Chemical Properties (HSDB, 1997)

Description	Colorless liquid
Molecular formula	C_3H_3ClO
Molecular weight	92.5
Density	1.181 g/cm^3 @ 20° C
Boiling point	116.5° C
Vapor pressure	13 mm Hg @ 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).

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 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 showed 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 U.S. EPA Reference Concentration (RfC)

Study	Quast *et al.* (1979); U.S. EPA (1994)
Study population	Rats and mice (10 per sex per concentration)
Exposure method	Discontinuous whole-body inhalation
Critical effects	Inflammation, focal erosions, hyperplasia, and metaplasia
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	0.095 ppm (gas with extrathoracic respiratory effects, RGDR = 0.11, based on MV = 0.14 L, SA(ET) = 11.6 cm^2)
LOAEL factor	1
Subchronic uncertainty factor	10
Interspecies uncertainty factor	3
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	300
Inhalation reference exposure level	0.0003 ppm (0.3 ppb; 0.001 mg/m^3; 1 $\mu g/m^3$)

The strengths of the inhalation REL 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 and 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 μg/m^3** (U.S. EPA-RfC) This document summarizes the evaluation of non-cancer health effects by U.S. EPA for the RfC
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_80
Molecular weight	72.12
Density	0.837 g/cm^3 @ 17°C
Boiling point	63.3°C
Vapor pressure	176 mm Hg @ 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

Epoxy butane 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 or propylene oxide (Reprotext, 1994).

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 were noted in both sexes at either concentration. Increases in granulocytic hyperplasia and splenic hematopoiesis were noted at both concentrations in female mice.

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, for 5 days/week. 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 U.S. EPA Reference Concentration (RfC)

Study	National Toxicology Program (NTP, 1988); U.S. EPA, 1994
Study population	Rats and mice
Exposure method	Discontinuous inhalation
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	1.7 ppm for LOAEL group (gas with extrathoracic respiratory effects, RGDR = 0.18, based on MV = 0.06 L, SA(ET) = 2.9 cm^2)
LOAEL uncertainty factor	10
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 $\mu g/m^3$)

The strengths of the inhalation REL include 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 adequate human exposure data, and the lack of observation of a NOAEL.

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CHRONIC TOXICITY SUMMARY

ETHYLENE

(ethene; acetene; bicarburetted hydrogen; olefiant gas; elayl)

CAS Registry Number: 74-85-1

I. Chronic Toxicity Summary

Inhalation reference exposure level	**20,000 μg/m^3**
Critical effect(s)	Central nervous system impairment
Hazard index target(s)	Nervous system

II. Chemical Property Summary (HSDB, 1997)

Description	Colorless gas; olefinic odor; slightly sweet
Molecular formula	C_2H_4
Molecular weight	28.05
Boiling point	-102.4°C @ 700 mm Hg
Vapor pressure	4270 kPa at 0°C
Solubility	Very slightly soluble in water (131 mg/L H_2O at 20°C). Slightly soluble in acetone, benzene and ethanol. Soluble in diethyl ether
Conversion factor	1.15 μg/m^3 per ppb at 25°C

III. Major Uses and Sources

Ethylene is a petrochemical produced in large quantities worldwide and is ranked 4th in weight made among organic chemicals produced in the U.S. (C&EN, 1995). Over 95% of worldwide annual commercial production of ethylene is currently based on steam cracking of petroleum hydrocarbons. In the U.S. ethane is the primary feedstock to produce ethylene. Commercially produced ethylene is then used as a feedstock for production of polymers and industrial chemicals. A small amount is used for controlled ripening of citrus fruits, tomatoes, bananas and other fruits, vegetables and flowers. Ethylene is ubiquitous in the environment, from both natural and man-made sources. It is a natural product of vegetation of all types and acts as an endogenous plant growth regulator. Endogenous but unidentified sources of ethylene exist in man and animals. A major anthropogenic source is burning vegetation. Ethylene is also released from agricultural wastes and refuse and from the incomplete combustion of fossil fuels. Small amounts are found in volcanic emissions and natural gas. There is little chance of inhalation exposure during its manufacture because the process takes place in a closed system. Exposure may result from spills, leaks or use of ethylene.

Ethylene concentrations of <1-5 $\mu g/m^3$ occur in rural and remote sites while concentrations of 2 to over 1000 $\mu g/m^3$ can occur in urban and indoor sites (IARC, 1994). High indoor concentrations generally depend on whether burning biomass is used as a source of energy. Exposure to ethylene is 10 times greater in cigarette smokers than the exposure in polluted urban air (Persson *et al.*, 1988).

IV. Effects of Human Exposure

The ACGIH considers ethylene to be a simple asphyxiant, an "inert" gas (ACGIH, 1995). Asphyxiants prevent oxygen from combining with hemoglobin. However, ethylene's use in anesthesia in the presence of oxygen indicates that it has inhibitory effects on the human central nervous system (Adriani, 1947; Brumbaugh, 1928; Hunter, 1956).

There is a lack of toxicological data on long-term ethylene exposure in humans. Inhalation pharmacokinetics of ethylene have been performed in human volunteers (Filser *et al.*, 1992). Due to ethylene's poor solubility in blood, the accumulation factor "body/air" at steady-state was determined to be only 0.33$\pm$0.13 (mean$\pm$SD). The rate of metabolism was directly proportional to the exposure concentration (1st order kinetics) in the range between 1 ppm and 50 ppm. The authors assume that at higher concentrations saturation of human ethylene metabolism occurs, similar to observations in rats (Bolt and Filser, 1987). Only 2% of ethylene inhaled was metabolized to ethylene oxide, whereas 98% of ethylene was exhaled unchanged. The half-life of ethylene was determined to be 0.65 hr. The researchers also determined that the endogenous production of ethylene in the human subjects was 32 nmol/hr.

The measurement of hydroxyethyl adducts to N-terminal valine in hemoglobin has been used as dosimetry for ethylene oxide in occupational studies of fruit store workers exposed to ethylene (Törnqvist *et al.*, 1989). With an average exposure of 0.3 ppm of ethylene, it was estimated from the levels of valine adducts that about 3% of ethylene was metabolized to ethylene oxide. This is in close agreement with studies of ethylene metabolism in human volunteers, which determined an average conversion of 2% inhaled ethylene to ethylene oxide (Filser *et al.*, 1992). Analysis of inhaled ethylene and of adducts from ethylene oxide to N-terminal valine of hemoglobin were performed in 2 smokers to determine the percentage metabolism of ethylene to ethylene oxide due to smoking (Granath *et al.*, 1994). The results were comparable to previous metabolism studies; 2% inhaled ethylene was metabolized to ethylene oxide with a detoxification rate of 1 hr^{-1} for ethylene oxide (corresponding to a $t_{1/2}$ of 42 min).

V. Effects of Animal Exposure

When the body weight and body surface differences between man and rats are taken into account, the pharmacokinetics of ethylene in the two species are similar (Shen *et al.*, 1989). The concentration "body/air" ratio at steady state in rats was 0.54, indicating that accumulation in body tissues does not occur. Ethylene concentrations in rats were highest in fat and lowest in blood after a 12 hour exposure to 300 ppm ethylene (Eide *et al.*, 1995). Twelve hours after cessation of exposure, ethylene was not detectable in the fat. In another pharmacokinetic study

in rats, ethylene metabolism was found to follow first-order kinetics at atmospheric concentrations below 80 ppm (Filser and Bolt, 1984; Bolt and Filser, 1984). Above this range metabolism becomes increasingly saturated, and reaches the maximum metabolic rate (V_{max}) at concentrations of 1000 ppm or more. In view of the saturability of ethylene metabolism, at which is found the maximal possible average body concentration of its metabolite, ethylene oxide, Bolt and Filser (1987) calculated that (theoretical) exposure of rats to ethylene at 40 ppm is equivalent to an ethylene oxide exposure of 1 ppm. However, because of the saturability of ethylene metabolism, ethylene concentrations of 1000 ppm or higher correspond to an ethylene oxide (theoretical) exposure of only 5.6 ppm. In a study of adduct formation among 1-alkenes, ethylene was found to produce a greater amount of hemoglobin and DNA adducts in rats (due to its metabolism to ethylene oxide) than other long-chain 1-alkenes (Eide *et al.*, 1995). In mice, S-(2-hydroxyethyl)cysteine was identified as a metabolite of ethylene in urine (3% of ^{14}C in urine) following inhalation of ^{14}C-ethylene (Ehrenberg *et al.*, 1977).

The available data indicate that ethylene has a low potential for non-cancer chronic toxicity in experimental animals.

In a 13-week inhalation study, 30 Sprague-Dawley rats/group/sex were exposed to 0, 300, 1000, 3000, or 10,000 ppm of ethylene for 6 hr/day, 5 days/week (Rhudy *et al.*, 1978; CIIT, 1977). Body weights, total weight gains and food consumption were not affected in any of the exposed animals. Hematology, clinical chemistry, urinalysis and histopathology did not find any treatment-related effects at any exposure level.

In a comprehensive lifetime inhalation study, 120 Fischer-344 rats/group/sex were exposed to ethylene concentrations of 0, 300, 1000 or 3000 ppm for 6 hr/day, 5 days/week, for up to 24 months (Hamm *et al.*, 1984; CIIT, 1980). Time-weighted average concentrations were 0, 301, 1003, and 3003 ppm. The maximum tolerated dose was not used since concentrations above 3000 ppm were hazardous due to ethylene's explosive properties. Over the 24 months, no differences were noted between exposure groups regarding 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.

VI. Derivation of Chronic Reference Exposure Level (REL)

Study	Hamm et al. (1984)
Study population	Fischer 344 rats (120/sex/group)
Exposure method	Inhalation exposure at 0, 300, 1000 or 3000 ppm
Critical effects	None
LOAEL	Not observed
NOAEL	3000 ppm (free standing)
Exposure continuity	6 hr/d, 5 d/wk
Exposure duration	24 months
Average exposure	535 ppm (3000 x 6/24 x 5/7)
Human equivalent concentration	535 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	1
Interspecies uncertainty factor	3
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	30
Inhalation REL for ethylene	18 ppm (20 mg/m^3; 20,000 μg/m^3)

The major strengths of the REL are the availability of long-term animal exposure data on ethylene and the observation of a NOAEL.

Weaknesses of the database for ethylene include the absence of a LOAEL for any toxic effect in the long-term study and a lack of multi-generation studies. Adverse effects on reproduction and development may occur where long-term chronic effects in adults have failed to reveal any toxicity. Rats appear to be tolerant to the long-term effects of ethylene. Toxicity tests in a more ethylene-sensitive experimental animal would strengthen the database for ethylene.

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CHRONIC TOXICITY SUMMARY

ETHYLENE DIBROMIDE

(1,2-dibromoethane; dibromoethane; alpha, beta-dibromoethane; EDB; ethylene bromide; glycol bromide)

CAS Registry Number: 106-93-4

I. Chronic Toxicity Summary

Inhalation reference exposure level	**0.8 μg/m^3**
Critical effect(s)	Decreased sperm count/ejaculate, decreased percentage of viable and motile sperm, increased semen pH, and increased proportion of sperm with specific morphological abnormalities in human males
Hazard index target(s)	Reproductive system

II. Chemical Property Summary (HSDB, 1995)

Description	Colorless, heavy, nonflammable liquid with a mildly sweet, chloroform-like odor.
Molecular formula	$C_2H_4Br_2$
Molecular weight	187.88
Boiling point	131-132°C
Vapor pressure	0.11 mm Hg at 20°C
Solubility	Slightly soluble in water, 3400 mg/l water at 20°C. Miscible with most organic solvents.
Conversion factor	7.68 μg/m^3 per ppb at 25°C

III. Major Uses and Sources

Ethylene dibromide (EDB) is used as a solvent for resins, gums and waxes, and as a chemical intermediate in the synthesis of dyes and pharmaceuticals (HSDB, 1995). EDB was once widely used as a fumigant for the control of pests in the U.S. Because of concerns regarding its carcinogenicity, the agricultural uses of EDB were banned in 1983 (RECT, 1988). EDB was also commonly used as a gasoline additive to scavenge inorganic lead compounds. The transition to the use of lead-free gasoline has drastically curtailed the use of EDB in this country (REPROTOX, 1995). EDB is now used mainly in industry. EDB may be formed naturally in the ocean as a result of macro algae growth. Exposure to the general population, via inhalation,

may occur in the vicinity of industries and in industrial settings where this compound is manufactured and used.

IV. Effects of Human Exposures

Pharmacokinetic studies of EDB in humans could not be found in the literature. However, *in vitro* studies of EDB metabolism in human liver samples have been performed (Wiersma *et al.*, 1986). These experiments have shown that the enzyme systems known to metabolize EDB in rodent liver also metabolize EDB in the human liver. EDB was metabolized by human liver cytosolic glutathione S-transferases (GST), microsomal GST, and microsomal mixed function oxidases (MFO). MFO activity resulted in adducts irreversibly bound to protein while GST activity was mostly responsible for adducts irreversibly bound to DNA. Rodent liver enzymes similarly activate EDB to metabolites that bind to cellular macromolecules. In human fetal liver (16-18 weeks gestation) cytosolic GST was also found to metabolize EDB with high efficiency (Kulkarni *et al.*, 1992). Since detoxification via MFO activity may be limited at this stage of development, the results suggest that the human fetus may be at greater risk from EDB toxicity than adults.

A study of mortality from cancer and respiratory diseases was conducted among 161 employees exposed to EDB in 2 production units operated from 1942 to 1969 and from the mid-1920s to 1976, respectively (Ott *et al.*, 1980). No apparent connection was found between mortality due to respiratory diseases and exposure to EDB, when compared to U.S. white male mortality figures.

Due to the structural similarity of EDB to dibromochloropropane (DBCP), a known toxic agent in human male reproductive organs, a number of epidemiological studies concerning male reproduction and spermatogenesis were conducted.

In a study of 59 employees exposed to EDB at the Ethyl Corporation plant in Magnolia, Arkansas, the sperm counts of the exposed men were divided into 2 groups depending on estimated exposure (Ter Haar, 1980). Twenty percent of the low exposure group (<0.5 ppm) had sperm counts below 40 million, whereas 42% of the high exposure group (0.5 to 5 ppm) had sperm counts below this figure. The sperm counts were intermediate between counts reported for 2 types of U.S. samples (for normal men). The observed births among the two exposure groups were found to be similar to the number of expected births. The author determined that EDB had no effect on sterility or reproduction in the workers. Weaknesses of this study include the small population of exposed workers and the lack of a concurrent unexposed control group. Taking these defects of the study into account, Dobbins (1987) concluded that the results provide evidence that EDB exposure between 0.5 and 5.0 ppm is associated with lower sperm counts.

A comparison of observed marital fertility with expected fertility (based on U.S. fertility rates) was conducted among 297 men working at 4 U.S. plants that manufacture EDB (Wong *et al.*, 1979). Fertility was 20% below expected for the four plants combined. This was largely due to plant D, which was 49% below the expected level. After omitting the incidence of vasectomies and hysterectomies among married couples, observed fertility was still 39% below the expected

figure for plant D but was now no longer statistically significant. Exposure levels of EDB at plant D were not known but were estimated to be no more than 5 ppm. Later review determined that expected (control) levels of fertility and the power of the study were too low, resulting in the inability to identify a possible adverse effect (Dobbins, 1987). The lower fertility at plant D indicates that EDB has the potential to reduce fertility, but the extent of the reduction cannot be estimated from this study. Further treatment of the data by a method that uses the proper statistical adjustments of reproductive experience in the U.S. population (used as the control) suggests borderline significance for reduced fertility among the combined workers at the four plants (Wong *et al.*, 1985). The fertility evaluation indicates that more in-depth epidemiologic or physiologic studies are needed.

Semen analysis of 83 pineapple workers at two plantations was performed by Rogers and associates (1981). EDB-exposed workers were removed from each group and placed in a separate group. The remaining two groups of workers acted as control groups. Sperm count, motility and morphology were similar among the three groups. However, 43.8% of exposed workers had abnormally low counts (<40 million/ml) while abnormally low sperm counts of controls were 34.2% and 17.8%. Of the workers that had fertility tests done, 4/4 of the exposed workers tested in the infertile range. Forty percent or less tested in the infertile range among the control groups. The results suggest that workers exposed to EDB had reduced sperm counts, but exposure levels were not known.

Semen analysis among 46 men employed in the papaya fumigation industry was conducted to determine if EDB affected semen quality (Ratcliff *et al.*, 1987; Schrader *et al.*, 1987). Average duration of exposure was 5 years and the geometric mean breathing zone exposure to airborne EDB was 88 ppb (8 hr time weighted average) with peak exposures of up to 262 ppb. The comparison group consisted of 43 unexposed men from a nearby sugar refinery. Following consideration of confounding factors, statistically significant decreases in sperm count/ejaculate, the percentage of viable and motile sperm, and increases in the proportion of sperm with specific morphological abnormalities (tapered heads, absent heads, and abnormal tails) were observed among exposed men. Semen pH was significantly more alkaline than that of unexposed workers. Other measured sperm quality parameters were unchanged. This study suggests that EDB can result in reproductive impairment. However, no measurement of male fertility was conducted.

In a study that examined similar indices of semen quality, 6 week exposure of 10 forestry workers to EDB (60 ppb time weighted average, with peak exposures of up to 2165 ppb) resulted in decreased semen volume and slower sperm velocity (Schrader *et al.*, 1988). Six unexposed men were used as controls. The researchers suggest that short-term exposure to EDB results in decreased sperm velocity while long-term exposure, as in the previous study of EDB-exposed papaya workers, results in sperm immotility and cell death.

V. Effects of Animal Exposures

EDB is readily and rapidly absorbed from the lung when breathed as a vapor, from the GI tract when taken orally, or through the skin when applied dermally (HSDB, 1995). In rats, the rate of absorption of EDB from the respiratory tract reached a plateau within 10 to 20 minutes following exposure to 75 ppm EDB for up to 2 hours (Stott and McKenna, 1984). About 58% of the EDB was absorbed. Intraperitoneal injection of [^{14}C]EDB into guinea pigs resulted in the highest concentrations in liver, kidneys and adrenals (Plotnick and Conner, 1976). Sixty-five percent of the dose was excreted as metabolites in urine, 3% in feces, and 12% excreted unchanged in expired air. In rats, the highest concentrations of [^{14}C]EDB label were found in liver, kidney and spleen following an oral dose of 15 mg/kg body wt (Plotnick *et al.*, 1979). Studies with rats have provided evidence that 2 pathways of metabolic bioactivation exist for EDB (RECT, 1988). The oxidative pathway yields the metabolite 2-bromo-acetaldehyde, which is associated with cell macromolecule binding and liver damage. The conjugative pathway principally yields glutathione products, such as *S*-(2-bromoethyl)-glutathione, which are mainly responsible for DNA binding and mutagenesis. In rats, orally administered EDB is excreted primarily in the urine as mercapturic acid derivatives (Jones and Edwards, 1968). The biologic half-life for elimination of [^{14}C]EDB in rats is 5.1-5.6 hours (Watanabe *et al.*, 1978) and less than 48 hours in mice and guinea pigs (HSDB, 1995). Besides the small amount irreversibly bound to cell macromolecules and DNA, EDB shows little, if any, bioaccumulation in mammalian systems.

In a subchronic toxicity study of experimental animals, rats and guinea pigs were given EDB by oral administration for about 4 months (Aman *et al.*, 1946). Body weights and mortality of animals at or below an average daily dose of 40-50 mg/kg body wt-day were unaffected. However, only one control animal/species was used, the dosing regimen was not well described, and pathologic examination was apparently not performed.

Subchronic exposure of rats (20/sex/group) to 50 ppm EDB for as many as 63 seven-hour exposures in 91 days resulted in no significant change in body weights (Rowe *et al.*, 1952). Liver and kidney weights were increased in both sexes while testis weights were decreased in males. Also, lung weights in males were elevated and spleen weights in females were decreased. Histopathological examination revealed no changes. Guinea pigs (8/sex/group) subjected to as many as 57 seven-hour exposures of 50 ppm EDB in 80 days exhibited reduced body weights. Organ weights were unchanged, but microscopic examination of the livers showed slight central fatty degeneration. In kidneys, slight interstitial congestion and edema with slight parenchymatous degeneration of the tubular epithelium were observed. Four rabbits exposed to 59 seven-hour sessions at 50 ppm in 84 days showed no signs of adverse effects. Clinical signs of monkeys exposed to 50 ppm EDB (49 seven-hour exposures in 70 days) included an ill, unkempt appearance and nervousness. Slight central fatty degeneration in livers was observed, but pathology was not seen in other tissues. Exposure of the same four species to 25 ppm EDB for up to 220 days (145 to 156 seven-hour exposures) showed no signs of adverse effects.

In a 13-week inhalation study, 5 Fischer 344 albino rats/group/sex and 10 B6C3F1 mice/group/sex were exposed to 0, 3, 15 or 75 ppm EDB for 6 hr/day, 5 days/week (Reznik *et al.*, 1980). At 75 ppm, rats and mice exhibited severe necrosis and atrophy of the olfactory epithelium in the nasal cavity. Squamous metaplasia, hyperplasia and cytomegaly of the

epithelium were also seen in nasal turbinals, larynx, trachea, bronchi and bronchioles. Minor alterations were seen in the nasal cavity of only a few male and female rats at 15 ppm. No compound-related lesions were observed in the olfactory and respiratory epithelium at 3 ppm. No lesions were seen in other tissues at any dose.

In another 13-week inhalation study, 40 male and 20 female CDF(F344) rats/group were exposed to 0, 3, 10 or 40 ppm EDB 6 hr/day, 5 days/week (Nitschke *et al.*, 1981). Male rats in the 40 ppm group exhibited decreased weight gain throughout most of the exposure period. However, reduced weight gain was never more than 6-8% below control levels. With the exception of decreased specific gravity of urine in females of the 40 ppm group, no treatment-related changes were observed in any rat group with respect to urinalysis, hematology and clinical chemistry. At the end of 13 weeks, relative liver and kidney weights of males exposed to 40 ppm EDB were significantly elevated while relative liver weights of females in the two highest exposure groups were significantly elevated. Absolute liver weight of females in the 40 ppm group was also significantly elevated. Histopathological examination revealed lesions primarily confined to the anterior sections of the nasal turbinates. Hyperplasia and nonkeratinizing squamous metaplasia of the respiratory epithelium were observed in nasal turbinates of rats exposed to 40 ppm EDB. Only slight epithelial hyperplasia of nasal turbinates was noted at 10 ppm. No treatment related effects were seen at 3 ppm. Livers of females in the 40 ppm group showed a slight increase in fat. After an 88 day recovery period, there was a reversion to normal of the nasal turbinates in all but one rat.

In what was originally scheduled to be a lifetime exposure study, 50 Osborne-Mendel rats/group/sex and 50 B6C3F1 mice/group/sex were administered EDB 5 days/week by gastric - lavage over a substantial portion of their life-span (NCI, 1978). Twenty untreated controls/sex and 20 vehicle controls/sex of each species were included in the study. Rats received initial doses of 80 and 40 mg/kg body wt-day for the first 17 weeks. Due to high mortality, dosing of high dose rats was discontinued for 13 weeks and resumed on week 30 at 40 mg/kg body wt-day. In week 42 all intubations of low and high dose rats ceased for 1 week followed by 4 weeks of dose administration. All surviving, treated male rats were sacrificed in week 49; all surviving, treated female rats were sacrificed in week 61. The resulting time-weighted average dosage over the test period was 38 and 41 mg/kg body wt-day for low and high dose males, respectively, and 37 and 39 mg/kg body wt-day for low and high dose females, respectively. Mice received initial dosages of 120 and 60 mg/kg body wt-day. In weeks 11-13, high and low dosages were increased to 200 and 100 mg/kg body wt-day, respectively. Original dosage levels were resumed after week 13. At week 40, administration of EDB was decreased to 60 mg/kg body wt-day for high dose mice. EDB administration was discontinued at week 54 with sacrifice occurring at week 78 for males and high dose females. Low dose female mice were observed for 37 weeks after intubation ceased. The resulting time-weighted average dosage over the test period was 62 and 107 mg/kg body wt-day for low and high dose mice, respectively. In rats, clinical signs by week 5 included reddened ears and hunched back in all treatment groups. By week 10, all treated rats had reduced body weights ($\geq$10%). Both female and male rats exhibited dose-dependent mortality. Many of the deaths occurred during or shortly after intubation, suggesting an acute toxic reaction. Pathology revealed hyperkeratosis and acanthosis of the forestomach in high dose males and females and in one low dose female. A small number of rats in both treatment groups showed adrenal cortex degeneration and peliosis hepatitis of the liver. Dosed

males showed early development of testicular atrophy. In mice, dose-related body weight reduction and mortality were observed. Clinical signs included alopecia, thin, hunched appearance, soft feces and body sores. Hyperkeratosis and acanthosis of the forestomach were seen in high dose male and female mice. One incidence each of hyperkeratosis (in a female) and acanthosis (in a male) was seen at the low dose. Splenic changes were present in high dose mice and testicular atrophy was present in high dose males.

In a long-term inhalation exposure study, F344 rats and B6C3F$_1$ mice were exposed to 0, 10 or 40 ppm EDB 6 hr/day, 5 days/week for up to 103 weeks (NTP, 1982). In male and female rats, the high dose groups had reduced body weights and increased mortality that began at about week 60. The treatment-related non-neoplastic pathology included hepatic necrosis (both sexes), epithelial hyperplasia and suppurative inflammation throughout the respiratory system (both sexes), and nephropathy (males only). Toxic nephropathy and mineralization were also seen in high dose female rats. Testicular degeneration and atrophy occurred with greater frequency in exposed rats but may be related to observed testicular tumors. Spermatic granulomas were also more frequently seen in high-dose males. Degeneration of the adrenal cortex appeared to be dose-related in females, but only one incidence each was seen in low and high dose males. Increased incidence of retinal atrophy was observed in exposed females. In mice, body weights were reduced at the high dose in both males and females. Many of the high dose animals exhibited a progressive weakness of the limbs or body during the second year. Increased mortality occurred in a dose-related manner in females and was significantly greater in low dose males. Non-neoplastic pathology included epithelial hyperplasia throughout the respiratory system and serous and suppurative inflammation of the nasal cavity in exposed mice. In all male mice, the principal cause of death was urinary bladder inflammation. However, bladder epithelial hyperplasia was only seen in exposed animals. An increased incidence of suppurative inflammation of the prostate was present but was also seen in controls. Dose-related spleen hematopoiesis was observed in females.

Another long-term inhalation study investigated the effects of 0 or 20 ppm EDB (7 hr/day, 5 days/week) on 48 Sprague-Dawley rats/sex/group for 18 months (Wong *et al.*, 1982). Significantly lower body weight gains (>10% difference from controls) occurred by the 15th month in males, and by the 18th month in females. Significantly reduced food consumption was not apparent. Increased mortality rates in both sexes occurred beginning in the 12th month of EDB exposure. All hematological findings were within normal ranges. The only recorded non-neoplastic gross or microscopic finding was atrophy of the spleen in males, which may be related to tumor formation (hemangiosarcoma). The nasal cavity was not examined.

In a study of the effect of EDB on sperm production in bulls (Isreal-Friesian breed), 4 calves were fed 2 mg/kg body wt-day for 12 months (Amir and Volcani, 1965). The bulls were then given EDB in gelatin capsules every other day for 2-4 months longer. EDB did not appear to affect the growth, health and libido of the bulls. However, semen density and motility were significantly lower compared to untreated control bulls of the same age. Many abnormal spermatozoa were also present in treated bulls. A NOAEL for this effect was apparently not determined. Cessation of EDB administration resulted in normal sperm within 10 days to 3 months. Further studies confirmed that EDB adversely affected sperm production without any other apparent effects on bulls (Amir and Volcani, 1967; Amir and Ben-David, 1973). However,

feeding rams 2-5 mg/kg body wt-day for 120 days did not result in any effect on sperm or on the health of the animal (Amir, 1991).

In a developmental toxicity study, 15-17 pregnant Charles River CD rats and 17-19 pregnant CD mice were exposed to 0, 20, 38 and 80 ppm EDB by inhalation 23 hr/day during days 6 to 16 of gestation (Short *et al.*, 1978). A significant increase in mortality occurred in adult rats exposed to 80 ppm EDB and in adult mice exposed to 38 and 80 ppm EDB. Mice exposed to the highest dose experienced 100% mortality. Reduced body weights and feed consumption occurred in both species at all doses tested. Fetal mortality was increased in rats at the highest dose and in mice at 38 ppm. Reduced fetal body weights occurred at 38 ppm in rats and at all exposure levels in mice. No anomalies were seen in rat fetuses. An increase in runts at 38 ppm and a dose-dependent increase in skeletal anomalies were observed among mouse fetuses. However, these anomalies were characteristic of delayed development and occurred at doses that adversely affected maternal welfare. Therefore, these effects are indicative of fetal toxicity rather than teratogenicity.

Male reproductive toxicity of EDB has been evaluated in some other experimental animals. New Zealand white rabbits, dosed subcutaneously with 0, 15, 30 or 45 mg/kg body wt-day, showed adverse effects at the highest dose (Williams *et al.*, 1991). Increased mortality, increased serum enzymes, and liver damage were observed at this dose level. With respect to sperm quality, sperm velocity, motility, and motion parameters were reduced at the highest dose. A dose related decrease in semen pH was also noted. However, male fertility and fetal structural development were unaffected.

In contrast, the dominant lethal assay in mice was negative following a single intraperitoneal injection of 100 mg EDB/kg body wt (Barnett *et al.*, 1992). Germ cell tests did not indicate that EDB was a germ cell mutagen in male mice.

VI. Derivation of Chronic Reference Exposure Level (REL)

Study	Ratcliff *et al.*, 1987
Study population	46 exposed men, 43 unexposed men; 89 total
Exposure method	Variable workplace breathing zone airborne exposure (88 ppb geometric mean 8-hour time weighted average exposure with peak exposures up to 262 ppb)
Critical effects	Reproductive toxicity; decreased sperm count/ejaculate, decreased percentage of viable and motile sperm, increased semen pH, and increased proportion of sperm with specific morphological abnormalities (tapered heads, absent heads, and abnormal tails) in human males
LOAEL	88 ppb
NOAEL	Not observed
Exposure continuity	8 hr/day (10 m^3/day occupational exposure rate), 5 days/week
Exposure duration	Average, 4.9 years (with standard deviation of 3.6 years)
Average experimental exposure	31 ppb for LOAEL group (88 x 10/20 x 5/7)
Human equivalent concentration	31 ppb
LOAEL uncertainty factor	10
Subchronic uncertainty factor	3
Interspecies factor	1
Intraspecies factor	10
Cumulative uncertainty factor	300
Inhalation reference exposure level	0.1 ppb (0.0008 mg/m^3, 0.8 $\mu g/m^3$)

The primary study by Ratcliff and associates (1987) found significant changes in sperm quality indices of papaya workers exposed to EDB vapors for an average of nearly 5 years. No other health effects were apparent. A level of EDB at which no toxicity was observed (NOAEL) was not determined.

In addition to the primary study of Ratcliff *et al.* (1987), several other epidemiological studies strongly suggest a correlation between EDB exposure and male reproductive toxicity (Ter Haar, 1980; Wong *et al.*, 1979; Wong *et al.*, 1985; Rogers *et al.*, 1981; Schrader *et al.*, 1988). This lesion appears to occur in humans at concentrations at which other toxic effects are not seen. EDB also shares some structural similarity to dibromochloropropane (DBCP), a known reproductive toxicant in human males. The evidence for male reproductive toxicity of EDB is not as strong as that for DBCP, probably because EDB is not as potent as DBCP in producing this toxic effect. However, the number of studies indicating a connection between male reproductive toxicity and EDB exposure cannot be ignored for the development of the REL.

Chronic oral exposure of bulls to EDB results in similar toxic effects at low concentrations (equivalent to 0.9 ppm) without affecting the general health of the animal (Amir and Volcani, 1965; Amir, 1991). Unfortunately, a dose-response effect for EDB toxicity, as well as a determination of the NOAEL, has yet to be determined in bulls. Long-term studies of EDB toxicity in other experimental animals suffer from some of the same data deficiencies. Two lifetime studies of EDB exposure in rodents did not yield a NOAEL (NCI, 1978; NTP, 1982). Evidence of testicular atrophy was found in both studies, but at concentrations that also produced toxic effects in other organ systems. The database for chronic toxicity of EDB in experimental animals would be enhanced if the proper doses were chosen to determine a NOAEL.

The strengths of the inhalation REL include the use of human exposure data from workers exposed over a period of years. Major areas of uncertainty are the lack of observation of a NOAEL, the uncertainty in estimating exposure, the potential variability in exposure concentration, and the limited nature of the study (fertility was not actually tested).

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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**
Critical effect(s)	Hepatotoxicity; elevated liver enzyme levels in serum of rats.
Hazard index target(s)	Alimentary system; nervous system

II. Physical and Chemical Properties (HSDB, 1995)

Description	Clear, colorless, oily liquid
Molecular formula	$C_2H_4Cl_2$
Molecular weight	98.97
Density	1.2351 g/cm^3 @ 20ºC
Boiling point	83.5ºC
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, 1995). It is also an intermediate in the manufacture of trichloroethane and fluorocarbons. EDC has been used as a solvent and a soil fumigant.

IV. Effects of Human Exposure

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 systems and liver effects in workers occupationally exposed to concentrations of 16 ppm EDC and below. Nervous system effects were also reported by Rosenbaum (1947) 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.

V. Effects of Animal Exposure

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). The rats were 5.5-6 weeks of age at the beginning of exposure. No significant increases in any tumor type were observed. Absolute and relative liver weights were not significantly different from controls.

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. No significant 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. Most notably, significant increases in alanine aminotransferase (ALT), lactate dehydrogenase (LDH) and uric acid were observed in addition to significant decreases in cholesterol and aspartate aminotransferase (AST). Blood urea nitrogen (BUN) and γ-glutamyl transpeptidase were also elevated but at non-significant levels. At 150 ppm, similar changes were observed with a statistically significant elevation in BUN. At lower concentrations, AST was significantly elevated while ALT was within normal range. 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), a non-carcinogen used extensively in the rubber industry and as a treatment for alcoholism, exposed rats to EDC concentrations of 300 ppm and greater 5 days per week for 30 days (Igwe *et al.*, 1986). Increased liver weights 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. 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. Guinea pigs exposed to this concentration 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 were 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 of determining 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 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 F344/N rats administered 1000 ppm or greater in drinking water. 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. 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.

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 (50 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 $\mu g/m^3$)

The strengths of the inhalation REL 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 lack of reproductive and developmental toxicity studies, the small groups tested in the study, and the lack of multiple-species health effects data.

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CHRONIC TOXICITY SUMMARY

ETHYLENE GLYCOL MONO-N-BUTYL ETHER

(EGBE; butoxyethanol; BE; Butyl Cellosolve®; butyl glycol; butyl glycol ether)

CAS Registry Number: 111-76-2

I. Chronic Toxicity Summary

Inhalation reference exposure level	**700 µg/m^3**
Critical effect(s)	Hematological effects in rats
Hazard index target(s)	Cardiovascular system

II. Chemical Property Summary (HSDB, 1997)

Description	Colorless liquid
Molecular formula	$C_6H_{14}O_2$
Molecular weight	118.2 g/mol
Boiling point	171-172°C
Vapor pressure	0.76 mm Hg @ 20°C
Solubility	Soluble in 20 parts water; miscible in most organic solvents
Conversion factor	4.83 µg/m^3 per ppb at 25ºC

III. Major Uses and Sources

Ethylene glycol mono-n-butyl ether (EGBE) is highly miscible with water and oil and therefore has numerous industrial and household uses as a solvent or cleaner. As of 1983, EGBE was the largest volume glycol ether produced (~10^8 kg/yr, HSDB, 1997). EGBE has uses as a solvent for protective coatings and metal cleaners, a component of hydraulic fluids, a chemical intermediate in the synthesis of di(2-butoxyethyl)phthalate plasticizer and 2-butoxyethyl acetate, and as a coupling agent to stabilize immiscible components of water-based coatings, textile lubricants, and cutting oils.

An approximate breakdown of EGBE use is 41% as a solvent in protective coatings, 18% as a solvent in metal and liquid household cleaners, 10% in the synthesis of 2-butoxyethyl acetate and di(2-butoxyethyl)phthalate, and 31% in other solvent uses (HSDB, 1997).

IV. Effects of Human Exposure

The only studies available which address the toxicity of ethylene glycol monobutyl ether to humans are case reports of toxicity from occupational exposure by inhalation or ingestion and a single study of effects related to short term exposure by inhalation (Carpenter *et al.*, 1956). In that study, six volunteer subjects were exposed to concentrations ranging from 98 to 195 ppm EGBE for 4 or 8 hours. Observations noted at all levels included irritation of the eyes and nose, runny nose, taste disturbances and, in one subject, vomiting. All three subjects exposed to 195 ppm EGBE agreed that this level caused discomfort. Based upon the studies of Werner *et al.* (1943a), in dogs showing increased erythrocyte fragility in vitro, Carpenter also examined erythrocyte fragility in vivo, but did not observe this effect in humans at the EGBE exposure levels studied.

Increased erythrocyte fragility has been observed in rodents following exposure to EGBE (Carpenter *et al.*, 1956). However, recent studies in people found no increase in the fragility of erythrocytes taken from normal and susceptible individuals (persons with hereditary spherocytosis or sickle cell disease and older persons) after a 4-hour incubation with butoxyacetic acid (the presumed EGBE metabolite responsible for hematotoxicity) (Udden, 1994; Udden and Patton, 1994; Ghanayem *et al.*, 1987; Ghanayem, 1989).

V. Effects of Animal Exposure

Experiments were conducted evaluating the toxicity of inhaled EGBE in Fischer 344 rats, including 9-day, and 90-day exposure regimens (Dodd *et al.*, 1983). In the subchronic (90-day) portion of the study, 10 rats/sex/dose group were exposed for 6 hrs/day, 5 days/wk for 13 weeks (66 exposures) to analytical concentrations of 0, 4.7, 25, or 77 ppm EGBE. Another subset of 6 rats/sex/dose group were exposed simultaneously for 6 weeks. No significant effects on body weight, organ weights, clinical chemistry or urine composition were identified, nor were any gross or microscopic lesions. The only significant changes observed were a slight decrease in red blood cells (RBC) among male and female rats and a slight increase in mean corpuscular hemoglobin (MCH) among female rats in the high dose group. Among female rats, the decrease in RBC was more pronounced after 31 complete exposures. Animals (6/sex/dose) in the 9-day study were exposed for 6 hr/day for 5 consecutive days and then for 4 more consecutive days (following a 2 day break) to nominal concentrations of 0, 20, 86, and 245 ppm EGBE. Among animals in the highest dose group audible respiration and nasal discharge were observed during exposure. Weight gain was also depressed in these animals, but returned to normal values during a two week recovery period. Animals in the highest dose group showed hematological toxicity including decreased RBCs, hemoglobin, and mean corpuscular hemoglobin. Decreased hemoglobin was also observed in the 86 ppm dose group, but the effect was not as pronounced as in the highest dose group. No significant changes were observed in the animals exposed to 20 ppm for 9 days.

Dogs (2/group) were exposed to 415 ppm EGBE for 7 hours/day, 5 days/week for 12 weeks (Werner *et al.*, 1943a). Weight losses of 6 and 9% were reported in exposed animals. Hematological effects included decreased hemoglobin, erythrocytes, and hematocrit. Effects

observed, but not quantitated, included increased microcytosis, hypochromia, and polychromatophilia. Changes in hematological parameters in the control animals during the course of the experiment made determination of compound-related effects difficult. The same group reported on the toxicity of EGBE to rats (23/group) exposed to 135 or 320 ppm EGBE for 5 hours/day, 5 days/week for 1, 3, or 5 weeks, including one group sacrificed 1 week post-exposure (Werner *et al.*, 1943b). In both dose groups, erythrocyte count and hemoglobin concentrations were decreased and reticulocyte count was increased.

Rats (4/sex/dose group) were exposed to 0, 20, 50, or 100 ppm EGBE for 15 exposures of 6 hours/day (Gage, 1970). Rats in the 100 ppm EGBE dose group showed increased erythrocyte fragility. No effects were observed in animals in lower dose groups.

Pregnant rats and rabbits (36 and 24 dams/dose group, respectively) were exposed by inhalation to EGBE at concentrations of 0, 25, 50, 100, or 200 ppm on gestational days 6-15 in the rats and 6-18 in the rabbits (Tyl *et al.*, 1984). Maternal toxicity was observed in rats at 100 and 200 ppm EGBE with decreased weight gain, changes in organ weight, changes in food consumption, indications of anemia, and clinical signs including eye wetness and nasal encrustation among the observed adverse effects. Rabbit dams showed signs of toxicity at 200 ppm EGBE, with two deaths reported during the exposure or post-exposure period and decreased weight and some clinical signs including eye and nose wetness and stained fur.

In a study examining the teratological effects from inhalation of 0, 150, or 200 ppm EGBE on pregnant rats, maternal toxicity was observed (Nelson *et al.*, 1984). Animals (N = 18 or 19 with 34 control animals) were exposed for 7 hours/day on gestational days 7-15 and sacrificed on day 20. Hematuria was noted on the first day, but not on subsequent days, in animals exposed to 150 and 200 ppm EGBE. No significant dose-related effects were observed with respect to developmental endpoints.

VI. Derivation of Chronic Reference Exposure Level (REL)

Study	Dodd *et al.*, 1983
Study population	Rats
Exposure method	Discontinuous inhalation exposure
Critical effects	Decreased red blood cells in females
LOAEL	77 ppm
NOAEL	25 ppm
Exposure continuity	6 hr/day, 5 days/week
Exposure duration	13 weeks
Average experimental exposure	4.5 ppm for NOAEL group (25 x 6/24 x 5/7)
Human equivalent concentration	4.5 ppm for NOAEL group (gas with systemic effects, based on RGDR = 1.0 using default assumption that lambda (a) = lambda (h))
LOAEL uncertainty factor	1
Subchronic uncertainty factor	10
Interspecies factor	1 (see below)

Intraspecies factor	3 (see below)
Cumulative uncertainty factor	30
Inhalation reference exposure level	0.15 ppm (150 ppb, 0.7 mg/m^3, 700 µg/m^3)

The hematopoietic system toxicity due to inhalation of EGBE has been clearly established from laboratory studies of animals (Dodd *et al.*, 1983; Werner *et al.*, 1943a; Werner *et al.*, 1943b; Gage, 1970; Carpenter *et al.*, 1956). Two studies report NOAELs of 23 ppm EGBE (Dodd *et al.*, 1983) and 50 ppm EGBE (Gage, 1970). The studies of Werner (1943a, 1943b) produced LOAELs of 415 ppm and 135 ppm EGBE, without an observed NOAEL. The lowest NOAEL comes from the study of Dodd *et al.* (1983) showing effects of EGBE on red blood cell levels in a 13-week study. Although only a single dose in the study produced the effect in both sexes (72 ppm EGBE), the shorter term (9 days) study also showed this effect. This value is thus accepted as the basis for the derivation of the chronic REL.

NOAELs of 50 and 100 ppm EGBE were observed in pregnant rats and rabbits exposed by inhalation to EGBE, respectively. Maternal toxicity (decreased weight gain, changes in organ weight, changes in food consumption, hematuria, indications of anemia, etc.) appeared in the 100 and 200 ppm EGBE dose groups (Tyl *et al.*, 1984). The proximity of these levels to those producing hematological effects suggests that both endpoints should be of concern near the chronic REL.

An uncertainty factor of 1 was applied for interspecies extrapolation in light of evidence that humans are not as sensitive as experimental animals for hematological effects of EGBE (Udden, 1994; Udden and Patton, 1994; Ghanayem *et al.*, 1987; Ghanayem, 1989).

An intraspecies uncertainty factor of 3 was used rather than the default value of 10 since the work of Udden (1994) indicates that the blood from patients with hemolytic disorders and from the elderly does not show increased sensitivity to the hemolytic effects of EGBE.

The strengths of the inhalation REL include the availability of controlled inhalation exposure data at multiple exposure concentrations and the observation of a NOAEL. Major areas of uncertainty are the lack of adequate human exposure data and the lack of chronic, multiple-species health effects data.

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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 μg/m^3**
Critical effect(s)	Neurotoxicity in humans
Hazard index target(s)	Nervous system

II. Physical and Chemical Properties (HSDB, 1995)

Description	Colorless gas
Molecular formula	C_2H_4O
Molecular weight	44.06
Density	1.80 mg/m^3 @ 25ºC
Boiling point	10.7ºC
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.

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 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	Klees *et al*. 1990
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 (see below)
Subchronic uncertainty factor	3
Interspecies uncertainty factor	1
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	100
Inhalation reference exposure level	16.8 ppb (30 $\mu g/m^3$)

In the Klees *et al*. (1990) investigation there was a statistically significant difference between controls and exposed. However, one control (out of 16) was judged to be neurologically impaired and less than half the exposed group (5/12) was impaired. The 2 raters could not agree whether a large percent in each group [30% of the controls and 45% of the EtO exposed] was impaired or not. Thus an intermediate LOAEL uncertainty factor was used since less than half the exposed group was adversely affected and the impairment was not conclusive for many subjects.

The strengths of the inhalation REL include the use of human exposure measurements taken from workers who had been working with EtO over a period of years and the use of an endpoint seen in both animals and humans. Use of the neurotoxicologic data in the Snellings *et al*. (1984) subchronic animal study resulted in an estimated chronic REL of 3 $\mu g/m^3$. This is in reasonable agreement with the REL of 30 $\mu g/m^3$ based on human chronic data, when the subchronic to chronic uncertainty factor of 10 used with the animal data is considered.

Major areas of uncertainty are the usual uncertainty in estimating human exposure, the potential variability in exposure concentration, the small number of subjects, the disagreement of the neuropsychologists, and the limited number of developmental toxicity studies.

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CHRONIC TOXICITY SUMMARY

FLUORIDES including HYDROGEN FLUORIDE

(hydrofluoric acid (aqueous solution); hydrogen fluoride (as a gas))

CAS Registry Number: 7664-39-3

I. Chronic Toxicity Summary

Inhalation reference exposure level	**30 μg HF/m^3; 30 μg F/m^3**
Critical effect(s)	Skeletal fluorosis
Hazard index target(s)	Bone; respiratory system

II. Physical and Chemical Properties (HSDB, 1995)

Description	Colorless gas (HF), or as particulates
Molecular formula	HF
Molecular weight	20.0
Density	0.83 g/L @ 25°C
Boiling point	19.51°C
Vapor pressure	400 mm Hg @ 2.5°C
Solubility	Soluble in water and alcohol
Conversion factor	1 ppm = 0.83 mg/m^3 @ 25°C

III. Major Uses or Sources

Hydrofluoric acid (HF) is a colorless, fuming liquid with a sharp, penetrating odor (Fairhall, 1949). This acid is used in the glass etching, electronic and chemical industries (Bertolini, 1992). These industries use HF in the manufacture of such things as metal cans, plastics, refrigerant chemicals, inorganic chemicals, soaps and detergents, high octane gasoline and aircraft parts (Wohlslagel *et al.*, 1976; Wing *et al.*, 1991). Sodium fluoride has been used as a topical and ingested anticaries agent. The optimal doses are not well established, but have been suggested to be approximately 0.080 mg/kg/day for 7 to 9 months old infants decreasing to 0.034 mg/kg/day at 13 years of age (Shulman et al., 1995). A commonly recommended dose of 1.0 mg F ingested per day was reported to reduce dental caries and to be associated with a greatly increased rate of tooth mottling (Van Nieuwenhuysen and D'Hoore, 1992).

IV. Effects of Human Exposure

The chronic exposure to fluorides, including HF, and the incidence of osseous changes were studied in the workplace by Derryberry *et al.* (1963). In this study, the 8-hour time-weighted average fluoride exposure was calculated for the employment period of each of 74 workers. The overall average fluoride exposure in these workers was measured as a time-weighted average of 2.81 mg F/m^3. In comparison, the 17 workers within this group who had evidence of minimally increased bone density had an average fluoride exposure of 3.38 mg F/m^3. The remainder of the workers were exposed to an average measured concentration of 2.64 mg F/m^3. An analysis of these data by OEHHA (see derivation section below) showed a statistically significant relationship between air fluoride and the minimal bone density increases. In addition, urinary fluoride levels were greater in the 17 individuals with greatest exposure compared to the remaining 57 workers (average = 5.18 mg F/L vs. 4.53 mg F/L). No differences between exposed and unexposed individuals were observed for gastrointestinal, cardiovascular, or hematologic systems, or in a physical exam. A significant ($p < 0.05$) increase in the incidence of historical acute respiratory disease was observed in fluoride-exposed individuals, however radiographic examination revealed a difference of lesser significance ($p < 0.10$) for pulmonary changes.

Largent *et al.* (1951) found significant increase in bone density in the lower thoracic spine, with calcification extending into the lateral ligaments of 3 workers exposed for 17, 14, and 10 years to HF (concentrations not estimated).

A group of 74 men, who were occupationally exposed to unspecified concentrations of HF for an average of 2.7 years, reported occasions of upper respiratory irritation (Evans, 1940). Repeated chest X-rays over a 5-year period did not reveal any visible evidence of lung changes. The death rate of these workers from pneumonia and other pulmonary infections was the same as that of unexposed plant employees.

The possible effects of HF on a population of 47 workers exposed to HF (concentrations unspecified) included back pain and stiffness, cervical spine, knee pain, and shortness of breath on exertion (Peperkorn and Kahling, 1944). Many workers had external HF burn scars and rigidity in the chest. Radiologic examination revealed skeletal fluorosis in 34 of the 47 workers. The first evidence of these osseous changes was in the pelvis and lumbar spine, followed by changes in the spinal column and ribs. Extremities were affected last. The degree of radiologic changes increased with duration of employment. First-degree radiologic changes (increased bone density and thickened and misshapen structure of the trabeculae with the marginal contours of the bones exhibiting slight blurring) were observed no sooner than after 3 years of employment. More severe changes took at least 7 years of employment to manifest.

Workers in a warehouse containing HF retorts experienced transitory hyperemia (Dale and McCauley, 1948). Twenty four of the 40 workers had definite changes in the thickness and number of trabeculae in the upper and lower jaw.

Examinations of 107 pot room workers in two aluminum plants with airborne fluorides revealed 22 subjects with limited motion of the dorsolumbar spine, compared with none in a control group of 108 workers with no history of exposure to fluorides (Kaltreider *et al.*, 1972).

In one plant, 76 of 79 workers had increased bone density as measured by roentgenogram, with diagnosis of slight to moderate fluorosis. Moderate and marked fluorosis was observed after 15 years employment. The 8-hour time-weighted average fluoride content in these workplaces was 2.4 to 6.0 mg/m^3. Balazova (1971) measured significant fluoride uptake and distribution in children living near an aluminum smelter but reported no incidence of fluorosis.

Oral supplementation of greater than 0.1 mg F/kg body weight daily has been associated with fluorosis (Forsman, 1977).

Fluoride ion produced by various fluorocarbons has been associated with toxicity to human kidney collecting duct cells leading to sodium and water disturbances (Cittanova et al., 1996).

V. Effects of Chronic Exposures to Animals

Stokinger (1949) studied the subchronic effects of HF inhalation in several animal species. Animals (dogs, rabbits, rats, guinea pigs, and mice; 1 to 6 per group) were exposed to 0, 7.2 mg/m^3, or 25.1 mg/m^3 6 hours/day, 6 days/week, for 30 days. Mortality, body weight, blood coagulation mechanisms, and gross pathology were measured. Exposure to 25.1 mg/m^3 for 30 days resulted in degenerative testicular changes and ulceration of the scrotum in all 4 dogs and hemorrhage and edema in the lungs of 3 dogs. Pulmonary hemorrhage was also seen in 20 of 30 rats, and 4 of 10 rabbits. Renal cortical degeneration was observed in 27 of 30 rats. All of the rats and mice at the 25.1 mg/m^3 concentration died. No mortality was observed in the other species tested. Blood fibrinogen levels were significantly increased in dogs, rats and rabbits exposed to 25.1 mg/m^3. Exposure to 7.2 mg/m^3 resulted in pulmonary hemorrhage in 1 out of 5 dogs. No other significant effects were observed at the lower concentration.

VI. Derivation of Chronic Reference Exposure Level (REL)

Study	Derryberry *et al.* (1963)
Study population	74 fertilizer plant workers (67 unexposed control subjects)
Exposure method	Occupational
Critical effects	Increased bone density (skeletal fluorosis)
LOAEL	1.89 mg F/m^3 (2.46 mg HF/m^3)
NOAEL	1.07 mg F/m^3 (1.13 mg HF/m^3)
Exposure continuity	8 hours/day, 5 days/week
Exposure duration	14.1 years (range = 4.5 to 25.9 years)
Average exposure concentration	0.27 mg HF/m^3 or 0.26 mg F/m^3
Human equivalent concentration	0.27 mg HF/m^3 or 0.26 mg F/m^3
LOAEL uncertainty factor	1
Subchronic uncertainty factor	1
Interspecies uncertainty factor	1

Intraspecies uncertainty factor	10
Cumulative uncertainty factor	10
Inhalation reference exposure level for F or HF	0.03 mg HF/m^3 (30 μg HF/m^3; 0.04 ppm; 40 ppb) 0.03 mg F/m^3 (30 μg F/m^3; 0.04 ppm; 40 ppb)

No studies regarding the chronic irritant or respiratory effects of HF exposure in humans or animals were available.

Changes in bone density in association with fluoride exposure have been observed in several studies, and appear to be the most sensitive health effect for chronic exposure. The minimally increased bone density in the Derryberry study was significantly ($p < 0.04$, Fisher's Exact Test) associated with "other osseous changes" which reportedly included disc lesions, arthritis, and calcified ligaments. An increase in pulmonary changes in the workers with high bone density was marginally significant ($p < 0.06$) and included emphysema, fibrosis, and healed tuberculous lesions. Although dental fluorosis is a sensitive endpoint in many fluoride studies, the dental examinations of exposed workers in this study showed healthier teeth than in controls. The increased bone density observed was considered as indicating adverse effects had occurred, based on the adverse effects associated with the increased density in the study, and on research showing increased bone density caused by fluoride exposure also leads to decreased bone strength and increased fragility (Riggs *et al.*, 1990). Symptoms of abdominal pain, backache, restricted joint movement and respiratory symptoms have been associated with airborne fluoride exposures and bone density increases in industrial settings (Zhiliang et al., 1987).

The absorption of particulate and gaseous fluorides is reported to be similar (Collings *et al.*, 1951). Therefore, it would be expected that the effects on bone density would be similar regardless of the form of fluoride. The raw data from the Derryberry *et al.* (1963) study are shown in Table 1. A Pearson correlation matrix of the variables measured in the Derryberry *et al.* study indicated that bone density was best correlated with mean air fluoride level, and to a lesser extent with the age of the individual. A log-logistic regression using the log air fluoride concentration as the independent variable showed a significant ($p < 0.033$) relationship between increasing air fluoride concentrations and probability of skeletal fluorosis. The parameters for the regression were $\beta_0 = -2.3468$ (std. error = 0.6462), and $\beta_1 = 1.1736$ (std error = 0.5508); the odds ratio for the occurrence of skeletal fluorosis was 3.24. Years of exposure were not correlated with increased bone-density, according to a Pearson Correlation procedure ($p = 0.63$). Bone density has been shown to decrease with age after the age of 40 among normal, non-fluoride-exposed males (Runge *et al.*, 1979). As expected, age was very highly correlated with years exposed ($p<0.00001$), therefore including years exposed in the dose-metric likely introduces a confounding variable. Similarly, Runge *et al.* (1979) found no association between years exposed and mineral content or bone width among 245 aluminum smelter workers exposed to 2.75 or 3.2 mg F/m^3. For these reasons, years exposed were not used as the dose-metric for bone-density in this analysis.

Although a threshold was not readily apparent from the logistic regression model, grouping the 74 individuals by air fluoride exposure level into quintiles of 15 each with one group of 14, allowed for a comparison of group mean responses (Table 2). The 14 employees exposed

to a time-weighted average concentration of 1.07 mg F/m^3 did not exhibit bone density changes. An analysis of the grouped responses using a binomial distribution showed a probability of p = 0.008 for obtaining 4/15 increased bone density observations in the 2.34 mg/m^3 group, and a probability of p = 0.047 for obtaining 3/15 positive observations in the 1.89 mg F/m^3 group. The 1.89 mg F/m^3 group was therefore considered a LOAEL for chronic skeletal fluorosis, and the 1.07 mg/m^3 group was considered a NOAEL. The above probabilities assume that a chance occurrence is, at most, 1 in 18 of skeletal fluorosis or other cause leading to an abnormally dense x-ray in the general population. Since osteosclerosis is a rare condition that is associated with several types of hematological malignancies such as myeloid leukemia, the actual incidence of conditions leading to osteosclerosis is far below 1 in 18. This lends strong support to the consideration of 1.89 mg/m^3 as a LOAEL for skeletal fluorosis.

The major strengths of the key study are the observation of health effects in a large group of workers exposed over many years, the availability of individual exposure estimates for each worker, and the identification of a NOAEL. The primary uncertainty in the study is the lack of a comprehensive health effects examination. Another source for potential concern is the relative susceptibility of children to the effects of inhaled fluorides, considering the rapid bone growth in early years. Although a number of studies were located that compared children and adult responses to environmental sources of fluorides, none of the differences in fluorosis were of a sufficient magnitude to warrant a greater than 10-fold uncertainty factor for individual susceptibility.

Table 1. Data on worker exposure to fluoride from Derryberry *et al.* (1963)

Obsv. #	ID	Bone density	Years exposed	Urine max F (mg F/L)	Urine min F (mg F/L)	Mean urinary F (mg F/L)	Age (years)	Air fluoride (mg/m^3)	*OEHHA exposure grouping*
1	119	normal	18.5	43.0	2.8	14.7	58	8.16	5
2	0	normal	8.4	24.7	5.3	9.6	42	3.19	4
3	41	normal	15.8	35.0	2.5	9.1	35	3.29	4
4	147	minimally increased	9.6	17.1	2.1	8.9	60	5.98	5
5	120	normal	16.7	20.5	3.4	8.6	55	3.29	4
6	54	minimally increased	17.0	44.0	4.0	8.6	56	7.73	5
7	148	normal	10.5	14.0	3.7	8.4	41	8.32	5
8	314	minimally increased	14.4	22.7	1.7	8.3	56	3.24	4
9	29	normal	17.0	18.2	2.5	7.7	50	2.60	3
10	14	normal	14.3	19.4	2.1	6.3	46	2.33	3
11	115	normal	15.2	18.5	1.4	6.3	38	2.11	3
12	10	minimally increased	10.3	22.0	2.3	6.1	38	2.72	4
13	4	minimally increased	7.1	7.7	2.0	5.7	54	3.22	4
14	51	normal	14.9	42.0	0.8	5.6	46	3.18	4
15	94	normal	16.2	15.4	3.3	5.5	56	5.12	5
16	217	normal	7.1	7.1	2.6	5.3	42	2.54	3
17	281	minimally increased	7.8	8.6	1.1	5.2	36	3.79	4
18	114	normal	10.4	13.2	2.8	5.2	38	7.66	5
19	7	normal	7.8	9.1	2.2	5.1	43	2.91	4
20	308	normal	11.9	6.7	3.5	5.1	44	1.89	2
21	301	minimally increased	15.2	9.5	2.5	5	36	2.56	3
22	72	normal	25.9	13.7	2.1	4.9	55	5.55	5
23	241	minimally increased	17.0	10.0	1.9	4.9	46	4.48	5
24	345	normal	10.5	7.1	2.0	4.9	47	1.49	1
25	26	normal	16.4	12.2	0.5	4.7	39	2.41	3
26	231	minimally increased	16.3	8.2	2.8	4.6	62	1.88	2
27	2	normal	24.7	8.9	2.1	4.6	46	3.53	4
28	295	normal	14.5	10.7	0.9	4.6	44	2.07	3
29	1	normal	8.9	5.9	2.4	4.5	30	1.92	2
30	203	minimally increased	18.2	6.8	1.6	4.4	43	2.66	3
31	63	normal	16.2	7.4	2.0	4.3	55	3.90	5
32	5	normal	4.5	11.5	1.9	4.3	43	1.12	1
33	460	normal	12.5	6.1	1.6	4.3	60	2.13	3
34	249	minimally	15.0	8.0	1.8	4.3	39	2.95	4

		increased							
35	3	normal	7.6	14.5	2.1	4.3	31	3.90	5
36	322	normal	9.3	6.3	2.0	4.3	35	4.23	5
37	8	minimally increased	24.8	5.9	3.0	4.2	55	2.50	3

Observation	ID	Bone density	Years exposed	Urine max F (mg F/L)	Urine min F (mg F/L)	Mean urinary F (mg F/L)	Age (years)	Air fluoride (mg F/m^3)	*OEHHA exposure grouping*
38	3	normal	15.2	12.2	2.1	4.2	42	1.14	1
39	309	normal	12.1	5.5	2.4	4.1	42	1.94	2
40	36	normal	9.1	13.2	0.8	4.1	33	1.94	2
41	45	normal	11.3	14.0	2.2	4.1	33	3.84	4
42	70	normal	17.9	8.0	1.0	3.9	44	4.00	5
43	250	minimally increased	9.8	6.7	1.5	3.9	35	1.78	2
44	38	normal	16.9	5.9	1.0	3.9	35	2.10	3
45	200	minimally increased	14.0	7.0	2.8	3.8	66	3.92	5
46	183	normal	9.8	4.9	2.2	3.7	48	1.67	2
47	32	normal	12.5	6.6	0.9	3.7	47	2.21	3
48	25	normal	13.6	5.5	1.5	3.7	44	1.86	2
49	21	normal	13.9	9.1	0.4	3.7	50	1.98	2
50	304	normal	13.4	5.0	2.1	3.7	36	2.62	3
51	132	normal	10.9	5.1	2.4	3.6	39	1.81	2
52	6	minimally increased	8.4	4.8	0.9	3.6	35	3.85	5
53	244	normal	16.6	7.1	1.4	3.6	62	2.87	4
54	30	normal	14.0	14.0	0.9	3.6	43	1.56	1
55	88	minimally increased	15.5	4.9	1.7	3.5	66	2.06	2
56	227	normal	16.6	5.7	1.0	3.5	41	1.18	1
57	271	normal	17.7	4.1	3.0	3.4	60	1.82	2
58	19	normal	13.9	10.0	1.8	3.4	41	1.32	1
59	190	normal	9.3	7.7	1.9	3.3	36	1.95	2
60	258	normal	17.8	5.6	1.6	3.2	58	0.87	1
61	278	normal	10.0	7.0	0.3	3.2	34	1.93	2
62	331	normal	12.8	5.6	1.5	3.1	34	1.23	1
63	91	normal	25.3	7.9	0.2	3.1	63	3.49	4
64	342	normal	18.5	6.0	1.3	3	40	2.73	4
65	261	normal	18.1	5.3	0.9	2.9	52	4.41	5
66	291	normal	13.5	4.5	1.5	2.8	34	2.14	3
67	149	normal	11.3	4.5	2.1	2.8	34	0.76	1
68	2	normal	24.7	4.5	1.5	2.7	51	1.15	1
69	4	normal	16.8	5.7	1.2	2.7	56	0.71	1
70	109	normal	8.3	5.1	0.8	2.7	36	1.89	2
71	242	normal	18.1	4.1	1.2	2.5	49	1.26	1
72	179	normal	18.9	3.9	1.0	2.4	46	0.50	1
73	325	minimally increased	11.8	5.0	0.5	2.2	40	2.10	3
74	159	normal	18.9	5.0	0.7	2.1	45	0.67	1

Table 2. Grouped mean exposure

Exposure group	Mean age ± SD	Mean air level mg F/m^3 ± SD	Number of responses	Probability of difference from group 1*
1	45.0 ± 7.0	1.07 ± 0.32	0/14**	Not Applicable
2	43.9 ± 11.2	1.89 ± 0.09	3/15***	0.047
3	43.0 ± 7.6	2.34 ± 0.23	4/15	0.008
4	45.9 ± 9.8	3.22 ± 0.35	5/15	0.001
5	48.5 ± 10.7	5.41 ± 1.72	5/15	0.001

* Probability of obtaining result assuming a chance occurrence of abnormally dense x-ray of, at most, 1 in 18 individuals, using a binomial distribution (Systat for Windows v.5.05, 1994).
** NOAEL
*** LOAEL ($p < 0.05$)

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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	**0.1 µg/m^3**
Critical effect(s)	Neutrophilic infiltration in the olfactory epithelium of the respiratory system of mice
Hazard index target(s)	Respiratory system

II. Chemical Property Summary (HSDB, 1996)

Description	Colorless liquid
Molecular formula	$C_5H_8O_2$
Molecular weight	100.13
Boiling point	187-189°C
Vapor pressure	17 mm Hg @ 20°C
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.

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). No studies addressing glutaraldehyde sensitivity from chronic exposure include the quantitation of the exposure levels that led to the sensitization.

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.

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.

VI. Derivation of Chronic Reference Exposure Level (REL)

Study	Gross *et al.*, 1994
Study population	Male and female F344 rats and B6C3F1 mice (20/sex/group)
Exposure method	Continuous inhalation exposure (0, 62.5, 125, 250, 500, or 1000 ppb)
Critical effects	Neutrophilic infiltration in olfactory epithelium
LOAEL	62.5 ppb (female mice)
NOAEL	Not observed
Exposure continuity	24 hr/day, 7 days/week
Exposure duration	13 weeks
Average experimental exposure	62.5 ppb
Human equivalent concentration	10.5 ppb (gas with extrathoracic respiratory effects, RGDR = 0.17, BW = 28 g, MV = 0.032 L/min, SA = 3 cm^2)
Subchronic uncertainty factor	3
LOAEL uncertainty factor	3
Interspecies uncertainty factor	3
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	300
Inhalation reference exposure level	0.035 ppb (0.1 $\mu g/m^3$)

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). The most thorough reporting of this effect is the study by Gross *et al.* (1994) showing neutrophilic infiltration in the olfactory epithelium in the lowest dose exposure group. (Female mice exposed to 62.5 ppb showed subepithelial neutrophilic infiltration.) This level was taken to be the LOAEL. This effect on the nasal epithelium was demonstrated to be both concentration- and exposure duration-dependent.

The major strength of the inhalation REL 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 chronic inhalation exposure studies, the lack of reproductive and developmental toxicity studies, the lack of dermal sensitization studies, and the lack of observation of a NOAEL.

VII. References

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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**
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)

Molecular formula	N_2H_4
Molecular weight	32.05 g/mol
Description	Colorless, oily liquid; white crystals
Boiling point	113.5°C (Merck, 1983)
Melting point	2°C
Vapor pressure	14.4 mm Hg @ 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).

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 which 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 were 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.

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 U, 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. 15/179 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.

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 incidence found to be increased 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
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))
Subchronic uncertainty factor	1
LOAEL uncertainty factor	10
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, (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 to 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).

The strengths of the inhalation REL 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.

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CHRONIC TOXICITY SUMMARY

ISOPHORONE

(1,1,3-trimethyl-3-cyclohexene-5-one; 3,5,5-trimethyl-2-cyclohexene-1-one; isoforon; isoacetophorone)

CAS Registry Number: 78-59-1

I. Chronic Toxicity Summary

Inhalation reference exposure level	**2,000 μg/m^3**
Critical effect(s)	Developmental effects (reduced crown-rump length of female rat fetuses)
Hazard index target(s)	Development; kidney; alimentary system

II. Chemical Property Summary (HSDB, 1995)

Description	Water-clear liquid with a peppermint-like odor
Molecular formula	$C_9H_{14}O$
Molecular weight	138.21
Boiling point	214°C
Vapor Pressure	0.44 mm Hg at 25°C
Solubility	Slightly soluble in water, 12,000 mg/L water at 25°C; miscible in organic solvents.
Conversion factor	5.65 μg/m^3 per ppb at 25°C

III. Major Uses and Sources

Isophorone is used extensively as a solvent in some printing inks, paints, lacquers, adhesives, vinyl resins, copolymers, coatings, finishes, and pesticides, in addition to being used as a chemical intermediate (HSDB, 1995). Since this compound has many different applications, release to the environment may originate from a wide variety of industrial sources including iron and steel manufacturers, manufacturers of photographic equipment and supplies, automobile tire plants, and printing operations. Coal-fired power plants may also emit isophorone to the air. Although it is mostly a man-made compound, isophorone has been found to occur naturally in cranberries (ATSDR, 1989). Due to its high water solubility and short half-life in the atmosphere ($t_{1/2}$ <5 hrs), the most probable route of exposure to isophorone for the general population is ingestion of contaminated drinking water. Individuals living near hazardous waste sites may also be exposed to isophorone dermally, but not by inhalation (ATSDR, 1989). Occupational exposure may occur by inhalation or dermal contact.

IV. Effects of Human Exposures

In occupational monitoring studies, the time-weighted average concentration in breathing zones and workplace air of a screening plant ranged from 8.3-23 ppm and from 3.5-14.5 ppm, respectively (Samimi, 1982). Up to 25.7 ppm was detected in air of a silk screening printing plant in Pittsburgh, PA (Kominsky, 1983). The concentration in breathing zone samples from a decal manufacturing plant in Ridgefield, NJ was 0.7-14 ppm (Lee and Frederick, 1982). It was suspected that the reported eye and nose irritation of workers at the silk screening plant and at the decal manufacturing plant were the result of acute and subacute exposure to isophorone vapors.

No information is available concerning long-term exposure or pharmacokinetics of isophorone in humans (ATSDR, 1989). However, workers exposed to 5-8 ppm (28-45 mg/m^3) of isophorone for one month complained of fatigue and malaise (NIOSH, 1978). When concentrations were reduced to 1-4 ppm, no adverse effects were reported. Acute exposure studies in humans (up to 400 ppm for 1 to 4 minutes) resulted in eye, nose and throat irritation, nausea, headache, and dizziness or faintness (Union Carbide, 1963). Fifteen minute inhalation exposure to 10 ppm isophorone produced only mild effects in human subjects while 25 ppm produced irritation to eyes, nose, and throat (Silverman *et al.*, 1946).

V. Effects of Animal Exposures

Few reports have been published regarding the pharmacokinetics of isophorone in experimental animals. Isophorone was widely distributed in the major organs of the rat following 4 hour inhalation exposure to 400 ppm (ATSDR, 1989). Oral gavage of 4000 mg/kg body wt to rats and a rabbit also resulted in wide distribution of the chemical. The highest blood levels of isophorone were reached by 30 min in rabbits following oral gavage and had decreased dramatically by 21 hours, indicating rapid absorption and elimination of the chemical. Preliminary results of a pharmacokinetic study indicate that rats treated orally with ^{14}C-isophorone excreted 93% of the radiolabel in the urine, expired air, and feces in 24 hours (ATSDR, 1989). The highest levels of ^{14}C-isophorone were found in the liver, kidney, preputial gland, testes, brain, and lungs. Several metabolites were identified in the urine of orally dosed rats and rabbits, including 3-carboxy-5,5-dimethyl-2-cyclohexene-1-one, 3,5,5-trimethylcyclohexanol, and some glucuronide conjugates (Dutertre-Catella *et al.*, 1978). A portion of the chemical was excreted unchanged in expired air.

In an early inhalation study, 10 Wistar rats/group and 10 guinea pigs/group, all of mixed sex, were exposed to 0, 25, 50, 100, 200 or 500 ppm isophorone 8 hr/day, 5 days/week for 6 weeks (Smyth *et al.*, 1942). Increased mortality and reduced body weights were observed at 100 ppm and up in both species. However, eye and nose irritation was noted only at the highest dose. Minor changes in blood chemistry (increased polymorphonuclear cells and decreased lymphocytes) and urinalysis (increased albumin) of guinea pigs were seen only at the highest dose. Histopathology of the livers revealed no convincing treatment-related effect. Dilation of Bowman's capsule and cloudy swelling of the convoluted tubular epithelium occurred in

kidneys of animals (assumed to be both species) at 50 ppm and up. However, two controls also had slight lesions of the tubular epithelium. It was reported that lungs were often congested but dose levels for corresponding lung lesions were not provided. Later investigations determined that the isophorone used in this study was contaminated with appreciable amounts of compounds more volatile than isophorone (Rowe and Wolf, 1963). Therefore, some of the adverse effects (i.e., the lung lesions) may have been due to the contaminants. The presence of highly volatile contaminants would also result in inaccurate concentrations of isophorone used in the study.

In a 90-day feeding study, 20 CFE albino rats/group/sex were given isophorone in their diet at concentrations of 0, 750, 1500 or 3000 ppm. Four beagle dogs/group/sex received isophorone in gelatin capsules at concentrations of 0, 35, 75 or 150 mg/kg body wt-day (AME, 1972a,b). High dose rats exhibited slightly reduced weight gain compared to controls (8-10%) for most of the study. Average weight gain among the exposure groups of beagle dogs remained essentially unchanged during the entire study. Urinalysis, hematology and clinical chemistry indices found no treatment-related effects in the animals at either the interim or final toxicological examinations. Gross pathology and a limited histopathological examination observed no treatment-related effects in either species. Data on isophorone purity and possible loss of isophorone from rat diet due to vaporization were not presented.

In the most comprehensive isophorone toxicity study to date, 50 F344/N rats/group/sex and 50 B6C3F1 mice/group/sex were administered 0, 250 or 500 mg isophorone/kg body wt 5 days/week by oral gavage (in corn oil) for 103 weeks (Bucher *et al.*, 1986; NTP, 1986). Clinical signs of toxicity were not seen during the length of the study. However, several deaths in male and female rats at the high dose occurred early in the study. A steep decline in survival rate of high dose male rats occurred after week 90. Male and female rats and female mice in the high dose group exhibited only a slight decrease in body weight (<10%) compared to controls. A 13-week range finding study for the 2-year study did not find compound-related lesions in the kidney (or any other organs) of rats and mice exposed up to 1000 mg/kg body wt-day. However, pathological examination of rats exposed to isophorone for 2 years revealed non-neoplastic lesions in the kidney. Increased mineralization of the collecting ducts in isophorone-exposed male, but not female, rats was observed. This lesion was characterized by basophilic aggregates of mineral most often found in the medullary collecting ducts and occurred coincidentally with lesions of chronic nephropathy. Nephropathy was observed in almost half the female controls and nearly all the male controls. Isophorone exposure appeared to increase both the severity of nephropathy in low dose male rats and the incidence of nephropathy in dosed female rats, but the effects were not pronounced. However, the isophorone potentiation of nephropathy in rats may be due to ‘male rat-specific nephropathy’ and not have any relevance to human exposure (Strasser *et al.* 1988). Other adverse effects in kidneys of isophorone-treated male rats include tubular cell hyperplasia (in a dose-related manner) and epithelial hyperplasia of the renal pelvis. In mice, an increased incidence of chronic focal inflammation was observed in the kidneys of males, but was not considered treatment-related. A dose-dependent increase in fatty metamorphosis occurred in the adrenal cortex of male rats, but the biological significance of this change is unknown. All isophorone-exposed male mice had an increased incidence of hepatocytomegaly and coagulative necrosis of the liver. However, treatment-related liver lesions were not observed

in female mice. Increased incidence of hyperkeratosis of the forestomach was observed in dosed male and high dose female mice, but was probably not a treatment-related effect.

Published studies on possible reproductive effects of isophorone are lacking. An unpublished inhalation study conducted by a commercial laboratory (Bio/dynamics, 1984b) studied possible teratogenicity due to isophorone in rats or mice at inhaled doses up to 115 ppm. Groups of 22 female rats and 22 female mice were exposed to 0, 25, 50 or 115 ppm isophorone (6 hr/day) on gestational days 6-15. Maternal toxicity in rats included dose-dependent alopecia and cervical/anogenital staining. Low body weights (7-8%) were occasionally observed in the 115 ppm group. In mice, maternal toxicity was confined to slightly decreased weight (7-8%) on one day in the 115 ppm group. No significant differences were found in uterine implantations, fetal toxicity, and external and internal malformations among the animals. However, a slight, but significant, growth retardation in the form of decreased crown-rump length was present among the high dose fetal rats. Also, a slight, but insignificant, increase in extra ribs and/or rudimentary ribs was seen in rat and mouse fetuses at the highest dose. In a pilot study for this developmental toxicity investigation (12 females/species), exencephaly was observed in 1 rat and 1 mouse undergoing late reabsorption and in 2 live rat fetuses from dams exposed to 150 ppm isophorone on gestational days 6-15 (Bio/dynamics, 1984a). Exencephaly was not observed at any dose level in the primary study.

Contrary to the findings of the above report, Dutertre-Catella (1976) did not find adverse reproductive or developmental effects in rats exposed to 500 ppm isophorone (6 hr/day, 5 days/week) for 3 months before mating. Females had been exposed throughout gestation as well. The pups were not examined for internal malformations so the study was incomplete for determination of developmental effects.

VI. Derivation of Chronic Reference Exposure Level (REL)

Study	Bio/dynamics 1984a,b
Study population	22 female mice/group, 22 female rats/group
Exposure method	Discontinuous whole body inhalation exposure during gestation (0, 25, 50 or 115 ppm)
Critical effects	Developmental effects (reduced crown-rump length of female rat fetuses) and teratogenicity (exencephaly in fetal rats and mice)
LOAEL	115 ppm for reduced crown-rump length of female rat fetuses
NOAEL	50 ppm
Exposure continuity	6 hr/day during gestation
Exposure duration	Days 6-15 of gestation
Average experimental exposure	12.5 ppm (50 x 6/24)
Human equivalent concentration	12.5 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	1
Interspecies uncertainty factor	3
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	30
Inhalation reference exposure level	0.4 ppm (400 ppb, 2 mg/m^3, 2,000 μg/m^3)

The inhalation study by Bio/dynamics (1984a,b) presents data that indicate exposure during gestation may be the most sensitive indicator of non-neoplastic toxicity by isophorone. Exposure of pregnant rats to 115 ppm isophorone during gestation resulted in significant growth retardation of female rat fetuses (reduced crown-rump length). Exposure to 50 ppm isophorone, the NOAEL, produced no developmental effects. The authors claim that removal of the two shortest female fetuses from the statistical analysis results in no significant difference for growth retardation; therefore, this adverse effect is not significant. However, this selective culling before the statistical analysis is not scientifically appropriate in this case. In addition, the authors did not perform some of the scheduled fetal examinations. Otherwise, the growth retardation might have had even greater statistical significance. The pilot study (Bio/dynamics, 1984a) observed exencephaly in a few mouse and rat fetuses at 150 ppm. Exencephaly was not considered significant by the authors because it was not present in any fetuses of the primary study (Bio/dynamics, 1984b). 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). Alopecia of adult female rats was observed in many of the exposed animals. However, this effect may be considered more of an acute dermal irritation than a chronic effect. In addition, cervical and anogenital staining seen in many exposed rats is not considered an 'adverse' effect.

A strength of the database for isophorone is the consistency of the REL when compared to the study by Bucher *et al.* (1986). Developing a chronic REL based on the adverse effects due to lifetime exposure (Bucher *et al.*, 1986) results in about the same REL (0.2 ppm) as that produced due to adverse effects during gestation (Bio/dynamics, 1984a,b). Weaknesses of the database for isophorone include the lack of human exposure data and the lack of long-term inhalation studies. However, the lack of human data may be due to isophorone's rather low potency for causing chronic, non-neoplastic, adverse effects. Also, inhalation of isophorone is most likely a minor route of exposure for the general population. Due to the insufficient characterization of the kidney nephropathy in the NTP study (Bucher *et al*, 1986; NTP, 1986), a subchronic or chronic study in a non-rodent species would enhance the database for isophorone. The conduct and publication of another comprehensive study of possible reproductive and developmental effects of isophorone in experimental animals would also strengthen the database.

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M E M O R A N D U M

TO: Winston H. Hickox
Agency Secretary

FROM: Joan E. Denton, Ph.D.
Director

DATE: December 24, 2001

SUBJECT: ADOPTION OF CHRONIC REFERENCE EXPOSURE LEVELS FOR AIRBORNE TOXICANTS

In accordance with Health and Safety Code, Section 44300 *et seq*. (The Air Toxics Hot Spots Information and Assessment Act, AB 2588, Connelly as amended by SB 1731, Calderon), the Office of Environmental Health Hazard Assessment (OEHHA) hereby adopts Chronic Reference Exposure Levels (RELs) for 12 chemicals (attachment).

OEHHA is mandated to develop risk assessment guidelines to be used by state and local agencies in implementing the Air Toxics Hot Spots program. Development of these guidelines is proceeding in stages. There are four technical support documents, which have been adopted. These describe the scientific basis for (respectively) acute RELs, cancer potency factors, chronic RELs, and exposure assessments. A fifth document, currently in preparation, is a guidance manual based on the four technical support documents.

The third technical support document, *Air Toxics Hot Spots Program Risk Assessment Guidelines. Part III. The Determination of Chronic Reference Exposure Levels for Airborne Toxicants,* was adopted on February 23, 2000. A chronic REL is an airborne level that would pose no significant health risk to individuals indefinitely exposed to that level. RELs are based solely on health considerations, and are developed from the best available data in the scientific literature. This technical support document provided chronic RELs for 22 chemicals, with a summary for each describing its chemical and physical properties, its chronic health effects, and the data used to calculate the REL.

The Scientific Review Panel, (SRP) has reviewed a number of other proposed chronic RELs at previous meetings, beginning in September 1999. At its November 28, 2001 meeting, the SRP endorsed 12 additional RELs, bringing the total number of chemicals for which chronic RELs are provided to 72. The expanded list and supporting summaries will be available on our

Web site. Additional RELs are currently undergoing review by the public and the SRP, and revision by OEHHA; these will be presented in due course.

Attachment

Chronic Reference Exposure Levels Adopted by OEHHA – December 2001

Substance (CAS #)	*Chronic Inhalation REL ($\mu g/m^3$)*	*Hazard Index Target(s)*
Acrylonitrile (107-13-1)	5	Respiratory system
Beryllium (7440-41-7) and beryllium compounds	0.007	Respiratory system; immune system
Chloropicrin (76-06-2)	0.4	Respiratory system
Diethanolamine (111-42-2)	3	Cardiovascular system; nervous system
Ethylene dibromide (106-93-4)	0.8	Reproductive system
Isophorone (78-59-1)	2000	Development; liver
Maleic anhydride (108-31-6)	0.7	Respiratory system
Methyl isocyanate (624-83-9)	1	Respiratory system; reproductive system
Methylene dianiline (4,4'-) (101-77-9)	20	Eyes; alimentary system (hepatotoxicity)
Selenium and selenium compounds (other than hydrogen selenide)	20	Alimentary system; cardiovascular system; nervous system
Sulfuric acid (7664-93-9)	1	Respiratory system
Vinyl acetate (108-05-4)	200	Respiratory system

OEHHA
December 24, 2001

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.

MEETING

OF THE

SCIENTIFIC REVIEW PANEL ON TOXIC AIR CONTAMINANTS

CALIFORNIA AIR RESOURCES BOARD

SOUTH SAN FRANCISCO CONFERENCE CENTER

255 SOUTH AIRPORT BOULEVARD

SOUTH SAN FRANCISCO, CALIFORNIA

WEDNESDAY, NOVEMBER 28, 2001

10:00 A.M.

JAMES F. PETERS, CSR, RPR
CERTIFIED SHORTHAND REPORTER
LICENSE NUMBER 10063

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APPEARANCES

MEMBERS PRESENT

Dr. John Froines, Chairperson

Dr. Roger Atkinson

Dr. Paul D. Blanc

Dr. Craig Byus

Dr. Gary Friedman

Dr. Anthony Fucaloro

Dr. Hanspeter Witschi

Dr. Ellinor Fanning

REPRESENTING THE CALIFORNIA AIR RESOURCES BOARD

Mr. Jim Behrmann

Mr. Peter Mathews

REPRESENTING THE OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT

Dr. George V. Alexeef, Deputy Director for Scientific Affairs

Mr. David Lewis, Staff Toxicologist

Mr. David Morry, Staff Toxicologist

Dr. David Rice, Staff Toxicologists

Dr. Andy Salmon, Chief, Air Toxicology and Risk Assessment Unit

REPRESENTING THE DEPARTMENT OF PESTICIDE REGULATION

Dr. Keith Pfeifer, Pharm.D, Ph.D., DABT, Senior Toxicologist

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PROCEEDINGS

CHAIRPERSON FROINES: We need to start given the fact that two people have to leave at 2:00 o'clock.

PANEL MEMBER FUCALORO: Three.

CHAIRPERSON FROINES: Pardon me?

PANEL MEMBER FUCALORO: Three people have to leave.

CHAIRPERSON FROINES: Who are the three?

PANEL MEMBER FUCALORO: Craig, I and Roger have to leave.

CHAIRPERSON FROINES: And Peter. So at 2:00 o'clock the meeting will end. We don't have really any choice. So I think we should begin. Now, we should have a brief discussion, at some point, about travel issues, but I think that given the fact that Gary and Paul aren't here, we probably shouldn't start with that because that would create a southern California bias.

PANEL MEMBER FUCALORO: B-i-a-s as opposed to B-y-u-s.

(Laughter.)

CHAIRPERSON FROINES: So anyway, we should officially open the meeting on November 28th, 2001 of the scientific review panel. And let's begin following the agenda and discuss at the outset the chronic REL issues that OEHHA is going to be bringing forward.

Andy.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Thank you. I thought I'd just start because we haven't been talking about the RELs for some little while now. I though I'd just remind you where we've got to with the noncancer chronic RELs.

(Thereupon an overhead presentation was presented as follows.)

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: We have been working on the review of the compound specific summaries and the proposed RELs. The methodology guidelines were reviewed by the panel and adopted in February of 2000.

We have had a first batch of RELs, which was included with the guidelines. Then two further addenda, which included additional RELs. And we're now in the process of dealing with an additional batch, which we're calling batch 2B.

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AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: You saw this initially on March the 5th and we haven't had any opportunity to do anything with it until now. But basically what we're doing is we received some public comments which we have responded to and incorporated any additional information which came up

during that process. We have, of course, responded to any comments which the panel provided to us on March the 5th.

And there are one or two areas where we've been updating the methodology. One of the particular points which we discussed with the panel was the use of the benchmark concentration approach for several of the RELs. There are a couple of instances where there are new data as well. And so we now have the presentation of the revised versions which you have.

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AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: The chemicals which you considered in March include the following. There are some which, in fact, were not considered at that meeting, but the first group is -- essentially, the review of the methodology is completed in March then some were deferred.

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AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: And there was another series where specific modifications and changes were required. So we are going to be looking at most of these.

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AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: There's an additional compound which is carbon disulfide, which is actually held over from an earlier

group. And the reason for this was that we identified the need to go back to the original data. The study that's used as the basis of the REL is an epidemiological study which is, in fact, reviewed by federal EPA. It turns out that it was originally actually done by NIOSH and we needed to go back to the original data to reevaluate the benchmark dose calculation.

We have now finally received the original data and performed the updates, so we'll be presenting that as well.

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AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: So another thing which we are doing this time around, which is a first for us, is that responding to the requirements of SB 25 and given that we now have some initial guidance available in the form of our document, which you've been looking at for most of this year, we are attempting to provide a summary section for each of the RELs we're presenting today, which address the question of whether the proposed REL is adequate to protect the health of infants and children.

And we asked particularly for your guidance on this as to whether the approach we're taking is a sensible one, whether it's adequate. We are very much constrained in many cases by availability of data as you will see.

But anyway, so this is a particularly new item in this series.

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AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: So these are the ones that we're actually going to be presenting today, and there are some which we have decided we can't deal with today because we were unable to complete the update and review to our satisfaction and -- mainly due to our -- well, when we went back and looked at the requirements of the panel and the requirements of the SB 25, we identified the fact that we did not have sufficient data available or methodology available to resolve the issue.

So in the case of ethylene glycol butyl ether or butoxy ethanol, one of the questions which the panel identified was that we should look at the dose response for irritancy. And this has clearly important for the suitability of the REL for protecting adult health, but it's particularly important for considerations of children's health as well.

And, at this point, we've not been able to identify satisfactory data or methodology for dealing with this, so we're going to have to work on this some more.

We've also not brought forward a revision of the fluoride REL, at this point, because we need to work out

with the Air Board, the exposure assessment people, whether this needs to be treated as a multi-media chemical. And if it does need to be, then as fluoride salts at least, may need to be -- then we need an oral REL as well as the inhalation REL.

Nitric acid --

CHAIRPERSON FROINES: Andy, would you say that again, about the fluoride issue?

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: The fluoride issue is the REL which we have proposed is basically a straightforward inhalation REL which has applicable vapor phase chemicals. But fluoride salts, in particular, of course, you know, it may initially be emitted as a particulate material or else become a particulate material in the course of atmospheric reactions.

And if it then is in particulate form, it may sediment out of the atmosphere, deposit on crops, deposit on soil and things like that. And for materials which behave like that, we need to provide an oral REL, which is used in the multi-media analysis defined by the hot spotss exposure assessment guidelines, and there are certain chemicals which are identified as potentially needing a multi-media analysis.

And so if it is concluded that emissions of

actually or potentially particulate fluoride is an issue in California, it certainly is some in other areas, things like brick works for instance are notorious for emitting particulate fluoride salts in some areas.

PANEL MEMBER FUCALORO: And this is way above what one would normally get in fluoridated water or toothpaste.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Depending on circumstances. There are examples in the world where there is at least locally a problem. I think the issue is whether that's important in California.

PANEL MEMBER ATKINSON: So how would you relate the, let's say, the atmospheric particle concentration of fluorides to what would be on soil or plants? I mean, there may be no relation whatsoever.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: There's only an indirect relationship. There's a methodology for dealing -- which is a sort of default approach, for dealing with multi-media chemicals, which is in the Part 4 hot spots guidelines which you reviewed fairly recently.

It uses various sorts of atmospheric modeling to handle the way the emissions are distributed and potentially deposited. So I'm not saying that it answers all the questions that might be asked, but it's an

approach which is used to determine whether or not there might be a problem there at least.

Clearly, this can be a very complex issue, but the question we have, at this point, is whether we need to include fluorides in that approach. And if so, then we need to develop an oral, as well as, an inhalation REL.

CHAIRPERSON FROINES: Do you have a sense --

PANEL MEMBER ATKINSON: We do have almost done a couple of almost, a couple of inhalation from the oral. It's the oral where you depend upon the concentration of the fluoride and whatever you're getting it from.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: It might be we should develop separate RELs for hydrogen fluoride and other fluorides versus fluoride salts which would be particulates. Certainly, I mean we will look into that.

CHAIRPERSON FROINES: Do you have a sense that there is still a continuing use of hydrogen fluoride in the petroleum refinery?

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: It's my understanding that there is some continuing use. I don't know that -- it's my understanding that some refineries are moving away from that, but the last time we checked the emissions data there was, you know, there were real numbers there. May

be if we come out with this REL, it might accelerate that transition who knows.

CHAIRPERSON FROINES: Has ARB or the local air districts done monitoring so that there is a database?

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: There are data on fluoride emissions in the hot spots database, yes.

The next one that we are not presenting today, which you have actually seen previously, it was nitric acid. And what we did here was we did a fairly standard analysis using, unfortunately, some rather old animal studies on nitric acid effects, and came up with a proposed REL which, you know, looks reasonable from the methodological point of view.

But when we examined this from the point of view of our SB 25 evaluation, we realized that there is a very significant problem with acid aerosols and the exacerbation of asthma, which is a big problem for children. I'm going to be discussing this a little bit more when I come to present sulfuric acid REL.

But the situation of the nitric acid was that it was fairly clear that the REL which we had using data available for nitric acid would not be protective of the children's health in relation to exacerbation of asthma by acid aerosols, if that is a problem with nitric acid, and

it seemed reasonable to us to suppose that it might be. So we're going to have to go back and do some more work on this one and figure out how to include that consideration.

The phosphine REL, there is a question of how we defined the NOAEL and which endpoint we're using. And we have to review those questions, again, in light of the fact that there are several potential endpoints with slightly different NOAELs, different quality of data in the experimental record and some implications for some of those endpoints needing to be further considered under SB 25 guidance. So we're, again, holding that one back so we can do more work on it.

And the final one, triethylamine, again, the end point is basically irritancy. And this will be apparent, I think, with the next group of chemicals. And when I do present the RELs, that irritancy appears to be quite an important and a fairly common endpoint. And there are implications which we need to consider in terms of the impact on children's health.

And in the particular case of triethylamine, there appears to be an inconsistency between animal and human data, which we're still trying to resolve. So this one we've proposed to defer.

I'll now start on the ones that we actually are going to present. And the first one of these is -- it's

been pointed out to me that the lead on this chemical was Dr. Blanc. And given that he is not here at the moment -- but I assume maybe later -- the suggestion was, Mr. Chairman, whether you would want us to defer consideration of this particular one until he's here?

CHAIRPERSON FROINES: No, go ahead. I think that it will be fine.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Okay. This is the basis of the REL which you have seen fairly similarly presented before. We haven't changed the key study, but what we have done is that we have actually gone back to the original data from that study which we obtained after a rather torturous process of inquiry through the federal agencies.

And we've actually now calculated a benchmark concentration, BMC05, which is the benchmark which we are proposing to use regularly for this sort of analysis. So the modification here, firstly, is the calculation of the new benchmark from the raw data in the study.

We also looked at some other information. There was another study in the literature that looked as if it might be informative, but we were not able to actually get the original raw data, so we couldn't do the calculation, but that's available as a comparison.

And additionally, we have considered the

implications of carbon disulfide toxicity for children's health. And obviously this was reviewed in the SB 25 document, which you've just finished working through.

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AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: The situation that we identified there was that there was some specific concerns about carbon disulfide, but it didn't quite reach the level of concern where we could actually identify a differential impact. So we haven't proposed changing the REL to reflect any such differential impact on infants and children, but we do review some of our remaining concerns.

We've also incorporated in the summary some of the information relating to potential impacts on children's health, which was discussed also in the SB 25 document. So I don't know whether you want to ask any further questions or make any points about this at this point, Paul?

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AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Well, I'll proceed to the next one now. The revised summary on acrylonitrile.

CHAIRPERSON FROINES: Why did you pick -- why didn't you use 250 instead of 300?

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

SALMON: I think because typically that -- well, that was the way the -- we normally round these things to one significant figure here. So the 300 is the number. The number didn't, in fact, change substantially from the previous version. Dr. Lewis was responsible for the analysis here, so I want him to respond.

STAFF TOXICOLOGIST LEWIS: We had done -- U.S. EPA had done the analysis. They used a BMC10, a ten percent benchmark dose. And their value by using their uncertainty factors was 700 micrograms per cubic meter, very similar to our 800 micrograms per cubic meter.

When we initially revised their approach before we had received the original data using a BMC10 and our preferred uncertainty factors, we had a value of 3,000 micrograms per cubic meter, so this is slightly lower.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: I think the issue which caused us to go back and reevaluate the benchmark was that our preference is to use the BMC05 with our defined range of uncertainty factors. Whereas, the U.S. EPA approach they tend to calculate a BMC10, and then, in fact, put in some additional uncertainty factors, which are not sanctioned by our guidelines, in order to allow for the perception that the BMC10 is, in fact, in effect level rather than being, broadly speaking, equivalent to a NOAEL.

So that's the reason for the slight differences in methodology between ourselves and the federal analysis. But, as you can see it comes out basically to approximately the same place in the end, and we feel that the approach we present here is more consistent with our guidelines and with the way we would like to use the BMC calculation methodology.

PANEL MEMBER FUCALORO: Just for the arithmetic, can I ask a question? In going from human equivalency concentration of 2.5 parts per million, rather going from 6.9 parts per million would be the BMC right, so 2.5 is computationally one half times five-sevenths, essentially, right?

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Yes.

PANEL MEMBER FUCALORO: And then you bumped it by a factor of 100, and then rounded it off to the next highest? I just want to be clear on that.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Yes.

PANEL MEMBER FUCALORO: And then you use a 3.1 micrograms per cubic meter to get to the conversion factor in order to go from 300 to 800; is that correct?

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: I think actually what we --

PANEL MEMBER FUCALORO: That's not quite right. I mean, it should be 900.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: What we actually do is we go back and we reround the calculation in micrograms per meter cubed, and supply the uncertainties and then do the rounding, so that we don't generate rounding errors.

STAFF TOXICOLOGIST LEWIS: Yeah, that's correct. There's no rounding till the end so we had -- it looked like we had 6.86.

PANEL MEMBER FUCALORO: Right, I understand.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: We always do the rounding at the last possible step to avoid generating propagated rounding errors.

PANEL MEMBER BLANC: I mean I think it's excellent that you modified the text to be consistent with the evaluations that you did for the childhood project. And on the same vein, do you think it would be useful to insert under a source of exposure as a byproduct of the breakdown of metam sodium in the first pair?

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Yes, that would be a -- we will do that.

PANEL MEMBER BLANC: And do you feel that in the process of the childhood literature review you've basically caught up with all of the recent literature,

which this is one of the chemicals of which there tends to be a more evolving literature list there?

STAFF TOXICOLOGIST LEWIS: Yes, I think we feel very confident that. We did literature searches as recently as a week or two ago on that on several sources.

PANEL MEMBER BLANC: Right.

CHAIRPERSON FROINES: Andy, I don't want to get into this right now, but this notion of the BM05 versus BM10, it seems to me that in using a benchmark, one also needs to look at the nature of the data that you're doing the benchmark calculation from, in terms of the degree of extrapolation that you're pursuing.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Yes.

CHAIRPERSON FROINES: And so it seems to me that one needs to have some flexibility within your guidelines in terms of the data set that's actually used for calculating the benchmark dose.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Yes.

CHAIRPERSON FROINES: So I wouldn't tie myself so rigidly to a specific value, because you may want to --

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Well, I think that our philosophy in picking the BMC05, at least when we're reviewing, what I call,

"generaltox" animal studies, is that our experience to date has been that the BMC05 has generally been found to have properties fairly similar to the NOAEL, which we're used to dealing with, so that's why we're choosing that.

Now, I think it's a very valid point and one which we're struggling with that that may not be suitable. For instance, in some cases we're looking at epidemiology studies, we're particularly depending upon the nature of the endpoint. So, yes, I agree that we need to take everything somewhat on a case-by-case basis. But the BMC is our choice for a starting point at this stage.

And the other thing is, of course, that when we are calculating a benchmark, we are using the statistical tools which come in the software to evaluate the quality of it, and, you know, basically to ensure that we are looking at a reasonable data set and not extrapolating too far outside what's defined by the data, so that we do those things.

CHAIRPERSON FROINES: I think that's good. I mean, I think that's important, especially when you get into occupational studies at high exposure levels, where obviously you can be in a very different place if you weren't careful.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Yes, I think our finding with the benchmark

calculation has been that, in general, it's proved a more satisfactory approach to do this calculation than to use the uncertainty factor NOAEL/LOAEL approach, when we don't have a NOAEL -- when we've basically got an unsupported LOAEL, we've often felt ourselves to be rather nervous about, you know, whether the LOAEL uncertainty factor of ten is, you know, appropriate.

In some cases it might be too large and in other cases too small. So particularly in that context I think we found the benchmark dose approach to be a more satisfactory way.

CHAIRPERSON FROINES: I'm a strong advocate of a benchmark dose approach. I think it's taken too long to be implemented for regulatory purposes. So you don't have an argument from me, but I still would argue that one has to look at the data carefully to make sure one isn't trying to use it when it wouldn't be appropriate.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Yes, absolutely.

CHAIRPERSON FROINES: Go ahead.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: So the acrylonitrile, the modifications which were requested by the -- so acrylonitrile REL, we're basically responding to modifications requested by the panel at the last meeting when we considered this, and

also again including some consideration of impacts on children's health.

We were able to provide more information on the key studies adding actual tables of data into the summary. And, again, we switched over to using a benchmark dose calculation based on the key study here. And we also looked at an alternate study for a different endpoint, which we wanted to evaluate partly for comparison with the selected endpoint for adult effects, but also because the endpoint in question for neuro-toxicity is one which is of significance from the point of view of the children's health evaluation.

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AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: And this is what the derivation looks like. Now, the key study is still as it was when you last saw it.

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AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: But we're now using a benchmark dose calculation. And the new REL is, I think, reduced a little bit from the previous one, but basically it's replacing the previous methodology with the superior --

STAFF TOXICOLOGIST LEWIS: What's the previous, nine parts per billion?

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

SALMON: Yes. Basically, we're using the benchmark dose calculation here, which we regard as preferable in this case.

And the other consideration which we've added here is the potential for impact on children's health. And there are two pieces of information that we were looking at here. One is that there is a developmental study, and that the chronic REL proposed for this endpoint was significantly lower than the developmental -- than a REL which you would propose on developmental effects.

So we feel that the processed REL is likely to be protective against developmental effects and neuro-toxicity again, as I was just saying now. We did look at that endpoint.

And although there is an neurotoxic effect from acrylonitrile in adults, this endpoint is less sensitive. And even allowing for the potential increased sensitivity of younger animals or humans to that endpoint, we feel that the proposed chronic REL, which is based on the histology changes in the upper respiratory tract, is likely to be protective of those endpoints for which we have concern as children having differential sensitivity.

So that's our proposed analysis on this one. Obviously, we're trying to work within the guidelines that we have put together on this issue, but this is an

exploratory exercise, so we very much welcome any input that you have on our approach here, if you think we're doing the right sorts of things and if this is adequate.

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AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: The next one up is beryllium. We updated the literature review for this analysis. There's been quite a number of things which have come out in the literature since the original version was put together. And in particular three references that Dr. Blanc suggested we should examine more closely have been included.

There was also discussion of the uncertainty. In fact, there's an issue here as to -- this is the intraspecies uncertainty factor, and there's a question of whether the responders are a sensitive subpopulation. And if so, whether -- you know, normally we're using a default of ten for this uncertainty factor, but in this case, we're using now an uncertainty of three. We had previously gone all the way down to one, but that was considered illadvised, so we've changed that.

Also, we did look for any evidence of differential effects on infants or children. We basically found no indication of any such effects, so we can't really add anything on that, other than to say there's no evidence that there was a problem here. The final thing

is that this is like the fluoride case, in that airborne beryllium is often going to be found in a particulate form, hence can settle out, and needs to be treated by the multi-media methodology in Part 4 of the guidelines.

So we need an oral chronic Reference Exposure Level. So we've included that, so that it can be included in the multi-media assessment on the Hot Spots Guidelines.

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AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: This is the actual derivation. Again, the study hasn't -- this is the derivation of the oral chronic REL. This is the inhalation REL, apart from the change in uncertainty factor hasn't altered. The chronic REL uses a dietary chronic oral REL was used in a dietary study in dogs. And the critical effect is intestinal lesions.

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AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: We're using a relatively standard benchmark dose methodology here, and come up with a chronic oral REL of 0.002 milligrams or two micrograms per kilogram per day.

And this is, I think, in fact, fairly similar to what the U.S. EPA has.

STAFF TOXICOLOGIST LEWIS: It's actually identical to the U.S. EPA RFD.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

SALMON: We've been through the arithmetic and found ourselves to be in agreement with the federal axis.

PANEL MEMBER FUCALORO: I clearly misunderstood something though. Two slides ago, you talked about a UF sub H from 1 to 3. Now, what uncertainty factor was that?

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: This is for the inhalation.

PANEL MEMBER FUCALORO: Got you. This is all right.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Apart from that change, the inhalation analysis has not -- you know, is not different than the version that you saw previously. The addition of the oral REL is the thing. And as you see in that case we're not looking at a sensitive subpopulation effect or anything like that, so we're using the standard default uncertainty factors.

PANEL MEMBER WITSCHI: I have a comment about your oral data. The effect in the study is they are probably close by the acidity of the beryllium sulfate. And if you go back to the literature on beryllium in the 40s and 50s, there are several papers which very conclusively show that beryllium is not absorbed at all into the blood stream from the gastrointestinal tract, because it's precipitated presumably as phosphate. And so this would be mentioned somewhere.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Okay. I think that we took note, I think, of your comment previously that the intestinal absorption is low to negligible, but maybe we need to amplify our language a little bit to make it clear that we're aware of that, and so we will do that.

Yes, I mean, it's a slightly curious situation, but, you know, there's a pathological endpoint here by the oral root, so we feel obliged to respond to it at some level.

PANEL MEMBER BLANC: Yeah. I mean the issue here is that the significance of oral exposure, even without systemic absorption is the same issue as the effect of skin contamination through airborne sources, which would tend to potentially sensitize someone as well. So if you sensitize someone through oral primate, and then have them exposed by inhalation, they'd be, well, theoretically, particularly more likely to respond to the beryllium that they inhaled.

So for that reason, the oral exposure would be meaningful as nerve sensitization viewed without any absorption. The implication is not that you're absorbing beryllium systemically and then depositing it preferentially in the lung, but rather that you're becoming sensitized theoretically, I guess, through some

oral contamination. It's, I think, much more likely you become sensitized through skin contact and then because you're systemically sensitized, once you inhale it, you've developed chronic beryllium disease.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: It would be nice if we had experimental data that would enable us to analyze that kind of situation more fully, but unfortunately, you know, what you see is what we can find in the literature here. So we hope that we've addressed those issues in some way at least with the approach we're taking here.

PANEL MEMBER BLANC: Well, since you don't take into account the skin root, it doesn't bother me that you have the oral thing in there, because one probably counter-balances the other, even if it's, you know, overly conservative having the added oral burden that you can't real calculate the skin content burden.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Yeah, that's right, we don't have a good way of dealing with that, at this point, so this is hopefully providing sufficient protection.

Thank you.

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AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: The next one I want to present is the

chloropicrin. This one has also been reworked with firstly responding to modifications requested by the panel, secondly, an inclusion of the benchmark dose calculation, and, thirdly again, consideration of the children's health impacts.

So this is the calculation as we have it, at this point, using BMC05 on the data from the Burleigh-Flayer and Benson study.

This compound obviously is a highly irritable material. In deed, that's its principle use, I believe. And the finding is irritation in the upper and lower respiratory tracts.

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AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: We have used, as I say, the benchmark concentration approach, coupled with a fairly standard uncertainty factor here, but, you know, we've got an uncertain intraspecies here of three because we're doing a human equivalent concentration using the RGDR methodology.

So this is basically similar to what we were doing before with the uncertainty with the NOAEL approach.

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AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: And the chronic REL proposed is 0.05 parts per billion or .4 micrograms per meter cubed, which is a

fairly low number reflective of the fact that there is a high irritant material.

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AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: When we looked at the children's health issue, we're conscious of the fact that this endpoint is potentially one which does have a differential impact on infants and children. The finding has generally been that irritants do exacerbate asthma at least in people already suffering from asthma.

There is some suggestion that actually induction of asthma or insensitive subjects including people who are atopic may also occur. But there, as you heard earlier, in the SB 25 discussions, there's a number of uncertainties about exactly what is going on here, particularly with agents like chloropicrin, which, frankly, there have simply not been studies with respect to this sort of consideration.

It's fairly easy to see why people have not done those response studies with chloropicrin on children. But nonetheless, from the point of view of undertaking this analysis, it represents a serious data gap. We are unable to point to any specific indications that the methodology is inadequate.

In particular, we do have the intraspecies

uncertainty factor of ten included in the calculation, which we believe, by default, allows for the existence of sensitive subpopulations within the general human population. And in particular we think that children, and especially asthmatic children, might be such a sensitive subpopulation.

So we're basically relying on the existing uncertainty factor of ten to accommodate that hypothesized sensitive subpopulation. We don't have any specific evidence or guidance, at this point, which would encourage us to do anything other than that, so this is what we're proposing.

CHAIRPERSON FROINES: One could argue that if one looks at the history dating back to the 1950s of risk assessment approaches, and the development of the uncertainty factor, safety factor approach, one would argue that the definition of the safety factor for intraspecies variability was never intended as a historical matter to address differences in adult versus children sensitivity.

And that there's no, sort of, underlying intellectual basis to make that assumption, so that it's something that I think needs to be reviewed as we move forward, because, in a sense, what you say is that we have a safety factor of ten and we assume that it includes

within the distribution children, but that's not necessarily an assumption that has an underlying basis to it. It's an add-on almost.

And I think that that's probably an inadequate way of looking at it. If you were writing it -- instead of putting up a set of numbers, if you were writing it in some sort of intellectual context, I don't think you would feel quite happy with that formulation, frankly.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: I agree. And obviously, this is an area where we are going to have to put in additional work. We have a mandate under the SB 25 program to develop improved risk assessment guidelines for specifically taking into account effects on infants and children. And this is clearly one of the areas where such development is needed.

I think the situation we have at the moment is that we are lacking in either a default guidance, other than we're sort of vaguely trying to adapt to the purpose here. And we don't have any specific data on chloropicrin. I think what we hope is that in the long term, we may be able to identify cases where there are sufficient data that we can perhaps come up with something more satisfying as a general guideline and will then be able to extrapolate that to other chemicals like chloropicrins, which we don't have the data.

And, of course, if during that process we identify something which says that we're not right in making this default assumption here, then we would have to, by definition, that would immediately identify any chemicals where we had made the assumption as chemicals which should be added to the list of critical materials for reevaluation, bearing in mind that we have a program for checking into and prioritizing all the toxic air contaminants. And we actually have to have reevaluated another ten by 2004.

CHAIRPERSON FROINES: I just think as a general matter and we have to move on because we have a lot to cover that's important, but I don't think that population heterogeneity, which brings about the safety factor of ten, really includes variations in children's exposure physiology, so on and so forth.

And so that, in a sense, it's broadening the distribution, and therefore assuming a factor of ten is okay, and I suspect that it may not be.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: If you can, you know, point us in a direction where we should go, at this point, with this REL, I think we'd be very happy.

CHAIRPERSON FROINES: Yeah, I agree. I think with this REL it's impossible, but even in terms of the

general premise, it's obviously a difficult one.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Yes, we're at a preliminary stage.

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AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: The next one is --

PANEL MEMBER BLANC: One very small question just on the -- this is a methodologic issue in terms of how you handle these in general.

But on this particular chemical for the physical properties when you get to the vapor pressure, you site a reference for the vapor pressure, and it's a 1921 reference, which is pretty long ago. You don't generally site, parenthetically, the reference source for vapor pressure in the introductions.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: I think --

PANEL MEMBER BLANC: And is that because you just couldn't confirm the vapor pressure from any other more recent source?

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: I think what happened here was that, I suspect, working from slightly different reference sources than this one, that we generally, use this, obviously is a slightly unusual chemical, and it has considerable

pesticidal uses and things of that sort.

And also --

PANEL MEMBER BLANC: It gives the impression of -- anachronism isn't the right word, but you now one would --

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Yes. In this particular case, the reference is from a treatise on chemical warfare.

PANEL MEMBER BLANC: I understand that.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: I suspect this is reflective of the unusual nature and terms and reference to the compound.

PANEL MEMBER BLANC: Yeah, but you should be able to find it in the MERCK Manual, too, I would think.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: We have been enjoined to use primary references where they're available. But maybe a more up-to-date reference, if we can find one, would be right.

CHAIRPERSON FROINES: Well, I think that the answer to the question would be to write the manufacturer of chloropicrin to the degree that anybody is making it.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Well, we could probably obtain a more recent statement through the Department of Pesticide Regulation.

PANEL MEMBER BLANC: Yes. And I assume that the

key papers that you have used that we're exposing animals through generating saturated vapors of this solution must have stated what the vapor pressure was?

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Yes. Well, they probably cited this reference.

PANEL MEMBER BLANC: That's how you got to it in the first place?

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Yes, I think probably it is.

Diethanolamine, again, we are responding to early comments by the panel, and also including consideration of children's health impacts. And there's a change in the critical study and endpoint. This new study is one which was actually submitted to us. It's basically a regulatory type study that was done more recently than the one that we previously had access to.

But it's not especially remarkable in other respects, but it is a newer and more comprehensive study than the one that we were using previously.

And so it's a chronic inhalation study, and we're using a NOAEL/LOAEL approach here. My sense is that we were looking -- we looked at the data table in the analysis. In fact, we haven't got a data set here for which we can use the benchmark dose methodology, because we've got basically close to 100 percent response in some

of the -- well, in fact, in virtually all of the categories, so we were not able to get a statistically acceptable analysis using the benchmark dose approach. So this one we're staying with the NOAEL/LOAEL methodology.

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AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: And so the LOAEL uncertainty factor we chose was an uncertainty factor of three based on the nature of the effect, which was the hyperplasia and metaplasia were in the larynx were in an extremely localized area. And the rest of the respiratory tract didn't show any changes until higher doses.

So we felt justified in arguing that this was a less severe effect than the more widespread irritation and pathological changes which we've chosen to regard as a critical effect in some other studies.

So we then applied the usual approach of uncertainty factors.

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AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Subchronic uncertainty factor of three relates to the duration of the study which is a 90-day study. And, in fact, we come up eventually with a cumulative uncertainty factor of 1,000, which is, you know, the highest that we normally consider.

The proposed chronic REL based on the upper respiratory tract effects is considerably lower than the comparison REL, which was based on fetotoxicity. So from the point of view of any developmental effects, we see this proposed REL as protective of infants and children.

Again, we're seeing it is a respiratory irritant which might exacerbate asthma, and have, thereby, an adverse effect specifically on some children.

However, we felt that in this case the inclusion of the overall uncertainty factor of 1,000 would probably be sufficient to reassure us that we were okay with the proposed REL in the situation where there's no direct evidence that diethanolamine exacerbates asthma or would allow us to quantify any other means for differential impact on infants and children.

PANEL MEMBER BLANC: Although, there are case reports of allergic sensitization of asthma by diethanolamine, aren't there not? This is not an irritant just as this would, sort of, be presumably.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: I don't know that we have any quantitative information about exposure that would allow us to use those.

PANEL MEMBER BLANC: You probably wouldn't. There would just be --

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: This is a recurrent problem with this sort of report, that, you know, it's something which may be out there but we don't know.

PANEL MEMBER BLANC: Well, you would have it to the extent that if it was one of the cases where someone did a specific inhalation challenge to document that causal relationship, then you would.

STAFF TOXICOLOGIST LEWIS: We did list one case report of a person occupationally exposed to diethanolamine with occupational asthma.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: I think the situation here --

PANEL MEMBER BLANC: Which reference is that?

CHAIRPERSON FROINES: Page A 28. It's under 4 Roman Numeral 4 on A 28.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Some of these in occupational studies are a little bit retro in terms of the methodology and conditions.

PANEL MEMBER BLANC: And when you pulled that case report, had they done an inhalation challenge, do you know?

STAFF TOXICOLOGIST LEWIS: I didn't see the report myself.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: I don't believe they did. No, I think it is literally just a case report.

PANEL MEMBER BLANC: You might just double check that, because that would give you at least that exposure level that would trigger a response in someone who's been sensitized. I'm not familiar with the case report, so I can't tell you.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: I think, but we'll check into it anyway.

PANEL MEMBER BLANC: Now, sometimes it's so crude that it's only to have him go into the workplace and then they prove that he has dropped his FEV1, but sometimes it's a control exposure, and they would actually have a concentration level that you could cite.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: We'll make sure that there isn't -- when we can have another look for that, but at this point --

PANEL MEMBER BLANC: I don't think it would change anything else you've done. It would be just good for your documentation.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: We would want to know. So we'll have another look and see if we can find anything.

PANEL MEMBER BLANC: In that particular paper,

yeah.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Right.

CHAIRPERSON FROINES: The interesting thing about this compound is that given the toxicologic data that you site, it has interesting implications for occupational exposures.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Um-hmm.

The level that we came up with was quite a bit lower than I think the -- you know, we received this study as part of a public comment, basically. And I think they were expecting us to come up with an evaluation which was rather less stringent than the one that we actually produced. I'm not quite sure why they had that expectation, but it may have something to do with their perception of how the material was seen in terms of occupational health at the present time.

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AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: The next one I'd like to present is ethylene dibromide. And this is one which we came up with the analysis in March, but I think is a -- I think I'm correct in thinking that this is one of the ones that Dr. Friedman was in charge of, and he wasn't at that meeting, so we

deferred consideration to the present meeting. So this is basically the first time the panel, as a whole, has reviewed this one.

It's, basically, an occupational exposure study. And the subjects in question are, I believe, pile workers in Hawaii. The effect is reproductive toxicity, reduction in sperm count, abnormal and viable sperm, and various other related changes.

And in this case, we used the LOAEL/NOAEL methodology. We don't have a NOAEL. We don't also have, at this point, have the sufficient detail on the raw data of the study to be able to do a benchmark calculation, so we're staying with the NOAEL here, and the exposure continuity and duration allowed for in the usual way.

And this results eventually in using standard methodologies in proposal of a REL of 0.1 parts per billion or 0.8 micrograms per meter cubed. And this reflects the fact that this is a, you know, certainly an effect of concern, and that we don't have, in fact, a full chronic exposure duration with the study in a period that was about four to five years on average.

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AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: As far as the impacts on children's health are concerned, there's an animal study which included

developmental toxicity endpoints in rodents. And we actually include an analysis of this in the summary for comparison, I think, which you -- anyway, basically the fetotoxicity in rodents was reported at significantly higher levels.

So we're thinking that the proposed REL should be adequately protected against those developmental effects. We have no direct evidence that the reproductive toxicity endpoints in humans would have a differential impact on infants and children, although it's possible, hypothesizing that adolescent boys might be more sensitive than adults then.

Given that metabolism is an important factor in the toxicity of this compound, there's a possibility that there might be metabolic differences between infants, children and adults. We don't have any evidence about this. So again, I think we're in a situation of wanting to put, if you like, put a thumb print on this as something that we should continue to look at carefully. But for the time being we are really stuck with, assuming that our regular methodology is sufficiently cautious, to protect the infants, children and adolescents as well as the adults.

PANEL MEMBER FRIEDMAN: Can I ask you about a different metabolic capability in children versus adults,

is there a certain direction that you would expect or could it go both ways, one they could metabolize it better or worse?

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: What we've seen so far, is that things can change in both directions. Typically the -- well, the differences from what you would call sort of childhood throughout adolescence and adulthood are typically not very large, but what you do see is quite significant changes between fetus, newborn and infant, you know, during that phase, there are changes.

And a lot of enzymes in the fetus are, you know, for instance, the cytochrome B450 enzymes are different. And the absolute level of their activity is often somewhat lower by the standard assays, but we often, in fact, see higher sensitivity in the fetus and the infant in spite of having lower activity of Phase 1 enzymes, because the activity of the Phase 2 enzymes is often lower, too, and obviously the toxicological outcome depends on the balance between the Phase 1 and the Phase 2 enzymes.

And in some cases the Phase 2 enzymes are more depressed in the infant or fetus than are the Phase 1 enzymes. So the answer is it can go either way in terms of the outcome.

PANEL MEMBER FRIEDMAN: And what is Phase 1 and

Phase 2 mean?

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Phase 1 is the activating enzymes that typically the oxidative actions of cytochrome P450s is sort of the classical example, which is the thing which actually generates reactive intermediates, such as epoxies or things of that sort.

And the Phase 2 is the detoxifying enzymes, typically glutathione transferases, and ultransferases, things of that sort.

CHAIRPERSON FROINES: Andy, I'm very concerned about this 2:00 o'clock cutoff that we have, and so I'm going to have you go till 11:30. I'm very anxious to have the pesticide discussion today and the findings for SB 25. So I'm going to go till 11:30 with your presentation, then I'm going to cut it off and move on the agenda, and then we'll come back to anything we haven't finished as we get finished with the other two.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Do you want me to try and --

CHAIRPERSON FROINES: So we should try and push ahead, you know, spending a lot of time on EDB is a exercise in futility, given how much, how little is used in the environment in California.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

SALMON: Well, if there are any comments or suggestions or additions that the panel wants to send us, obviously we'd be happy to deal with them.

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AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: The next one to look at is isophorone. The panel has reviewed the REL development for this compound in March. We're bringing it back to you here because we've added a section on differential impacts on children's health.

And in this particular case the REL is based on a developmental study. And we feel it's therefore reasonable to expect that it should be adequately protective of infants and children. However, there is no direct evidence in the literature that would quantify any differential effects of isophorone in children relative to adults.

So apart from this conclusion that since we're using developmental endpoints as the critical endpoint and that that's the basis of the REL, really we don't have anything else to add and we haven't otherwise changed the analysis significantly from when you last saw it.

So if this is seen as a reasonable response to the data from the point of view of considering the impacts on children's health, then this is it.

PANEL MEMBER BLANC: Given your allusion to children's health and given the aside that this chemical occurs naturally in cranberries, and given the fact that children's intake of juice per kilogram is rather high, do you need to include one of your orals or is it such a trace trivial?

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: I think it's a relatively minor component. I don't, of course at this point, have an analysis for you on oral toxicity specifically. We don't have a mandate to consider food and constituents under the hot spots program. And I don't think that this qualifies as multi-media. So in this particular context, we don't have much of a handle on that issue, but it may well be that although this -- let me get to the right data here.

We don't have a particular reason for including oral isophorone at this point, and for the hot spots purpose, but it may well be relevant certainly in more general terms in consideration of children's health.

PANEL MEMBER BLANC: Okay.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: I think, I mean the question of oral exposures and sensitivity of children is clearly an important one with implications for our overall consideration of how we think about children's health impacts. And isophorone is

one of those things that we should probably look at, because as you point out there is a relationship to special exposure of children, so we should look at that.

And if we find anything which has any implications for this, then we can put it in, but I don't anticipate there being a direct implication at this point.

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AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: The next one that we are presenting, I'll try and get through this one as quickly as I can, we presented this previously to the panel, and we responded to the panel's comments including drawing our attention to some additional studies that we should review in the summary.

This is using a benchmark dose calculation on the rat data, which is an improvement on our earlier methodologies. Again, we're moving to the improved methodology here. It doesn't create a huge difference in the outcome of the analysis, but we feel that it's a methodological improvement.

The other thing, which we did, was we examined several papers where there was occupational exposure to maleic anhydride to see whether we could actually get a human basis for a derivation.

The problem with this is is that all the occupational exposures described, in fact, were mixed

exposures including, in particular, trimaleic anhydride which is a rather notoriously irritant and sensitizing material. So we don't really have a very good quantitative basis for a derivation from human data here.

However, what we did see is that even if you assume that all the anhydride is maleic in those studies, we still do have a somewhat reasonable protective basis using the REL, which we calculate from the rat data. So what we're doing is we're using the human data basically as a comparison to make sure we're not missing anything too crucial.

And apart from that, we're proposing to stay with the rat study, but to use the benchmark. We prefer the use of the benchmark dose calculation, because there isn't, in fact, an observed NOAEL. And as we were saying earlier, we feel, under the circumstances, that a benchmark approach is greatly preferable when you don't have a NOAEL.

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AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: And the other interesting feature of this is that although the key study, which is statistically the one we chose to analyze by the benchmark approach, is the rat study, there were also studies in other species including monkeys. And the benchmark, which we calculate from the

rat study is consistent with the data observed in the monkeys.

So in this case we're proposing an intraspecies uncertainty factor of only three, which we generally propose when we have indications of the dose response in nonhuman primates, which we feel are more similar to humans and therefore justify a lower intraspecies uncertainty factor.

On that basis, we propose an inhalation REL of 0.7 micrograms per meter cubed.

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AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Again, this gives us some concern in terms of children's health. And the endpoint is irritation and the maleic anhydride is a known respiratory irritant and inducer of asthma. And this would be an endpoint that does have a more severe impact on children and adults.

However, there is no evidence that we can use to quantify that effect. So until we have such evidence to quantify, we are, again, proposing to rely on the ten-fold intraspecies uncertainty factor to provide a margin of safety, but recognizing that asthmatic children will clearly be a sensitive subpopulation who might be marginally protected only, at this point, with this REL, but the aim of the REL being basically to protect the

majority of the population.

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AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: The next one -- I'm looking at the time here, I hope I'm not rushing you too much here.

The next one I want to present is methyl isocyanate, and the changes are quite limited. One of the things that the panel asked us to do, the earlier review, was to actually include some data on the amount or some indication of the amount that might be involved as a breakdown product from metam sodium use. It has been identified as a minor breakdown product in the environment after metam sodium use.

And this, in fact, looks as if it might be by a significant margin the largest single source of the material, at least in the Californian environment and possibly apart from a couple of specific industrial hot spots. So this is a value.

We don't have a number for the amount of methyl isocyanate that might be involved, but we do have a number of metam sodium used and it clearly is fairly considerable. This is an average over the years of '95 to '99.

The other issue is the differential impacts on children's health. We do have a reproductive study which

did not identify any increased sensitivity of the fetus relative to the parent. So we're thinking that, at least from that point of view, the chronic REL should be protective of infants and children.

Again, we have this concern that because it's a severe respiratory irritant, there may be a variety of different impacts on infants and children. And the fact of the matter is we don't a have a direct quantitative indication of what that might be. So, again, we are having to rely on the defaults on intraspecies uncertainty factors at this point.

PANEL MEMBER FUCALORO: Can I ask you a quick question on the major uses and sources, maybe you mentioned this before. Based on the most recent inventory, the annual statewide industrial emissions from facilities reporting under the toxics air hot spots at California estuaries to be .29 pounds.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Yeah.

PANEL MEMBER FUCALORO: That's it. .29 pounds.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: The major --

PANEL MEMBER FUCALORO: I know the major isn't the metam sodium, but --

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

SALMON: I mean, obviously this material is used in various kinds of industrial processes, but it appears that those industrial processes are not ones which typically are carried out in California. So our concern --

PANEL MEMBER FUCALORO: .29 pounds, they'd even report that.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Yes.

PANEL MEMBER FUCALORO: I mean, are you sure the number is right?

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Let's say I have as much confidence in that as in the other numbers we've pulled off the hot spots data.

PANEL MEMBER FUCALORO: No, no, seriously, is there not a typo or something?

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: I don't think so.

CHAIRPERSON FROINES: It's clearly wrong. We should check it. It's years old.

PANEL MEMBER FUCALORO: You may be wrong in terms of not --

CHAIRPERSON FROINES: A lot of the data that gets cited under the toxic hot spots is really one wouldn't want to bet one's life on by any means. So I think that I always just take it with a grain of salt and go on and

don't take it seriously for the most part.

Unfortunately, that's the state of that data and we probably should talk about it sometime in another meeting where we go back and look and see how dated that information is and really how much confidence one can put to it, because it ends up in all these documents as though those are realistic figures and they're not.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Well, it's obvious that any reporting under that hot spots database is somewhat constrained by who chooses to report.

PANEL MEMBER FUCALORO: I guess I'm asking -- I mean, I don't want to belabor the point, but the hot spots reported as, estimated as -- I mean, you actually have a list of things that are saying that this toxic thing was under a pound a year in all of California.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: That's the numbers we came up with.

PANEL MEMBER FUCALORO: That's the numbers you see.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Whether it's right, we need to check.

PANEL MEMBER FUCALORO: I can understand something like a dioxin, but I mean this is something --

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

SALMON: We'll check into that and make sure there isn't --

CHAIRPERSON FROINES: I think that the selection of values all have a certain ridicule value associated with them. And when you put something into a document that has a super high ridicule value, that's probably been a bad judgment.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: You feel we should simply delete that.

CHAIRPERSON FROINES: I would not -- yeah, I would.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: We can do that if you think that's appropriate.

CHAIRPERSON FROINES: .29 pounds?

PANEL MEMBER FUCALORO: First check it.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Yes. Well, we'll check it and if we're not happy with what we find, we'll --

PANEL MEMBER BLANC: Well, the simple solution would simply be, the remainder of the sentence after it says "...in California were negligible."

PANEL MEMBER FUCALORO: And the metam sodium was not.

PANEL MEMBER BLANC: They're not reporting anything other than that.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: I think that's probably the most accurate way and diplomatic way of characterizing it, so we'll do that.

PANEL MEMBER BLANC: What you expect, because nobody uses those chemicals as a direct intermediate, it's an unanticipated byproduct by and large except in very, very limited -- I think it's Hopewell, West Virginia is the only place in the United State where it's used regularly as a chemical.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Well, nobody is making a carburil in California.

PANEL MEMBER BLANC: So nobody should be reporting release of it.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Yeah.

PANEL MEMBER BLANC: In fact, if anybody reported any release of it, it would make you wonder what they were doing.

(Laughter.)

CHAIRPERSON FROINES: But I think, at some point, at a meeting in the future, it would be worthwhile to have a discussion about the hot spots program, because we haven't had one in years and years and years, and it would be very useful to discuss the validity of the data that's currently in the hot spots program, because I won't go

into more detail, but my understanding of the program is that it's been on hard times. And so it's something that would be good for this panel to be aware since we have -- since every chemical that we get has a value essentially from the hot spots program or very many.

And it would be useful to have a sense of how do we view that information. And I look back and Lynn's nodding his head and George is nodding his head, so I feel comfortable saying that.

But I think this is an area that's somewhat problematic, because our information on exposures tends to be a limiting factor in some respects.

Now, as a related question, and Lyn Baker may have an answer, which is it would be useful to know something about what kinds of exposures are occurring to MIC. And it's my understanding that whereas there has been some studies of MITC, I don't know if there has been any attempt to quantify MIC. Is there a comment, because I think that's a -- obviously, given the sensitivity of MIC because of Bhopal, it's not a trivial issue, potentially anyway.

MR. BAKER: Hi, Dr. Froines. Lynn Baker from the Air Resources Board. I can address that briefly. We did do some MITC monitoring a couple of years ago around a specific application, and we did do monitoring also for

MIC, but that was just a short-term study.

However, this year, we did do eight weeks of monitoring in Kern County for both MITC and MIC, so ambient monitoring, which we don't have the data yet, but early next year we will have that data available.

CHAIRPERSON FROINES: Well, that will be interesting to come back to, given the 15 million pounds currently in use, to see what it looks like.

Thanks Lynn.

And, Andy, one final question, at Bhopal do you have any sense, and I realize this is a very poor question, but was there any indication that children were differentially affected?

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Not --

CHAIRPERSON FROINES: I mean clearly there was such a horrendous event that it's hard to ask that question.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Not that I'm aware of in terms of the acute effects. There were reports of some adverse reproductive and developmental outcomes, which would come within the purview of our consideration here, but those are hard to quantify, because of the -- among other things, because of the difficulty of collecting data in that population. In

fact, they have a fairly high level of disease related reproductive problems in the population already.

So that's a little bit of a gray area. But it's my belief that there are some reports of developmental issues following the Bhopal accident, but nothing specifically to say that the acute damage to the eye or the lung was particularly severe in children.

CHAIRPERSON FROINES: Thanks. I think we'll call a quit for a moment, hopefully getting back to it, if that's okay.

Does the panel want to take a five minute break so the court reporter can take a break?

Then we'll talk about the SB 25 findings.

(Thereupon a recess was taken.)

CHAIRPERSON FROINES: The next item on the Agenda is going to be the panel consideration of the findings of our deliberations based on SB 25.

You have an updated version of the document, which is most of the changes that have been put in are small and editorial in nature. There is one major change which I'll call your attention to that we thought was important under Section 15 on pesticides.

We've added a sentence, it's on page 615, and it states as follows, "In the toxic air contaminant program, there is" -- this is not, perhaps, written -- "there is a

parallel program where the Department of Pesticide Regulations identifies pesticides as Toxic Air Contaminants. The panel recommends that parallel or similar consideration of children be given in the evaluation of pesticides and their pesticidal use."

The intent of that sentence is to say that the decision to leave pesticides out of SB 25 needs to be reconsidered in the future, so that we can have inclusion of pesticides as well as other chemicals. And that's the purpose of that sentence, and that's consistent with the dialogue that occurred over the four meetings that we had on SB 25 where there was continually stated concern about the absence of pesticides. And so that's the one difference that you have over the draft that you've already seen.

So we need to decide whether this draft is satisfactory and whether we can send the findings forward. So I guess the best way to do that is to ask each individual for comments. We have comments from Stan Glantz who said that he thought that the document was fine, except we needed to make changes where we change PAHs to POMs to be consistent with the TAC listing, and so we've made those changes and you can see that in the text that you're currently looking at.

So why don't we proceed.

PANEL MEMBER BLANC: Can I just ask one clarification. The way you have the arrows drawn for that final -- for what would then become the next to last statement regarding methyl bromide, "one exception is methyl bromide noted in finding 13 above." And you have this little arrow suggesting that you're going to move that to proceed the sentence, "However SB 25 reiterated and confirmed by statutory," you were going to move that before that? That's the way I would interpret that arrow.

CHAIRPERSON FROINES: That was what we thought would work.

PANEL MEMBER BLANC: I would leave it where it is.

CHAIRPERSON FROINES: Where it is, okay, and put the other in between.

PANEL MEMBER BLANC: And you were proposing to put the other at the very end and I think that's fine where you have it. I just wouldn't -- it doesn't make logical sense to put the methyl bromide sentence, but I think ending with the sentence that you propose which is, "In the air contaminant program, there is a parallel program in which the Department of Pesticide Regulation identifies pesticides as Toxic Air Contaminants. The panel recommends that parallel or similar considerations of children be given in the evaluation of pesticides in

their pesticidal use" is fine as the final two sentences.

CHAIRPERSON FROINES: So do you have other comments, Paul?

Why don't we go to you first.

PANEL MEMBER BLANC: I don't have any problems. I think the version, as proposed, reflects the previous discussion.

CHAIRPERSON FROINES: Roger.

PANEL MEMBER ATKINSON: No, I don't have any comments.

CHAIRPERSON FROINES: Gary.

PANEL MEMBER FRIEDMAN: I thought it was fine. I just would like to ask for clarification of the handwritten item at the end of number six, I can't read the last part of it, "add sentence, health effects discussed." Is it --

DR. FANNING: Maybe I can address that.

Ellinor Fanning.

PANEL MEMBER BLANC: Can you just read it to start with?

DR. FANNING: The language isn't set yet, but it says here, "Health effects discussed are those pertinent to SB 25 and not necessarily all health effects associated with a specific substance."

So the idea being that your findings that a

particular compound should be listed as a high priority for children's health may not fully articulate all the important health effects that that compound has, but will really focus on the ones that you used in your deliberations to select that compound.

CHAIRPERSON FROINES: Let me give you an example of what's meant there. In the decision to list diesel, for example, emphasized asthma, the adjuvant effects of asthma, the enhancing effects of diesel on asthma. And so the basis for the listing of diesel was a noncarcinogen respiratory endpoint.

However, we also know that this panel has found diesel as a carcinogen in the past and so that -- but that was not the basis of identifying diesel within the SB 25 context. But we wanted to call attention to the fact that there are other health endpoints that are not necessarily listed that may have consequences beyond their -- beyond the differential toxicity criteria.

PANEL MEMBER FRIEDMAN: I wonder if it wouldn't be worthwhile giving an example here like that because otherwise it's sort of unclear as to what you're talking about, whereas when you discussed that diesel example just now, it became very clear to me what you were talking about.

CHAIRPERSON FROINES: Okay.

PANEL MEMBER FRIEDMAN: I don't know if the others feel that this is clear what you mean and the other readers will know it's clear, then I don't feel strongly about that. To me, it would help to give an example like that.

CHAIRPERSON FROINES: Does everybody agree?

PANEL MEMBER BLANC: Do you mean -- when you say specific example, do you mean generically adult carcinogenicity or do you mean carcinogenesis due to diesel associated with diesel exposure?

PANEL MEMBER FRIEDMAN: Something like that.

PANEL MEMBER BLANC: So you mean specifically with a specific chemical citation?

PANEL MEMBER FRIEDMAN: Right, right.

PANEL MEMBER BLANC: I would actually recommend a middle ground where we simply said carcinogenesis in adults without going into -- because it would unduly weight it if we cite one chemical and we're not citing another one.

PANEL MEMBER FRIEDMAN: That would be fine. I would accept that.

PANEL MEMBER BLANC: Let me propose the precise language, since I think the record really needs to reflect what the precise sentence is we're adding. And therefore reading Ellinor's writing, I would say -- and putting in

the missing words, the sentence would be, "The health effects discussed are those pertinent to SB 25 and not necessarily all of the health effects associated with each specific chemical, for example, adult carcinogenesis."

PANEL MEMBER FRIEDMAN: That would be fine. I don't know if you need the word specific in there, just each chemical.

PANEL MEMBER BLANC: Fine, delete the word specific.

CHAIRPERSON FROINES: Gary, are you done?

PANEL MEMBER FRIEDMAN: Yes, sorry. No, I was happy with it except just clarifying that.

CHAIRPERSON FROINES: But you have no further comments.

PANEL MEMBER FRIEDMAN: Right.

CHAIRPERSON FROINES: Tony.

PANEL MEMBER FUCALORO: Under number 5, the second sentence says, "Available data on ambient air concentrations and health assessment values, including Reference Exposure Levels and Unit Risk Factors, were gathered for all TACs and used for a screening level risk ranking."

Now, that's a jumble of gerrands, participles and nouns used as adjectives, and I'm not sure I know what it means, so I think perhaps a clarification of that is

suggested.

Down several lines --

CHAIRPERSON FROINES: Wait, wait. Let's finish each thing before we go forward, because then we'll be finished with the document and we can go.

PANEL MEMBER BLANC: I would suggest the following change then to finish the sentence "...were gathered for all TACs and used for ranking risks at a screening level."

PANEL MEMBER FUCALORO: Yes. Then several lines down it says, "From the 37 compounds for which literature reviews were developed OEHHA and this panel identified 17 TACs..." Is that accurate?

CHAIRPERSON FROINES: No.

PANEL MEMBER FUCALORO: Was it not just OEHHA who did it?

CHAIRPERSON FROINES: Yes. Well, no not entirely.

DR. FANNING: Well, actually that was intended to reflect the discussion where originally there were 11 on a list that OEHHA had brought to you. And the panel did act to add five or six more, I can't remember the numbers at this point, to that list. So perhaps it's not quite correct to say you both identified that.

PANEL MEMBER BLANC: I would say "...OEHHA,

responding to panel feedback..."

DR. FANNING: Okay.

CHAIRPERSON FROINES: Yeah, I think it's better for us not to -- we don't identify things.

PANEL MEMBER FUCALORO: I was concerned about that.

And this is my last one, this is a typo, it's very easy. The last sentence in that, it seems to be all in here, it's not the only one I read, but it's the only I have comments about. "Thus extensive exposure was a key criterion..." rather than "an key criterion." Just a typo.

That's all.

CHAIRPERSON FROINES: That shows that you were thorough, however, when you changed "ands" to "As", so we give you a gold star.

PANEL MEMBER BLANC: That means he has a good liberal arts education.

(Laughter.)

PANEL MEMBER FUCALORO: I didn't have one, I'm just teaching liberal.

CHAIRPERSON FROINES: Peter.

PANEL MEMBER WITSCHI: Yeah, I would say I'm very happy with the table on page five. I have a small suggestion since we identified benzene and vinyl chloride

as new carcinogens. We might as well also define arsenic as a human carcinogen.

What's the status of formaldehyde, by the way?

CHAIRPERSON FROINES: I don't think -- I think it's still probable.

PANEL MEMBER WITSCHI: It's still probable.

CHAIRPERSON FROINES: I believe it's still a 2A.

PANEL MEMBER WITSCHI: That's fine, but we definitely should identify arsenic as a known one. But I think this table is very well done. It reflects my concern I had with the longer descriptions quite well.

CHAIRPERSON FROINES: Yeah, I think the table really is a major improvement.

PANEL MEMBER FUCALORO: It was very helpful.

CHAIRPERSON FROINES: Craig.

PANEL MEMBER BYUS: Yeah, I was quite pleased. I think it was very nice findings considering the difficulty we had, a lot of the deliberations and the discussions, and I think it reflects it quite well. And I particularly like the pesticide addition to the report.

CHAIRPERSON FROINES: Ellinor, in between taking care of her newborn daughter, put in some very good work, obviously on these and so we appreciate her efforts.

So, at this point --

PANEL MEMBER BLANC: Can I just -- this is a very

technical point but the only wording therefore that has not gone on the record is actually the precise wording in the arsenic box. And so I would just suggest the following word change in the box, instead of "...epidemiologic data on lung cancer," it would be "...known human carcinogen based on epidemiologic data for lung cancer..." and then the rest of the sentence would be --

CHAIRPERSON FROINES: Well, I think that's okay but I think that we then need to change the vinyl chloride and benzene to be consistent with that.

PANEL MEMBER BLANC: Well, if you change the vinyl chloride to insert the word "known" before the word "human", then you would be consistent enough, I think, throughout.

DR. FANNING: Okay. Then also the language in finding 11 on PAHs to POM, you mentioned, John, that those changes have been made, but it's not actually on the record, so I don't know if we need to read through them briefly. But just that where the findings in the preceding version had been discussing polycyclic aromatic hydrocarbons, that language has now changed to the correct Toxic Air Contaminant Polycyclic Organic Matter. And I believe that has been changed throughout.

There's still reference to PAHs in the finding in

situations where we're talking about specific research studies looking at PAHs which are a subset of POM.

PANEL MEMBER BLANC: I think that's sufficient without reading the actual changes, but I do think that the -- I assume you were going to then have a formal vote.

CHAIRPERSON FROINES: We're about to.

Yes. Since we have comments on an individual level from each member of the panel, we now need a motion to adopt the findings.

PANEL MEMBER FUCALORO: So moved.

PANEL MEMBER FRIEDMAN: Second.

CHAIRPERSON FROINES: Any discussion?

All those in favor?

(Hands raised.)

CHAIRPERSON FROINES: The vote is unanimous.

Thank you very much.

This was a good effort, albeit difficult at times.

Okay. So moving on Paul Gosselin and DPR are going to update us on the organophosphate issues.

Is George here? Has George left?

I'm looking all around you. George, assume that this letter on our SB 25 findings goes to Joan Denton, and historically we would send our TACs to either Paul Helliker or Alan Lloyd, is I assume this goes to Joan

Denton. I assume that we can also copy Alan Lloyd and Paul Helliker as well.

DR. ALEXEEFF: I believe that's correct. It actually goes to the Director of OEHHA. And the director OEHHA has already sent a letter to Alan Lloyd as well, but it would make sense for you to CC the Air Board as well.

CHAIRPERSON FROINES: And I'm assuming that we will not CC Winston Hickox. We'll assume that Joan will communicate our findings to Winston Hickox.

DR. ALEXEEF: Right. I don't know what your normal process is for sending in comments.

CHAIRPERSON FROINES: We never have in the past.

DR. ALEXEEF: Right.

CHAIRPERSON FROINES: But SB 25 is a little different than anything we've done previously, so that we'll assume that you will send it forward.

Welcome.

Ready?

DR. PFEIFER: Sure. Good morning -- afternoon. I'm Keith Pfeifer with the Department of Pesticide Regulation. And I'm here today with Dr. David Rice from OEHHA and we are the joint coordinators for this cholinesterase work group project, and we will share the presentation today.

(Thereupon an overhead presentation was

presented as follows.)

DR. PFEIFER: And the first slide up there is an acknowledgement of the staff for both OEHHA and DPR that have worked quite diligently on this project.

Our last presentation to you was back in March, and I can say with very few exceptions, the work group has met every two weeks consisting of paper presentations, discussions, ideas of where we're going forward with this cholinesterase workgroup project.

So in saying that, I am here today as a representative for the people that you see up on the first slide. Can we go to the next slide, please.

--o0o--

DR. PFEIFER: And basically today, what we'd like to do is give a brief overview of the process for developing the discussion papers; the format and general content of the discussion papers; an overview of the discussion paper topics, and one of your handouts was a more detailed paper on the topics with the exact titles and the authors; also a status of where we are with the various discussion papers; and then future workgroup activities.

So, as you can see, the first paper there, which I'll -- or first overhead, which I'll go through in the development of these discussion papers, we produced, what

we call, an initial draft. And this is reviewed and discussed by the cholinesterase work group, it's presented by the lead author.

Then based on the discussion, suggestions, comments, critique, we come up with what we call a revised draft. And, at this point, we would consider informal review, which can be done either by SRP members or also by a few, what we call, external experts. And we did this with two papers as far as the external experts.

On one paper on the functional observation battery, we solicited comments from Ginger Moser, who's one of the foremost experts in this area. On the paper on analytical variability, we got comments back from Barry Wilson at UC Davis and also Stephanie Padilla from U.S. EPA who, I think, are two of the foremost experts there.

And they were quite willing to look at these papers and give us good constructive comments.

CHAIRPERSON FROINES: What bullet are we are on here? Are we on the third bullet?

DR. PFEIFER: Bullet number two.

CHAIRPERSON FROINES: Bullet number two, okay.

DR. PFEIFER: And then based on those comments, we call the next draft a final draft based on the informal review.

Now, our idea and our plan for the final draft is

to have that draft reviewed by SRP members at their selection and also selected external experts. This is our plan.

We're currently developing a list of possible scientists that are considered experts in the field of cholinesterase inhibition and testing and research or neuro-toxicity. So this is one area that we're looking towards the future in.

And then when we complete these discussion papers, and, again, this is another area that is open for suggestion or discussion, we'd like to present these two, either all of them, some of them to the SRP.

And the format, I think, has yet to be decided, whether it would be a combination of written presentation and verbal or some type of workshop format. So the latter two there are still in the stages of development and discussion of exactly how we'd like to proceed.

Could I have the next slide, please.

--o0o--

DR. PFEIFER: This is just a brief slide on how the formats for the various discussion papers have, more or less, evolved.

They all consider or include an introduction and some background information. The second bullet, which is very important, is the presentation of the topic and the

relevance to risk assessment for these compounds.

Then there's generally a technical summary and/or conclusions. And one thought is that for the various papers, these technical summaries will be folded into some type of final executive summary.

And then the final point, and this was not presented to the SRP last March, but it's something that the workgroup came up with, and it is very important, is at the end of each discussion paper the author comes up with as many questions as he or she feels need to be put out there for the development of the important guideline issues that are going to be addressed.

If I could have the next slide, please.

--o0o--

DR. PFEIFER: This next slide is just highlighting the various groups or categories that are presented in more detail in the hardcopy handout that you have.

And I won't go through all these, but when we started out this project, we did prioritize these in an order to develop discussion papers underneath these various groups. And the reason we did that is we basically started, more or less, from more general basic type information that we felt needed to be presented, discussed for inclusion and discussion and development of

the more specific areas that were to come.

So the first grouping has several papers on the physiological, toxicological significance of cholinesterase inhibition. And then as we move down the list, some of the topics get more specific and more important as far as developing eventual guidelines.

PANEL MEMBER FUCALORO: May I ask a question at this point?

DR. PFEIFER: Sure.

PANEL MEMBER FUCALORO: Where in here will you discuss the additive effects of people being exposed to more than one toxin with the similar endpoint or --

DR. PFEIFER: The accumulative exposure, under miscellaneous. And if you look at the --

PANEL MEMBER FUCALORO: Of course.

(Laughter.)

DR. PFEIFER: And I can just say briefly how that evolved. If you look at the handout, the more detailed handout, under that you'll see there's going to be a paper authored by Dr. Ruby Reed in my group at DPR and Dr. Reed is a member of the U.S. EPA Scientific Advisory Panel on the cumulative guidelines that are currently being developed.

And so she has firsthand information on where they're going and the methodologies. And these guidelines

are due out in draft form, I believe, in December and we will look at those and consider them in the context of where we want to go. And Dr. Reed will subsequently write-up a discussion paper on that.

And I know in March there was, I don't know specifically, which panel members here brought this up. It may have been yourself, Dr. Fucaloro, but I know Dr. Byus, in subsequent discussions, wanted that topic added to our group. So that's one reason that we're including it.

PANEL MEMBER FUCALORO: Thank you.

CHAIRPERSON FROINES: As long as we're on this, what would you prefer, would you prefer that you go through the entire presentation and then take questions or take them as we go along?

DR. PFEIFER: Yeah, I think the former, because I'm going to turn it over to Dr. Rice now and let him go through and --

CHAIRPERSON FROINES: Go through the whole thing and then questions.

DR. PFEIFER: And then if you have some that would be great.

DR. RICE: Hi. I'm Dave Rice from OEHHA. Is that loud enough?

I'm just going to take a couple of minutes here

and present some information regarding the progress we've made, what we need to do and what we're doing right now. And if I could have the next overhead.

--o0o--

DR. RICE: It's pretty straightforward, referring to the list of all the individual discussion papers that you've been provided with in the handout. Of the 27 papers, or 27 different discussion papers listed in that handout, we've completed final drafts on 19 of them, and they're ready for either SRP and/or external review. We have five drafts that are at various stages that have already been presented to the work group. And no revisions are in progress.

And we have three drafts that have yet to be presented to the work group, but they're scheduled to be completed by the first week or first meeting or so in January, I believe.

--o0o--

DR. RICE: On the next overhead it gives you an idea of what we still need to do, and obviously we need to, the first bullet, finish our discussion papers. We need to complete the review of those discussion papers by the Scientific Review Panel and/or external experts. The next bullet we need to, or actually we have already established risk assessment guideline categories for

grouping of the questions that have been developed as a result of the individual papers. And I'll talk about that more on the next overhead, but I don't want to go to it yet.

I will say that, you know, what we've come up with as a process is it's pretty clear that our guidelines are going to be a result of the discussions that come out of these issue questions that are at the end of each paper.

So we wanted to kind of formalize our approach to talking about those particular issues, and so we've established -- we revisited the topics that we have for the individual papers, taking a look at the questions that have come out of the individual papers and reprioritized the various topics based on that information and our needs in terms of risk assessment.

And, again, I'll talk about that a little bit more on the next overhead.

The next bullet we're going to go through those guideline categories after we've plugged in all the issue questions and consolidate those questions and eliminate duplications and set aside any questions that may not be particularly relevant to our needs.

We then also need to formulate the recommendations based on discussion of those issue

questions. We still need to determine really the scope and the format of our actual product is are we going to end up with two documents. One document that's going to be all the discussion papers and another document that's going to be guidelines, you know, being connected with some sort of executive summary or have one big document. We're just not quite sure what the final product is going to look like.

And then, of course, after we get past that, we are going to need to present our guideline recommendations to this panel.

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DR. RICE: The next overhead, which is pretty busy, but I'll try to get through it real quick, is this is just our grouping for the issue questions that have come out of the discussion papers. And we have four main headings, as you can see. We've got the relevance of cholinesterase inhibition to risk assessment. We obviously thought that was a most important question to ask here. Something that has come up out of our discussions is the next major heading and that's the use of human cholinesterase data, since more and more human data is being submitted in the area of pesticides in support of registration.

Our next major topic area is, you know, how are

we going to deal with the LOAEL/NOAEL determination, and the impact of analytical variability, biological variability, biological significance and what kind of uncertainty factors we need to apply.

And the last major grouping is the relationship of cholinesterase inhibition to other endpoints, such as endpoints we see in the functional observational battery, developmental neuro-toxicity, ocular toxicity, immuno-toxicity, endocrine disruption and structure activity relationships, that's really not an endpoint, but we included that there just so we can continue or finish our discussion on the topic.

And that's pretty much all I have. I guess if there are any questions.

CHAIRPERSON FROINES: Thank you. Could we have the lights.

PANEL MEMBER BLANC: So the relationship between the working papers and then this final slide is that multiple group papers would inform the same or overlapping topics.

DR. RICE: Exactly, and vice versa, I guess that's the overlapping part. A given set of issue questions from the paper may plug into different topics as well.

PANEL MEMBER BLANC: Well, just looking at the

outline of the discussion papers, one of the things that may come up as a possible source of unnecessary confusion may be times when you're using cholinesterase as an umbrella term in times when you're using acetylcholinesterase specifically and butrylcholinesterase, so you might want to just go back and make sure that you're consistent in your terminology.

DR. RICE: Certainly.

DR. PFEIFER: Yeah, I think when we use the term cholinesterases, it means all of them, and then we try and be specific. And I know in developing our risk assessments that question has come up. And generally my suggestion in some cases is to clearly define which cholinesterases you're talking about, just so there isn't any misinterpretation.

PANEL MEMBER BLANC: Right. Because, for example, topic 2C.2 Acetylcholinesterase in Neural Development. I assume you would be concerned about neuro target esterase and neuro development also, so that implies you're only looking at cholinesterase and others, and then you talk about acetylcholinesterase in topic 2C.4, when I guess you mean cholinesterases. I mean, you should try to be consistent, because you're going to engender unnecessary confusion, I think. At least when it comes back to us, it may be confusing.

Now, also about that is just in how you've divided things up. For example, Topic 1C, which is Acetylcholinesterase in Different Brain Regions, and then the next one is Cholinesterase Inhibition in Blood and Peripheral Tissues. Is the implication that the peripheral nervous systems is going to be covered in 1D or that the peripheral nervous system is not a different brain region. So it's odd in that constellation that there is not a separate peripheral nervous system paper then or -- do you see what I'm asking?

DR. RICE: Yeah.

DR. PFEIFER: Not entirely on the latter. I'm trying to focus in on the consistency with the terminology.

PANEL MEMBER BLANC: Well, you're dividing up the physiologic significance of cholinesterase inhibition in a broad way. And so you've got one paper that's going to be on the central nervous system, I guess, because when you say the brain, I assume you mean the central nervous system.

DR. PFEIFER: Specifically the brain. And in the blood, I believe, the focus was on acetylcholinesterase, but sometimes its blood measures both butryl --

PANEL MEMBER BLANC: And so where would the peripheral nervous system be?

DR. PFEIFER: Pardon me?

PANEL MEMBER BLANC: Where would the peripheral --

DR. PFEIFER: Oh, the peripheral tissue such as the lung and diaphragm, that's one area.

PANEL MEMBER BLANC: So you're saying that topic 1D would address the peripheral nervous system?

DR. PFEIFER: Well, peripheral tissues, specifically lung, diaphragm, because one of the areas of interest is developing formats methodological for and requiring that for submission for registering a pesticide, and as an indication of peripheral cholinesterase inhibition.

PANEL MEMBER BLANC: Well, I guess what I'm trying to say as you're going to be presenting it to us, there are going to be issues that are going to be classically related to sites of neuro transmission, and then there are going to be cholinesterase effects in ways that are not related to neuro transmission, I suppose.

DR. PFEIFER: Well, that one is related to neuro transmission.

PANEL MEMBER BLANC: However you slice up the pie, there will need to be some clarity for the people receiving these, so that they understand what's included and what isn't and to make sure that everything is

covered.

CHAIRPERSON FROINES: But I think that there's an approach that relates to the science and there's an approach that relates to regulatory demands. I think the generic term is the peripheral nervous system, and I think within that generic concept then there may be specific tissues that have more specific relevance. And it seems to me that it's in that order that one wants to address it. I think that's what Paul is saying.

PANEL MEMBER BLANC: Well, what I can't tell you that topic 1D is what it actually covers. All I'm saying is that here I'm looking at this title of what this working paper is on, and I have no idea what you mean, because I'm coming at it from a different disciplinary point of view.

DR. PFEIFER: Well, quite frankly, when I made this list up, I went back and looked at some of the titles. And I had to kind of clarify them a little bit too, because they weren't that specific from my interpretation, so I understand that.

CHAIRPERSON FROINES: But I think the 1C, when you say, again, the generic term is the central nervous system, the specific term is various brain regions. I think one wants to make sure that the broad title is the starting point and the details come below.

DR. RICE: I would agree. I think we need to go back and look at those, because we do discuss the CNS and the peripheral system in both of these papers or in either one of the appropriate papers. And we need to make sure that we address it completely and, you know, be precise about our title.

PANEL MEMBER BLANC: Because the problem is how will you know that you haven't missed a topic, because one person thinks they're doing it and the other group thinks that the other group is doing it based on --

DR. PFEIFER: There will be some overlap, but we tried to get pretty focused on, you know, this specific one.

PANEL MEMBER BLANC: You know, I'm actually less worried about overlap than I am about something getting not addressed.

DR. PFEIFER: We haven't missed very much, if anything, believe me.

CHAIRPERSON FROINES: But I think that this body is a body of scientists not regulators. And so to the degree that there are specific issues about registration, approval, regulatory considerations, then that needs to be a subset where you're educating the panel about those specifics, because you can't assume that scientists in universities or this panel or in general will necessarily

be knowledgeable about those more --

DR. PFEIFER: I hope I didn't, you know, mislead you on that, when I was talking about this peripheral. No, these papers don't get into, you know, any regulatory or registration type.

PANEL MEMBER BLANC: And then topic 4A Organophosphate Toxicity Heterogeneity in Humans. Conceptually, what is that addressing?

DR. PFEIFER: Variability in the human population.

PANEL MEMBER BLANC: I mean, is it narrowly a genetic variability or are you addressing age variability in responsiveness or --

DR. PFEIFER: I think both.

DR. RICE: As I recall the paper, we addressed just variability in humans as a broad stroke. And any sort of information we could collect on variability, particularly in terms of response, that that's what's included.

PANEL MEMBER BLANC: So it includes both sensitivity and susceptibility?

DR. RICE: Correct.

DR. PFEIFER: And then if you look at Group 8, these two papers are in the category of still being developed and there will be some information there that

will relate back to topic 4 and 4A.

PANEL MEMBER BLANC: Because you already had a question, I guess, about topic 9A, but if you think about looking ahead to see what are the errors in which we have to grapple at this end or are likely to be raising questions on individual chemicals as they come forward, these are the more difficult areas that we face and are likely to be areas of particularly intense concern.

DR. PFEIFER: You mean the human susceptibility and sensitivity?

PANEL MEMBER BLANC: Yes. They're generic. I mean they're not specific -- they're not as specific to this as obviously the issues about what does it mean to measure butrylcholinesterase versus acetylcholinesterase or any of these other questions. But nonetheless, they're quite relevant.

I would encourage you to throw a broad net in that particular evaluation, and look very closely at not just age and genetic factors, but also look at nutritional status and some of the other things that have been areas of concern, particularly in cholinesterase inhibition effects.

Time line to the panel. I mean, when would we be likely to need to be thinking about a workshop or discussion time or agenda time?

DR. PFEIFER: Well, we talked about this briefly this week, and based on the task in front of us, not so much the discussion papers, but discussions on developing recommendations of the guidelines and then having some type of external review, we're probably looking at the second quarter of 2002, probably at the end of the second quarter, so it would be close to June, I would think.

PANEL MEMBER BYUS: Your original time line was now, right. I'm not saying anything.

DR. PFEIFER: Actually, I looked at that.

PANEL MEMBER BYUS: It was a little optimistic.

DR. PFEIFER: No, I looked at that. And the fourth quarter of 2001 I said finish discussion papers, which, you know, we're probably a month behind there. And it said start formulating guidelines. And we've already started doing that, but I think there's, you know, going to be quite a bit of discussion and work ahead.

There are some papers that are quite important to this whole thing that are being revised, so that we can call them a final draft. And I think it's appropriate to, you know, where needed, that they be revised, because in our workgroup there is a lot of open discussion a lot of individual opinions presented about, you know, people's perceptions, concerns and scientific opinions that all, I think, added to the quality of these papers.

So, yeah, you're right, we probably were a little optimistic. But the idea of having, what I would call, experts outside the regulatory community pretty much review these, I think, would add a tremendous amount of credibility to not only the papers, but to the eventual recommendations, because obviously the people are going to take this information and compare what we have come up with directly with what the federal government has come up with and how to apply it.

And that has been, you know, my goal from the beginning to have it as best a footing on science to develop these as possible. And I think, like I said, we had Stephanie Padilla and Barry Wilson and Ginger Moser look at our papers, and I can tell you that their comments were quite favorable, but they were also very pointed in their critique of some of the things that they didn't agree with.

CHAIRPERSON FROINES: I have a number of comments that I'd like to -- some are substantive, some are procedural.

The first thing I think I'd like to ask you to do is, I think, there needs to be a Chapter 1. And Chapter 1 needs to lay out the issues that will be dealt with in the subsequent list of papers and the overall objectives of the exercise in producing these documents. And I'm not

talking about an executive summary.

I'm talking about Chapter 1 should tell the reader, tell the public what are the issues that are going to follow in these, however many, documents there are and that will be addressed and what are the fundamental issues that we are -- why this is going forward?

In other words, to tell the reader in Chapter 1, in essence, the basis, the objectives for everything that is to follow. There needs to be obviously an executive summary produced separately than that. But, I think, at the outset, we need to inform everybody about why are there now 12 to 15 to 19 documents that are going to follow, and what are the very specific issues. And so that's the first point.

I think the last chapter obviously has to be, and I assume that that's what you were going to do, is I'm not -- I don't think I agree that the last chapter is cholinesterase issues, questions for guideline development. I think the last chapter has to be your recommendations for the guidelines.

DR. PFEIFER: That wasn't meant to be the last chapter. That's just in each individual paper, that's the last part that gets extracted out for using the guidelines -- developing the guidelines.

CHAIRPERSON FROINES: So the first chapter tells

everybody what it's all about. The last chapter tells everybody where you've come to. And in between you develop the scientific basis for that, so that they're basically -- this is basically a three-part per exercise as I would look at it. And I think that will help clarify it, because the current first chapter which I've read starts out going through the physiologic consideration of acetylcholinesterase, and then at the end of the document, it gets into various policy issues.

And so you kind of have a little bit of apples and oranges in the first chapter, and I think it's important to be able to make sure that people understand what the procedural policy, scientific questions are that need to be addressed and then get into the actual technical details.

The second thing that I wanted to say is I think that, as far as I'm concerned, obviously this is your process and you can invite external experts all you want to help you as you go forward, and I certainly would support that and encourage it.

I think in the end, I would like to propose a joint effort. And that is in the end, at the end, however, you may have gotten Stephanie Padilla to look at five chapters in the beginning or Barry or whoever, but in the end before the document -- the final draft review, I

think that should be, in essence, a joint effort between the SRP, OEHHA and DPR.

And that what we do is the SRP -- because this is going to help us do the review, and that's what I'm thinking about. I'm trying to think about how are we going to review 20 documents with this small panel. So what I would propose is that at the final draft review stage that we put together a list that comes from this panel, from DPR and from OEHHA.

And out of that list, we develop a final list of external experts who we want to review the document. We send it out and we get their comments back and then you go back and make changes, and then the final document comes forward.

So something like that so we are all participants in defining who the external experts are, because I think that will benefit this panel. And so we'll have confidence that we've come up with a list of names and OEHHA has come up with a list of names and so on and so forth.

DR. PFEIFER: I think that's fine. I mean, that's something I probably wasn't very clear on, but certainly, you know, I think that would be a good idea.

CHAIRPERSON FROINES: The third thing that I'd like to say, and this is not a criticism meant at all, it

is an attempt, on my part, to preserve the energy level of the SRP participants, and to, in a sense -- but more importantly that the role of the panel is to review a document in terms of its adequacy. And I don't know the exact statutory language, but I think we have to be careful to preserve our review function from our being intimately involved in the document development.

In other words, I want to keep Craig Byus from performing a staff function for DPR and OEHHA, because that then makes it harder for him to be an independent reviewer when the document actually comes to us.

He may not agree, but I think that we just have to be careful. We also have to make sure we don't wear him out, by the time -- so when he comes here with the final document, he's able to be an objective thinker about it.

So I would suggest that during the document, when you're going through multiple drafts, and this is -- I mean, I'm just suggesting this. The panel has to decide how it wants to deal with the lead person. That's up to the panel. But I would suggest that the panel not be as deeply involved in the various chapters as one might think, because there may be multiple drafts and what have you, but that the panel more or less reserves itself to the final draft review, so that when we're having these

outside speakers do the review, we also have the leads doing the review at that point.

So that, in a sense, the SRP reviewers are in sync with the external reviewers, and that's a kind of dynamic process. And that's different than say Craig being involved in draft 3 of Section 2B.2.

And so I would say that the SRP leads would play their most important role at the final draft review when also the documents were going out to external reviewers would be my suggestion.

And so I think -- pardon me, I made some notes.

I think that covers it from my standpoint. I think the only other thing that is a matter of concern to me, and this is opening Pandora's Box, and I admit that I'm doing it, is when we have -- when the panel had the OP workshop last year, one of the key questions that we asked that really wasn't dealt with very effectively, and it came at the end of the day, was toxic effects associated with cholinesterase inhibitors, but that are independent of cholinesterase inhibition.

In other words, we have a whole spectrum of effects associated with cholinesterase inhibition, but are these compounds capable of causing toxicity via other mechanisms, even in addition to delayed neuro-toxicity?

And you haven't really got that in here. It

seems to me -- or at least, I missed it. But it seems to me that the sort of other toxic endpoints via other mechanisms is an issue of -- that we shouldn't not address those. Those are my comments.

DR. RICE: Well, with respect to the last comment, we agree completely and we do -- we are attempting to look at any other forums of toxicity for these particular compounds as we're reviewing the literature.

And in the -- I don't know what the best -- in the risk assessment guideline categories for the issue questions, the very last category, to a large degree addresses that, where we look at the relationship of ChE inhibition to other endpoints, and that means in terms of sensitivity.

CHAIRPERSON FROINES: Where am I looking?

DR. RICE: Oh, the very last overhead where we look at things such as ocular toxicity, immuno-toxicity, endocrine disruption, and, you know, the reasons down at the bottom of the list, so far we haven't seen any indication of any of these aspects of toxicity from these compounds to be anymore -- or to be more sensitive than inhibition of the different cholinesterases.

So, in a general sense, we're looking at that.

CHAIRPERSON FROINES: Yeah, be careful, because

you're making a judgment about -- you're doing risk assessment at the same time that you're doing -- by the sentence, by saying if you're considering sensitivity, you're making a judgment call there, I think.

DR. RICE: Right.

CHAIRPERSON FROINES: But I read this -- but this relationship of cholinesterase inhibition to other endpoints, I'm saying it differently. I'm saying relationship of cholinesterase inhibitors to other mechanistic pathways leading to other endpoints.

DR. RICE: Oh, I understand. And that's why I couched that, in terms of -- the risk assessment in terms of sensitivity.

DR. PFEIFER: I mean, obviously, the focus of this work group was on the inhibition of cholinesterase. So the question was are there other -- you can characterize types of systemic toxicity that are or are not related to cholinesterase inhibition. So that was basically the question before the authors. And so they went through the literature and looked at those aspects.

PANEL MEMBER BLANC: Well, perhaps the way of melding these two things together would be in the introductory section that Dr. Froines has alluded to, if you're in agreement with drafting such a section, that it would delineate both the terminology and the potential

mechanistic implications.

Because there are really three things that are embedded in what we're talking about. One would be toxicity related to cholinesterase inhibition at sites other than sites of neuro transmission, that would be inhibition of cholinesterase with effects that the cholinesterases have that are unrelated to neuro transmission.

The second would be inhibition of other enzymatic functions that are not precisely cholinesterases.

And the third would be toxic effects completely independent of enzymatic inhibition that it has a structural, functional relationship to cholinesterase like structures, I guess.

Those are three possible different path ways. And as you get farther away from anything resembling cholinesterase inhibition then there's less and less data, and less and less likely to be broad links, that there may be one acetylcholinesterase inhibitor which on an idiosyncratic basis, tends to be a sensitizer because of a side group, and can't really generalize to other acetylcholinesterase inhibitors, because it's a peculiarity of that particular one for all I know.

So I suppose as you get farther afield, it's less generalizable, where I wouldn't see any reason why this

shouldn't be a general pattern of effects.

Does what I'm saying fit into your -- does that correspond to your, sort of, categorization or one way of categorizing it or is there a space in one of these documents where those issues are delineated?

DR. PFEIFER: I don't know that we're considering looking at how you characterize other enzymatic -- I mean, we're considering looking at the inhibition of cholinesterase certainly as an endpoint. And then we wanted to look at other types of, what I would call, systemic toxicity and see if we could say that was related to cholinesterase inhibition or it was independent of cholinesterase inhibition.

And then the next question would be, are these other endpoints of toxicity as sensitive, more sensitive or less sensitive than the inhibition of cholinesterase for risk assessment purposes?

CHAIRPERSON FROINES: I understand that. I think coming from a toxicologic standpoint, one of the questions I'd be interested in then though is what are the mechanistic considerations that suggest, that underlie other systemic toxicity that might occur separate from cholinesterase inhibition.

DR. PFEIFER: And where known, that is addressed. If it isn't known, then --

DR. RICE: We do address those three areas that you talked about. We don't specifically identify them as such. But as an example, in one of the papers on butrylcholinesterase, there's a discussion of the potential stereo chemical role, if you will, that butrylcholinesterase may have in neurodevelopment, for instance, and/or in nervous system transmission, not an enzymatic role or actually an unknown role.

In the paper on immuno-toxicology, immuno-toxicity of the Cholinesterase inhibitors, there's a very large discussion of the effect of cholinesterase inhibitors inhibiting enzymes important in the immuno response that aren't cholinesterase, but other --

PANEL MEMBER FUCALORO: That are not.

PANEL MEMBER BLANC: Yeah, there are other esterases.

DR. RICE: Other esterases of unknown, you know, function and known function. And so we address those issues as we find out information in each of the topic areas.

DR. PFEIFER: But they are specific to the topic, which is, I think, what you were getting at, and not just other general toxicity.

DR. ALEXEEFF: George Alexeeff with OEHHA, just a point of clarification, now there's two ways one could

approach this overall issue. One is to develop guidelines for cholinesterase inhibitors. In other words, chemicals that cause inhibition, but that may or may not have the sensitive most sensitive health effect or the most important health effect, which is, I think, what you're referring to.

The other is to come up with guidelines on if you're evaluating cholinesterase inhibition, how you actually do that. You know, what would the procedures for evaluating that?

And I think what staff has indicated that they're looking at other endpoints, but at the same time that they're looking at these particular compounds to see how cholinesterase plays out in terms of other endpoints.

But I guess my question comes back with the panel in terms of just your expectations as to what you think this work product will look like, is it your expectation that, okay, if we're taking a particular cholinesterase inhibitor, what will be the guidelines in evaluating it? In other words, how will we look at cholinesterase and how will we make sure that there isn't some other endpoint missed?

That's why it's not clear, when you're bringing up these other endpoints, that by working out other mechanisms, which are important, we might normally do that

in our normal evaluation of any TAC. You know, we'd always like at -- for example, we looked at death and carcinogenicity was the endpoint.

So that's why, I guess, it was not clear and not to try to expand the scope of this series of work products.

CHAIRPERSON FROINES: Well, I think that's a good point. And that's why even when I raised it, I raised it with some hesitation. But I think that clearly there has been some debate and controversy, or however one wants to phrase it, about cholinesterase inhibition in and of itself. So that's a box that we can clearly recognize that we want to address from a risk assessment standpoint, risk assessment methodology standpoint.

But we also don't want to just look for the keys under the light-post either, because people have been looking at OP compounds in terms of cholinesterase inhibition for the last umpteen million years. And so we keep looking at that and should. But the question is, are there other keys out there in the darkness that we're missing, and that's what I think we can't simply avoid, because I think that could lead to an error in --

DR. ALEXEEF: I think that would normally be picked up on a case-by-case evaluation of the compound hopefully. Granted, there may be some overreaching

issues, but that would be pretty hard for us to look at all cholinesterase inhibitors and come up with a list of likely other noncholinesterase things that could also happen in the document, I mean, like this.

But I think that maybe we could somehow in, as we formulate the guidance, be clear that just because something inhibits cholinesterase, that's not necessarily what the ultimate NOAEL development will be based on, because that may not be the most important relevant, sensitive or appropriate endpoint.

DR. PFEIFER: Well, also not all the cholinesterase inhibiting compounds exhibit a lot of these other systemic toxicities, liked delayed neuro-toxicity, ocular toxicity and some of these other points.

PANEL MEMBER BLANC: Well, I mean let's come back to that as a good example. Let's talk about delayed neuro-toxicity in response to your question, George. I think that this panel, whenever organophosphate comes forward, is going to want to know if the appropriate tests were done that had evaluated its potential for delayed neuro-toxicity.

And to the extent that these documents illuminate what is the best way in which one assesses neuro target esterase effects, that is something that we'll be for.

The parallel to that would be if there is a

generalizable structure function effect that cholinesterase inhibitors have on an esterase, which is present in leukocytes and which can be related to antigen presentation. Then we need to know about that so that every time a cholinesterase inhibitor chemical comes forward, we say have the appropriate tests and structure function assays been looked at.

What I think there's less need for and less interest in the panel would be a sort of idiosyncratic miscellaneous effect of a peculiar cholinesterase, which has a very odd side group, which is associated with met hemoglobin emia, but in no way do the data suggest that the class, even a subgroup of acetylcholinesterase compounds, cause met hemoglobenemia. Is that helpful to you?

DR. ALEXEEFF: Yeah, and I think we've tried to address that. You can see how some of the topics are set up. I'm just looking at like 2C.3, Ocular Toxicity Associated with Organophosphate Exposure.

That's not necessarily only cholinesterase mechanism. Maybe it is, I don't know. I don't know the literature. But I'm just saying we could look at ocular toxicity, in general, since that is an effect that occurs and look for things that you're, you know, mentioning that may be there's some other generalized effect that occurs

possibly --

PANEL MEMBER BLANC: But look at 2C.4, acetylcholinesterases and the Immune System. The title of that suggests that the only esterases for which the discussion there would focus on would be acetylcholinesterase and the immune system.

I understand from your oral comments that, in fact, you'd be looking at other enzymatic effects of chemicals which are acetylcholinesterase inhibitors. And comes back to my earlier comment about being sure that the titles of your topics or the subtitles, you should make it clear how you're dividing up the pie, so that we're assured that everything that we want to be covered is being covered.

DR. RICE: We do need to be more precise, because a more appropriate title for that particular paper would be something like effects of cholinesterase inhibitors on the immune system. And that would take into account any effects it may have on other enzymatic processes.

CHAIRPERSON FROINES: I did not understand what you just said.

DR. RICE: What I said was changing the title. Instead of saying acetylcholinesterase is in the immune system, the effect of cholinesterase inhibitors on the immune system would not limit it just to

acetylcholinesterase, nor would it limit to --

CHAIRPERSON FROINES: But the question is the cholinesterase inhibitor operating via noncholinesterase inhibition mechanism may produce immuno-toxicity.

DR. RICE: I understand that.

PANEL MEMBER BLANC: It's not easy. To get the right wording it's not -- it's completely convoluted and laborious, but you can see the problem here.

CHAIRPERSON FROINES: So, for example, for 20 years, I think it's getting 30 years now I've been interested in issues of degeneration, and I've always been a skeptic about neuro target esterase, because I think it's too simple a view of that process.

And so I, in my own personal professional scientific career, have been interested in OP compounds that have some potential or exonil degeneration. And so I continue to have that kind of interest, and I'm not pushing it on you, but it's just an area that I think we don't want to exclude, even though we recognize that we have these key questions around cholinesterase inhibition to answer.

Can I ask -- I want to ask Craig Byus a question, because I propose, basically, that the panel leads play their most dramatic role at the final draft review stage. And, actually, Craig can do as much as he wants in

between. That's clearly up to him as an individual investigator. But are you comfortable?

PANEL MEMBER BYUS: I was going to ask you for that guidance today, in actuality, and what level, how each detail Peter and I should spend during this process?

Let me say I think the process is going along well. I mean, I have all of the chapters. I was much more proactive in the beginning in reviewing these chapters than I have been lately, simply because of the amount of effort and time that it takes.

And I think it's going along well. I think there's a problem -- I see there are several problems. One is this sort of bottom up approach as opposed to a top down approach. We would like to see sort of a global overview and defining of the key issues, and then a working down from the top.

And their approach, this is my own opinion, it's been more from the bottom up, these guys are in the trenches working with this day to day all the time, year after year. And so they have a lot of procedural issues, which have a lot of scientific basis, and so they're looking at it pretty much, sort of, from the bottom up.

I think that's fine. I originally thought top down was better, but as I read these things, I agree there's sort of a dichotomy between what's in the titles

of these chapters and what's actually here, so that there's a lot of editorial work that's going to have to be done ultimately.

But I think the process is ultimately fine. I think that going from the bottom up will ultimately work out, bottom up will work out fine, if somebody at the end does what you suggest with Chapter 1, does a big global overview and really does do the editorial job that's going to need to be done to tie everything together.

And consistency, this was another problem I had. It's great to have all these people doing this, and I really applaud this, because I think it does bring in all of these other viewpoints.

But it makes it more difficult from an editorial consistency point of view to make the kind of document that we would all like to see here, as a university professor and whatever, so that's going to be one of your problems, I think, ultimately. So how you solve that, you know, it's going to be somewhat difficult, but that's what I foresee.

And then the other big thing is the policy issues. I mean, I really think the policy issues, when you have the science here, and it may be spread apart in various places, but really the science is good, the references are good. It's kind of the classic old

pharmacology coupled with toxicology, and a lot of these as you know -- as you said a lot of these issues have not been resolved. Relatively simple things you would think could have been resolved many years ago have not been.

And I think really the key thing is going to be -- one of the key things is going to be the policy, what you have developed as policies, and that's where we need to really -- I don't know whether -- so I would say to you, I agree about allowing them to develop this document as they want and -- but are they going to want our input before they develop the policy, that's where I see maybe we could put some input in --

DR. PFEIFER: Well, our goal --

PANEL MEMBER BYUS: -- before or after. But I mean that is the key thing, because you're going to come back and you're going to say butrylcholinesterase is irrelevant, and it means nothing. Now, that's what you've said in the past. Now, clearly, I would disagree with you with this.

So if that's your policy, that's where we're going to be -- and maybe that is the best time to argue it out, after you have developed the policy and after there is the document with the data here in front us that we can all look at.

DR. PFEIFER: I think our goal is to give you

recommendations, which will be guidelines/policy recommendations, and then --

CHAIRPERSON FROINES: I would like to actually disagree with something Craig just said. I would almost like to avoid the word "policy", because that sounds like something that we should give a call to Paul Helliker and ask him what he wants to do or Winston Hickox, and I don't want to do that.

DR. PFEIFER: This is a guideline.

CHAIRPERSON FROINES: Exactly why I want to stay away from the concept of policy, because what I would like and I think this panel has an obligation to view it this way, is that based on the science comes recommendations for how to approach risk assessment, and then we can debate that.

We may have the head of Cal EPA may decide as a matter of policy to change all that. That's a different issue. I think ours should be based on the review of the science rather than a review of somebody's point of view on this subject.

So I think what we need to do is to have the forest, then we have the trees, and then we have the forest again with what --

(Laughter.)

PANEL MEMBER FUCALORO: This is Chapter one

little chapter zero.

(Laughter.)

PANEL MEMBER BLANC: You're the Lumber Jack?

(Laughter.)

PANEL MEMBER WITSCHI: Well, except it's going to be the second forest after the beavers have gone through it.

(Laughter.)

PANEL MEMBER FUCALORO: That's appropriate, we're talking about pesticide.

CHAIRPERSON FROINES: Well, we can get lost in any one of those three places. As we've seen, we can get lost pretty easily.

I had a question about where -- since I think that toxicokinetics are really quite crucial to cholinesterase inhibitors. Is toxicokinetics incorporated within these sections or is there going to be separate discussion of toxicokinetic issues?

DR. PFEIFER: Well, you have to understand in looking at these papers as well as all the other things I believe that Drs. Kellner and Moore in Topic 1A went through some of the toxicokinetics.

DR. RICE: Dr. Byus disagrees.

PANEL MEMBER BYUS: I'm trying to remember.

CHAIRPERSON FROINES: I read 1A, if that's -- I

wouldn't agree with that.

DR. PFEIFER: I know there is some papers where there's a lot of enzymatic, but I can't recall specifics.

DR. RICE: I can't recall specifically either, but I think it more -- it would tend to be towards the latter and come up on an individual case-by-case basis or topic-by-topic basis and more reflective, not directly in toxicokinetics, but, you know, exposure duration. So it's really not head on addressed as toxicokinetics, per se.

CHAIRPERSON FROINES: It's a major issue.

I would also caution you about the notion of adverse effects. I would be careful to not come in and state something shouldn't be done because it doesn't constitute an adverse effect, because a change may have physiologic implications that may result in adverse effects. And so I think that one needs to look at the issue broadly on that. That issue has come up here before with this panel. Do you know what I mean?

PANEL MEMBER FUCALORO: You mean something may not have a toxicological endpoint that anyone has seen, but one has seen a biochemical change?

CHAIRPERSON FROINES: And those changes may have implications for adverse effects.

PANEL MEMBER FUCALORO: They've not been identified.

CHAIRPERSON FROINES: And maybe adverse effects in and of themselves and we may not just know enough.

PANEL MEMBER FUCALORO: When you said it, I had a sense of deja vu. I guess you've said it before.

CHAIRPERSON FROINES: No, I think Paul's raised it before.

PANEL MEMBER FUCALORO: Well, someone has.

CHAIRPERSON FROINES: Paul.

PANEL MEMBER BLANC: I think that there was one of their sections that was -- at least one of their topics, I think, was trying to get at that which was 4B Evaluating Clinical Signs and Symptoms in Humans versus Animal Studies. I would just point out that it's very difficult to elicit symptoms from an animal.

DR. PFEIFER: We understand that.

PANEL MEMBER BLANC: You may want to think about how you word that as well. But I imagine that that was part -- that's driving that section to some extent, I suppose.

What John was just alluding to in terms of what is the clinical correlation of a biochemical abnormality perhaps, I don't know.

PANEL MEMBER BYUS: Again, I would like, John, some clarification on what you would like Peter and I to do with this document, because I was going to ask you this

and I appreciate you're input.

I mean do you want us to review it for the science, particularly? Do you want us to review it -- I mean, clearly that is the main point, but how editorial,I guess, is the best word to use, do you want us to be or should we be?

CHAIRPERSON FROINES: My concern is that I want -- I need to reserve your independent evaluation of their document. That's what we are required in a statutory context, that we need to tell them whether we think it's good or not, and that to over simplify it. And to a degree that we begin to become -- play a staff role and really work out the details of a document, I think we begin to have -- it becomes more difficult to have an independent evaluative position with respect to the document.

So I would -- but at the same time, we've also seen the lead as helping to facilitate the process. But I think that one has to be a little careful about that so that one doesn't get so deeply involved that you lose one's independent function. So I would basically leave it up to you and Pete's discretion, but I would suggest that the most important place of review will be at the final draft review. Although, I think one can give suggestions along the way.

PANEL MEMBER FUCALORO: Especially, if they sense things are going in the wrong direction, we certainly don't want at the end their to be major changes. But if they believe that there are problems, really significant problems early on, I think it's important that they get that information to the authors.

PANEL MEMBER WITSCHI: You know, I really would like to side with you and see what you said. If memory serves correctly, the whole thing started with a very simple question. This was one of the risk assessments, some data on cholinesterase inhibition and I've forgotten what species were not considered to be other elements.

And the panel asked why not? And the answer was, well, the EPA doesn't do it either or something along those lines and this really triggered the whole workshop and the whole symposium and the process.

And so clearly the panel eventually has to agree with the conclusions which are being drawn from the science. And I'm perfectly happy to draw some conclusions from the science. I would be very uncomfortable to go into all the detail, whether all the science is there or not, because that's not my field of expertise.

But what I really would like to see eventually is a document, that I have from -- I've seen so far, is going to be a very good document.

But what I really want to see is a document which spells out the issues, and you've come to some conclusions and then our task is whether we can agree with those conclusions.

CHAIRPERSON FROINES: I agree. I think it's -- I've said it twice, I don't want to repeat myself, but it's important to preserve the independent evaluation of the panel. It's also important to preserve the energy level of the panel and both those things are significant, especially given the fact the we had four and today is the fifth meeting on SB 25, so people have been really dragged through the mud in a sense in that effort.

PANEL MEMBER BLANC: Or drive through the forests.

(Laughter.)

CHAIRPERSON FROINES: I'm not doing to well at metaphors today.

And I'm assuming that since Paul Gosselin or Keith haven't stood up and started to scream that this notion of having a joint effort with OEHHA and DPR and ourselves to find some of the external experts, so we can all feel comfortable with that, is --

DR. PFEIFER: That's perfectly acceptable. I mean, we're formulating a list based on people we know professionally in this field. But there are others that

you may not know of who -- and the other question that's come up, do we want to have each outside expert review every paper or let them pick papers or, you know, that's another question that I think we need to address.

CHAIRPERSON FROINES: Well, I would -- well, that's not -- this is something we'll have to work on together, because it's not a trivial issue, because on the one hand you might say well, we would pick people based on their expertise and who would be best at looking at a particular issue. That's the easiest answer.

But at UCLA we have a Department of Pharmacology with some people who have spent their lives on acetylcholinesterase. And that they are not necessarily toxicologists, but who they have such an incredible depth of science, that they could look at the science without necessarily knowing all the toxicology and look at your document and give vital input to it. So that it seems to me that who you actually ask to do the review is a creative undertaking.

So I think the answer to the question is yes, meaning, you know, it's to be worked out. It's an ongoing process.

PANEL MEMBER WITSCHI: I would like to call your attention to something that you probably don't know, because it's very exotic. And this is in certain

aircraft, there are once in awhile leaks of hydraulic fluid or engine oil into the cabin. And some of those contain organophospherous compounds in trace amounts, but there is some concern out there among pilots and flight attendants that this might represent a toxic hazard.

DR. PFEIFER: I would agree with that. And there's also, as most of you may know, on international flights going to like New Zealand, Australia and Jamaica, they routinely either preboard or actually while the plane is in flight, fumigate.

PANEL MEMBER WITSCHI: But those are the lights they use. These are not organophospherous compounds.

DR. PFEIFER: Oh, well, that's true. I don't know. I really would kind of take exception to being dosed while I'm going on vacation.

(Laughter.)

PANEL MEMBER FUCALORO: They have a sprinkler system with malathion.

CHAIRPERSON FROINES: Well, see that's what the Government has in mind when they started thinking about this new way of doing human experiments. They're going to use people on airlines as the study population.

CHAIRPERSON FROINES: Thank you very much. I think we're finished for the moment, unless somebody else on the panel has further comments?

And it's obviously an ongoing effort.

Congratulations.

DR. PFEIFER: George had a question.

DR. ALEXEEFF: I'll just ask my question. It sounded like the way you -- because David had asked -- talked about the structure of the documents. It sound like the panel, basically in the end, wanted one document as opposed to one document with the science, another document discussing the implications of the science, the guidelines, it sounded like you wanted it more integrated.

PANEL MEMBER BLANC: Yes.

CHAIRPERSON FROINES: It's quite an undertaking. Congratulations so far.

DR. PFEIFER: Thank you.

CHAIRPERSON FROINES: So we have a little bit of time left. Maybe Andy can come back. But before Andy comes back, I wanted to raise a question that hopefully Peter -- Peter Witschi. Clearly, the situation has changed since September 11th. Airlines have cut back flights. There are significant security concerns. And the panel had some difficulty, because there are three people who are coming from Ontario, and United -- there are no current nonstop flights from Ontario to San Francisco anymore, strange as that may seem.

And so Craig and Roger and Tony had to go to

Oakland and take a cab across. And so that -- and when they arrived, they were in less than a good mood, to say the least.

And so the question for the panel is what shall we do about location of meetings and travel, as we start planning for next year?

PANEL MEMBER WITSCHI: Well, first of all, if those guys are unhappy sitting in a cab across the bridge, I'd encourage them to drive themselves.

PANEL MEMBER FRIEDMAN: That's even worse.

May I suggest that if we meet in the bay area -- when we meet in the bay area, that we meet in Oakland, that would make their life a lot simpler and it's not that hard for us to get over at least not for me.

CHAIRPERSON FROINES: Well, Gary, it's interesting you say that, because I personally agree with you, I like going into Oakland, but the one member who's missing is Stan Glantz who hates the idea of having to go to Oakland. So there's no unanimity. I don't what Paul's position on this.

PANEL MEMBER FUCALORO: Is it because he's a snob?

(Laughter.)

PANEL MEMBER BLANC: Well, I don't think that there's any difference for -- any major difference between

if we're having a meeting, you know, at this location and having a meeting at the Oakland Hyatt or whatever it is. I think there have been times where we've had meetings at UCSF itself, and those have been for logistical reasons that would make it as hard to get here as to get to Oakland, but those have been the exceptions rather than rules.

But there have been one or two times meetings, because neither Stan or I -- there was no way to come otherwise because we had to be -- and you know we were only there for part of the meeting.

CHAIRPERSON FROINES: Jim should join us, I think.

But if we are in a situation like today, there wouldn't have been any substantive difference for me to go to Oakland or San Jose, if that would help and have people fly in and out of San Jose.

CHAIRPERSON FROINES: But you're coming from Davis, right?

PANEL MEMBER FRIEDMAN: I live up north and so it would be difficult, very difficult.

PANEL MEMBER FUCALORO: San Jose is tough. Oakland is --

PANEL MEMBER WITSCHI: What about Sacramento?

PANEL MEMBER BLANC: Yeah, Sacramento is a looser

for everybody.

PANEL MEMBER BYUS: Sacramento is another easy one for us to fly in.

PANEL MEMBER BLANC: No, Sacramento is basically your -- I mean, that's like two hours each way for -- I'd rather go to Ontario than go to Sacramento.

PANEL MEMBER FUCALORO: Is that right?

CHAIRPERSON FROINES: You would?

PANEL MEMBER FRIEDMAN: It's a long drive.

CHAIRPERSON FROINES: You can fly to Sacramento.

PANEL MEMBER WITSCHI: You can take the train.

(Laughter.)

CHAIRPERSON FROINES: I have done it a number of times.

PANEL MEMBER WITSCHI: You can take the train. It's not bad, the train, actually.

PANEL MEMBER BLANC: I can drive to San Luis Obispo and take the train to LA, too.

CHAIRPERSON FROINES: Now, the fact of the matter is --

PANEL MEMBER FUCALORO: Oakland is the best.

CHAIRPERSON FROINES: Let me suggest something that Paul may be forgetting, which is if Roger and Tony and Craig couldn't get a nonstop flight from Ontario, that probably means they can't get a nonstop flight to Ontario.

So when you say you'd just as soon go to Ontario, you're not going to have a nonstop flight.

PANEL MEMBER BLANC: I can't get to Ontario and back in the same day anyway, by and large. So I always went down the evening before, if it was Ontario and then just flew back.

But I mean the last time I looked at it -- from here, I think that was the difference, in fact, is that the first flight up --

PANEL MEMBER ATKINSON: There are no flights, period.

PANEL MEMBER BLANC: No, but I'm saying in the old days where there was a flight to San Francisco, there was still never a flight early enough from San Francisco to Ontario to go in the same day. And so whereas to LA --

CHAIRPERSON FROINES: So not to prolong this, so what -- we clearly have a vote for Oakland is one option.

PANEL MEMBER BLANC: Then there's the more generic thing, which is that there has been a traditional commitment to alternate meetings between southern California and northern California, not every other meeting -- I mean, we've been doing it like -- we were doing it two up here, one down there.

It seems like we sort of strayed into four up here and one down there, instead of two up here and one

down there.

PANEL MEMBER FUCALORO: We noticed.

PANEL MEMBER BLANC: So I think that it's certainly time for us to have a meeting in southern California.

CHAIRPERSON FROINES: I think we should also consider --

PANEL MEMBER BLANC: That would certainly make their lives a lot easier.

CHAIRPERSON FROINES: -- trying to find a place at USC perhaps at the medical school or someplace in that vicinity, because then the people from Riverside can come a distance, and the people from the westside, like me, can come from a distance. But we should also clearly have meetings over in the Riverside area as well.

PANEL MEMBER FUCALORO: Speaking of lights, it is not quite a flight of fancy, but what is the legal constraints or requirements regarding being physically in the same room. I'm thinking of teleconferencing. Is that completely off the wall or is it something we could actually consider?

CHAIRPERSON FROINES: I don't know what the legal constraints are. I don't think it's as good a way of communicating as one --

PANEL MEMBER FUCALORO: It's not.

CHAIRPERSON FROINES: But if we could look at it as an option -- I mean, we need to -- I think what we would need to do would be to check into our various institutions about the facilities that are --

PANEL MEMBER FUCALORO: I believe I have the facilities. I think you guys do too, right?

PANEL MEMBER BLANC: UCSF certainly doesn't, not even remotely.

PANEL MEMBER BYUS: There's new Internet teleconferencing procedures now that are much more inexpensive that you can actually do on your own computer in your own office. I mean, it might be something to look into. I mean for certain issues, I mean, for example, like reviewing the findings today to meet a deadline. It seems we're always having meetings to just review, to get the findings out in a timely manner.

PANEL MEMBER FUCALORO: It seems to me the legal --

PANEL MEMBER BYUS: That would be easy to do over teleconferencing. You know, when an issue came up where we didn't have to have a full meeting and fly everybody all over to do something. I don't know about the legality though.

PANEL MEMBER FUCALORO: The public has to somehow be able to plug in, so to speak, I mean put a television

here or something.

CHAIRPERSON FROINES: So from what I here in this meeting, Peter is in Sacramento, so there's some advantages to him to stay and go to a meeting in Sacramento. Some people said Sacramento is okay. Paul doesn't care for it.

But what I'm hearing is that for the next few months, we should be planning meetings in southern California, to try to --

PANEL MEMBER FUCALORO: Well, I understand the next two meetings --

CHAIRPERSON FROINES: -- to balance things out. Oakland is an option, and that's probably all we have to really decide at this particular moment.

PANEL MEMBER FRIEDMAN: Can I just pursue this a little. Was the problem with the cab ride the Bay Bridge traffic tie up? Is that why it was a problem to get over here this morning, why you guys were in a bad mood?

(Laughter.)

PANEL MEMBER FUCALORO: Listen, the meeting was at 10:00, right? We've been up for six hours by the time the meeting started.

PANEL MEMBER FRIEDMAN: Oh, okay.

PANEL MEMBER FUCALORO: And there was no bad traffic between Oakland and here. In fact, the traffic

was beautiful.

PANEL MEMBER FRIEDMAN: I was going to suggest that BART was an alternative, because it picks you up at the Oakland Airport, but that's not the problem. But when we go to southern California, we often stay overnight, why can't the same thing happen when people come up here?

PANEL MEMBER FUCALORO: That's a point. I'm an honest man, I concede that that's a point.

CHAIRPERSON FROINES: I think we've gone as far as we're going to go on this particular topic.

So it's only 1:25. Andy, do you want to try and finish out?

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Can we take a five minute break?

CHAIRPERSON FROINES: If we can bring this as close to closure, I think we will have done a good job.

(Thereupon a brief recess was taken.)

CHAIRPERSON FROINES: Everybody should note that we are not going to vote on these chemicals today, because we're going to try and get as far along as possible. And one of the chemicals, carbon disulfide was not noticed, so we couldn't take a vote anyway on carbon disulfide. So we will finish this off and take a vote on a later date.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Okay. So the next chemical that I'm going to

talk about is the methylene dianiline. The panel reviewed the derivation in March and there's a couple of changes we've made in response to comments by the panel. We more accurately described the disease seen in humans and we also made a point of mentioning the carcinogenicity. We've adopted this as a principle now that when a material, which is up for review for a chronic noncancer REL, is also, in fact, a carcinogen on the hot spots universe, that we should mention that in the REL summary.

We looked for evidence of any differential effects on infants and children and basically found nothing that gave us any indication.

So the endpoint is retinal toxicity. I mean, it was a possibility that this would have a differential effect, I suppose, since it's somewhat neurologically related. But we don't really, I think, know enough even about the mechanism to do anything other than speculate at this point, so we have to stay with the defaults.

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AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: The next one I want to present --

PANEL MEMBER BLANC: Can you just take note that you need to correct your footer in the process.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: I'm sorry about that. Unfortunately, the wrong

section break got deleted when we were in the process of -- thank you for pointing that out. I'm sorry. That is a typographical error, and hopefully we will be presenting phosphine in due course with a proper footer.

Selenium, again, this was one which the panel has looked at previously. The complexity here is that we are doing a root to root extrapolation. The critical effect is the induction of symptoms of selenium and excess in humans in dietary studies and epidemiological studies in, I think, China.

And the concern was that it's possible to inhale enough selenium possibly to induce similar symptoms by this root. So what we have done is calculated an overall intake based on the oral root using similar methodology to the U.S. EPA's reference dose.

And then we have made a number of assumptions in the root to root extrapolation, which we have clarified in response to discussion at the last meeting.

The other thing we've done is looked at the potential implications for children's health. And in this case, the key study being basically environmental epidemiological study does, in fact, include children as young as one year old. There is also in the database on the compound, a developmental study in hamsters. And so we do have some reasonable basis in this case perhaps

uniquely for feeling that the chronic REL should be protective of infants and children.

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PANEL MEMBER FUCALORO: And, of course, the inhalation REL is 20 micrograms of selenium itself,

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Yes, to the compounds, then the actual gravimetric amount would be adjusted to --

PANEL MEMBER FUCALORO: Grams of selenium?

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Yes. That refers to selenium.

PANEL MEMBER ATKINSON: On the next page, I think you should leave back in the vapor pressure of elemental selenium, ten to the minus three. It's a rather important number, because it means it's going to be at least partially in the gas phase in the atmosphere.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: So we should not have deleted that.

PANEL MEMBER ATKINSON: So leave the one at 20 degree C and don't leave the one at 356, but leave the selenium at zero.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Okay.

CHAIRPERSON FROINES: Roger, what page are you on?

PANEL MEMBER BLANC: The very first page.

PANEL MEMBER FUCALORO: A92.

PANEL MEMBER ATKINSON: And on A93, the first sentence after, "Effects of human exposures," I think it would be wise to delete the word "gas" after CO2. It can't be a gas. It's got to be present in the particulate phase.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Yes. Okay.

PANEL MEMBER ATKINSON: I'll just throw another one at you. You didn't make any consideration of dimethylene selenide, which is volatilized bacterial or microbial degradation of sulfur that leads to dimethyl selenide. I don't know whether I'm really being facetious or not, but it's probably present in the atmosphere in some places.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Yes, we're not -- I don't think we have any evidence of it being an issue for the hot spots program, but it's probably something that we should just check because these things do have a habit of appearing in strange places.

I mean, maybe we could ask whether anybody has got a hot spots measurement on that near a sewage works or something.

PANEL MEMBER ATKINSON: Well, the other place would be if you're trying to bioremediate high levels of selenium, you'll end up with dimethyl selenide.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: I'm not aware we have such a situation. We'll check into that.

The next one that we're going to talk about is sulfuric acid. And the panel reviewed this in some detail back in March. And the issue here is how do we accommodate the children's health impacts. The derivation that we proposed for the REL has not changed.

However, there's extensive epidemiological work, which interalia was reviewed by the air quality advisory committee, the corresponding panel for the criteria pollutants when they were looking at the criteria pollutants for SB 25.

And they actually have reviewed a number of epidemiological studies. It appears that the critical exposure, which results in exacerbation of asthma in children, is generally described as sulfate aerosol. But an important component of that response appears to be generic to acid aerosols of which obviously sulfate is a large component in some situations where exposure to the criteria pollutants is occurring.

But anyway, we felt that in view of this

important impact on children's health from sulfate aerosols that we should review that evidence in relation to our proposed chronic REL for sulfuric acid.

And one of the problems with the epidemiological data is that it doesn't show a clear threshold for that response. It sort of goes down, more or less, linearly about to a level at which the effects disappears due to sensitivity of the study as much as anything else.

But if there is -- the statement from the papers and from the reviewers is that if there is a threshold, it's probably something around two micrograms per meter cubed. This is the general consensus as to where the effects start.

And if taking that into account and taking into account that we believe that the asthmatic children, the most sensitive subpopulation that we're likely to have to deal with in a hot spots situation, we feel that this chronic REL, which was proposed on the basis of the animal studies in nonhuman primates, the proposed REL of one microgram per meter cubed is adequate in that it is sufficient, just about, to protect asthmatic children.

And because they are a highly sensitive subpopulation, we wouldn't expect to have a large safety margin, but we feel that this is probably a case where the proposed REL is appropriate.

PANEL MEMBER FUCALORO: You've mentioned this and I just want -- it bears repeating it, at least to me, is that you expect all atmospheric sulfuric acid pretty much to be in aerosol form.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Yes.

PANEL MEMBER FUCALORO: You don't expect it into a gas form?

PANEL MEMBER ATKINSON: No.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Not by the time --

PANEL MEMBER FUCALORO: Low pressure.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Certainly not by the time it makes it over the fence, and into the --

PANEL MEMBER FUCALORO: Yeah.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: One of the reasons why I wanted, you know, to discuss this particular one with you and, you know, may be get a little bit of feedback, is that we're looking at the same database.

And at our proposed REL for nitric acid, which as I mentioned earlier, we're not bringing forward as a proposal at this point, and thinking that well, you know, it's an acid which is probably going to be turning up in

aerosol form in the environment, as a result emissions of nitric acid are indeed in nitrogen oxides from hot spots sources.

And we would basically anticipate that the same kind of constraints on what would be an acceptable exposure for children that we've identified for the sulfuric acid aerosols, is probably going to be -- it would probably be reasonable to assume that we should regard that as a limit for nitric acid aerosols, as well. And in the case of the nitric acid proposal, partly because, frankly, I think it's based on some older and less exhaustive animal studies in terms of the critical study.

That the nitric acid, the level we had originally put forward in the draft would not be protective of asthmatic children. So this is the reason why we pulled this one back. And what we're thinking is that we need to take account of this data on acid aerosols in relation to the nitric acid.

PANEL MEMBER ATKINSON: Nitric acid can be present in the gas phase quite easily. It's got a fairly high vapor pressure. So unless there is something to neutralize it, like ammonia, it will be present in the atmosphere in the gas phase.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

SALMON: Well, I think this is a further reason why we need to spend more time thinking about nitric acid.

But as a starting point, we feel we ought to look at the impact of acid aerosols as possibly a constraint on what would be acceptable as a chronic REL for nitric acid.

PANEL MEMBER ATKINSON: You just used the words acid aerosol and nitric acid won't be present in on -- May not be present.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Depending on the nature of the emission.

PANEL MEMBER ATKINSON: Or on the other components in the atmosphere.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Yes. That's something that we should perhaps consult with the Air Board as to exactly what's likely to be out there.

PANEL MEMBER BLANC: This may have come up the last time we discussed sulfuric acid, but the compound was involved in a couple of big releases in the east bay, which was a trisulfuric acid --

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: The olium.

PANEL MEMBER BLANC: Yes, olium breaks down to sulfuric acid?

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF

SALMON: I think basically, by the time, it's been out in the atmosphere and had a chance to react with a certain amount of ambient moisture, it's reasonable to regard it as being primarily the same as a sulfuric acid aerosol.

PANEL MEMBER BLANC: So in your major uses and sources, given the historical importance of these olium releases, do you think you should have a sentence there about olium breakdown.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Yes we will add that.

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AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: And then the next item the --

PANEL MEMBER BLANC: One other question, I'm sorry. Is there any release of sulfuric acid in natural volcanic or thermal sources?

PANEL MEMBER ATKINSON: Yeah, it's released from volcanoes.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Volcanoes, certainly. I think the biggest problem that I'm aware of from the sort of the geothermal type of sources is, in fact, hydrogen sulfide to reduce rather than to oxidize is safe. But certainly I think there are plenty of circumstances when sulfur oxides release from volcanic sources. The general ambient levels

of sulfur pollutants in California from both natural and anthropogenic sources is fairly low.

I mean, in the criteria pollutant universe, sulfur oxides are a large problem on the east coast due to particulate.

PANEL MEMBER BLANC: Sulfur containing coal burning.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Sulfur containing coal into a somewhat lesser containing fuel oil. Whereas, California has a habit of using relatively low sulfur oil for diesel and fuel.

PANEL MEMBER ATKINSON: It might be good to add a sentence or two right at the first page stating that any sulfur oxides emitted into the atmosphere will end up converted in that gas phase or through rain or cloud drops into the sulfuric acid.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Yes.

PANEL MEMBER BLANC: Well, because Mount Lassen was, but not extinct actually.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Clear, there's a possibility for episodic excursions. It's not on a very large scale. I don't know that we can regulate against them.

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AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Vinyl Acetate. This one was one in which the panel hasn't looked at in detail in March. And so this is -- here it is.

The proposed REL is based on historical legions of the nasal epithelium in rats, a long-term inhalation study. There's an observed LOAEL end and an observed NOAEL.

And we have calculated on this basis a proposed REL of 50 parts per billion. And a fairly high quality study in terms of the source data and not having to apply too many uncertainty factors. And the human equivalents concentration includes the RGDR calculations. And so the additional intraspecies factors on top of that is three.

And we have included an intraspecies uncertainty factor of ten for human diversity.

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AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: The chronic REL here basically doesn't have any very noticeable allowance for children's health. I think the statement which we have in the summary is -- well, we have this usual problem that we've got a somewhat irritant related sort of endpoint, but no data on children.

But on the other hand, at least here we do have a comparison REL, which is on a developmental study. So we

have a safety margin relative to that in the proposed REL.

And we are, for want of better information, relying on the uncertainty factors, both of intraspecies extrapolation and for the human intraspecies uncertainty factor to species to conclude that the proposed chronic REL would be sufficiently protective of children's health.

PANEL MEMBER BLANC: And the reason that you couldn't use a benchmark approach was because the -- or was it just too steep?

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: Basically. Basically, it's too steep a dose response to get a very clear analysis. The other problem is just the way the data reported.

We have, at this point, a little bit of a problem converting the -- this table where it's reported as very slight, slight moderate, and severe, and then, you know, the incidents of those different levels. That's a little bit complicated to --

PANEL MEMBER BLANC: Translate.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: -- to actually translate into something where our standard use of the benchmark doses software we expect a single parameter input. Maybe this is something where we need to, you know, think about how perhaps we could tackle that in the future as a method development issue, but we

don't really have the technology to do that well at this point.

CHAIRPERSON FROINES: Given where we are, there's nothing to preclude the panel from adopting the chronic RELs that you've presented today with the exception of carbon disulfide. So that unless there are major objections, it seems to me that we would cut down having to take up the issue again for these compounds at a later meeting if we did go ahead and vote. So what's the motion?

PANEL MEMBER BLANC: The motion is bearing in mind -- no, that's too wordy. Taking into account the changes agreed to in the draft document, the panel approves the specific chemicals presented, with the exception of carbon disulfide.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: So it's the batch 2B chemicals that this motion refers to, not the batch 2A chemicals?

PANEL MEMBER FUCALORO: Right.

CHAIRPERSON FROINES: Is there a problem, George?

DR. ALEXEEFF: No. I just thought you might want to list the chemicals.

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: It's shown on the slide.

DR. ALEXEEFF: And for the record, these Batch 2B

chemicals are acrylonitrile, beryllium, and compounds chloropicrin, diethanolamine, ethylene dibromide, isophorone, maleic anhydride, methyl isocyanate, 4,4-methylene dianiline, selenium and compounds other than hydrogen selenide, sulfuric acid and vinyl acetate.

PANEL MEMBER FUCALORO: Is there a second for that?

CHAIRPERSON FROINES: Are you seconding?

Discussion?

All those in favor?

(Hands raised)

CHAIRPERSON FROINES: Vote is unanimous. The resolution is approved.

I should say that I think that vinyl acetate is more likely to exert its toxicity through acid aldehyde, but you guys don't agree with that. But I think vinyl acetate is more probable, is more benign.

So, Andy, you have one more slide, which is where do we go from here. And if you can do it in five minutes, we can --

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: I trust I can do it considerably faster than that.

So I'm just making sure I've got the right one. Okay, so the next steps for the chronic RELs. Well, we

have completed 2B, but we still have the 2A compound which we will bring -- we will notice and bring to your attention at the next meeting for appropriate, further instruction and or resolution.

We now have batched three. We have a second draft, which has yet to go through the public comment process. So we will be releasing the second draft for the period of notice and public comment, and also, of course, sending it to the panel in due course.

When we send it to the panel, we will include the public comments and the response -- our response to those comments.

And then the panel will, I assume, want to review the Batch three chemicals in groups of not more than about 15 or 20 at a time.

It may be that the batches are a little smaller than that, because there are some materials in batch 3 which, quite frankly, I don't think we're going to propose a REL for, because there is our further investigation that identified an either no-use in California or no-significant hot spots toxicity issues.

So I think for those things for which there is absolutely no use in California identified, I think we will probably not be bothering you with those ones. But there are, in fact, a couple of interesting chemicals in

there as well, so I hope it won't be too distressingly boring.

PANEL MEMBER BLANC: Thank you.

CHAIRPERSON FROINES: Thank you. Do we have a list of these chemicals, at this point, because we'll need to assign them?

AIR TOXICOLOGY AND RISK ASSESSMENT UNIT CHIEF SALMON: I will Email you a list -- the list which, you know, is potentially out there is the same as the first public comment draft list of things remaining. But as I say, we need to actually go through the list and review some of them before we have it absolutely finalized.

So what I can do is I can Email you the list as soon as we have it, which should be fairly soon.

CHAIRPERSON FROINES: So Email me the list and I'll take a resolution to close the meeting, before people walk out of the room.

PANEL MEMBER FUCALORO: Second.

CHAIRPERSON FROINES: We need to vote.

PANEL MEMBER BLANC: All in favor?

(Ayes.).

CHAIRPERSON FROINES: Congratulations, we did the entire agenda, and we're early.

(Thereupon the California Air Resources Board, Scientific Review Panel was adjourned at 2:00 p.m.)

CERTIFICATE OF REPORTER

I, JAMES F. PETERS, a Certified Shorthand Reporter of the State of California, and Registered Professional Reporter, do hereby certify:

That I am a disinterested person herein; that the foregoing Scientific Review Panel meeting was reported in shorthand by me, James F. Peters, a Certified Shorthand Reporter of the State of California, and thereafter transcribed into typewriting.

I further certify that I am not of counsel or attorney for any of the parties to said meeting nor in any way interested in the outcome of said meeting.

IN WITNESS WHEREOF, I have hereunto set my hand this 13th day of December, 2001.

JAMES F. PETERS, CSR, RPR
Certified Shorthand Reporter
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