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

CHRONIC TOXICITY SUMMARY

ACRYLONITRILE

(Acrylonitrile monomer, cyanoethylene, propenenitrile, 2-propenenitrile, VCN, vinyl cyanide.)

CAS Number: 107-13-1

I. Chronic Toxicity Summary

Inhalation reference exposure level	**5 µg/m^3** (2 ppb)
Critical effect(s)	Degeneration and inflammation of nasal epithelium in rats
Hazard index target(s)	Respiratory system

II. Chemical Property Summary (HSDB, 1994)

Description	Clear, colorless to pale yellow liquid (technical grades)
Molecular formula	C_3H_3N
Molecular weight	53.1 g/mol
Density	0.81 g/cm^3 @ 25^{o}C
Boiling point	77.3^{o}C
Melting point	–82^{o}C
Vapor pressure	100 torr @ 23^{o}C
Solubility	Soluble in isopropanol, ethanol, ether, acetone, and benzene
Conversion factor	1 ppm = 2.17 mg/m^3 @ 25 ^{o}C

III. Major Uses or Sources

Acrylonitrile is produced commercially by propylene ammoxidation, in which propylene, ammonia, and air are reacted by catalyst in a fluidized bed. Acrylonitrile is used primarily as a co-monomer in the production of acrylic and modacrylic fibers. Uses include the production of plastics, surface coatings, nitrile elastomers, barrier resins, and adhesives. It is also a chemical intermediate in the synthesis of various antioxidants, pharmaceuticals, dyes, and surface-active agents. Formerly, acrylonitrile was used as a fumigant for food commodities, flour milling, and bakery food processing equipment (HSDB, 1994). The annual statewide industrial emissions from facilities reporting under the Air Toxics Hot Spots Act in California based on the most recent inventory were estimated to be 3948 pounds of acrylonitrile (CARB, 2000). US EPA (1993) reported a mean ambient air concentration of acrylonitrile at four urban locations in the U.S.of 0.66 µg/m^3.

IV. Effects of Human Exposure

Many occupational epidemiology studies have investigated retrospectively the morbidity and mortality of acrylonitrile exposed workers. An increased incidence of lung cancer was associated with acrylonitrile exposure. No significant excess mortality has been observed for any noncarcinogenic endpoint. One early cross-sectional study (Wilson *et al.*, 1948) observed multiple deleterious effects in synthetic rubber manufacturing workers acutely exposed (20 to 45 minutes) to various concentrations of acrylonitrile (16 to 100 ppm, 34.7 to 217 mg/m^3). Mucous membrane irritation, headaches, feelings of apprehension, and nervous irritability were observed in the majority of workers. Other less common symptoms observed included low-grade anemia, leukocytosis, and mild jaundice. These effects were reported to subside with cessation of exposure. Human volunteers exposed for a single 8 hour period to acrylonitrile vapors exhibited no deleterious CNS effects at concentrations ranging from 5.4 to 10.9 mg/m^3 (2.4 to 5.0 ppm) (Jakubowski *et al.*, 1987).

A cross-sectional study (Sakurai *et al.*, 1978) found no statistically significant increases in adverse health effects in chronically exposed workers (minimum 5 years) employed at 6 acrylic fiber factories (n = 102 exposed, n = 62 matched controls). Mean acrylonitrile levels ranged from 0.1 to 4.2 ppm (0.2 to 9.1 mg/m^3) as determined by personal sampling. Although not statistically significant, slight increases in reddening of the conjunctiva and pharynx were seen in workers from the plant with the highest mean levels (4.2 ppm arithmetic mean). However, this study has limitations, including small sample size and examiner bias, since the medical examiner was not blind to exposure status. The time-weighted average exposure of the group occupationally exposed to 4.2 ppm (9.1 mg/m^3) acrylonitrile can be calculated as: TWA = 9.1 mg/m^3 x (10/20) m^3/day x 5 days/7 days = 3 mg/m^3. This level is comparable to the LOAEL (HEC) of 2 mg/m^3 derived by the U.S. EPA from the animal study of Quast *et al.* (1980).

Czeizel *et al.* (1999) studied congenital abnormalities in 46,326 infants born between 1980 and 1996 to mothers living within a 25 km radius of an acrylonitrile factory in Nyergesujfalu, Hungary. Ascertainment of cases with congenital abnormalities was based on the Hungarian Congenital Abnormality Registry plus review of pediatric, pathology and cytogenetic records. Particular attention was paid to indicators of germinal mutations (sentinel anomalies, Down's syndrome, and unidentified multiple congenital abnormalities) and to indicators of teratogens (specific pattern of multiple congenital abnormalities). Three congenital abnormalities: pectus excavatum in Tata, 1990-1992 (OR = 78.5, 95%CI = 8.4-729.6), undescended testis in Nyergesujfalu between 1980 and 1983 (8.6, 1.4-54.3) and in Esztergom, 1981-1982 (4. 2, 1.3-13.5) and clubfoot in Tata, 1980-1981 (5.5, 1.5-20.3) showed significant time-space clusters in the study area. The risk of undescended testis decreased with increasing distance from the factory. An unusual increase for the combination of oral cleft and cardiac septal defects was seen in multimalformed babies in Tatabanya in 1990. Unfortunately there were no data on levels of acrylonitrile or any other exposure.

V. Effects of Animal Exposure

Quast *et al.* (1980) exposed Sprague-Dawley rats (100/sex/ concentration) 6 hours/day, 5 days/week for 2 years to concentrations of 0, 20, or 80 ppm acrylonitrile vapors (0, 43, or 174 mg/m^3). A statistically significant increase in mortality was observed in the first year among 80 ppm exposed rats (male and female). Additionally, the 80 ppm exposed group had a significant decrease in mean body weight. Two tissues, the nasal respiratory epithelium and the brain, exhibited treatment-related adverse effects due to acrylonitrile exposure. Proliferative changes in the brain glial cells (i.e., tumors and early proliferation suggestive of tumors) were significantly increased in the 20 ppm (8/100) and 80 ppm (20/100) females versus female controls (0/100), and in the 80 ppm males (22/99) versus male controls (0/100). Noncarcinogenic, extrarespiratory effects were observed in the nasal turbinate epithelium at both exposure concentrations, 20 and 80 ppm (see table below). Thus the LOAEL was 20 ppm. No treatment-related effects in the olfactory epithelium, trachea, or lower respiratory epithelium were observed at either concentration.

Effects of acrylonitrile reported by Quast *et al*. (1980)

Effect	Sex	0 ppm	20 ppm	80 ppm
Respiratory epithelium hyperplasia in the nasal turbinates	Male	0/11	4/12	10/10*
Hyperplasia of the mucous secreting cells	Male	0/11	7/12*	8/10*
Focal inflammation in the nasal turbinates	Female	2/11	6/10	7/10*
Flattening of the respiratory epithelium of the nasal turbinates	Female	1/11	7/10*	8/10*
Lung: pneumonia, consolidation, atelectasis, or edema	Male	14/100	27/100*	30/100*
Lung: pneumonia, consolidation, atelectasis, or edema	Female	7/100	2/100	7/100

* statistically significant difference from controls ($p<.05$)

Maltoni and associates exposed Sprague-Dawley rats (30/sex/concentration) to 0, 5, 10, 20, or 40 ppm acrylonitrile vapor for 5 days/week over 52 weeks, and at 60 ppm for 4 to 7 days, 5 days/week for 104 weeks (Maltoni *et al.*, 1977; Maltoni *et al.*, 1988). Histopathologic examinations were performed, including on lungs, brain, kidney, and liver. No noncarcinogenic effects were reported.

Gagnaire *et al*. (1998) studied motor and sensory conduction velocities (MCV and SCV, respectively) and amplitudes of the sensory and motor action potentials (ASAP and AMAP) of the tail nerve in male Sprague-Dawley rats during chronic treatment with acrylonitrile. (Four other unsaturated aliphatic nitriles were also given orally to other rats.) Rats were given doses of 12.5, 25, and 50 mg/kg of acrylonitrile once a day, 5 days per week for 12 weeks. Rats were also exposed by inhalation to 25, 50, and 100 ppm of acrylonitrile vapors for 6 h/day, 5 days per week, for 24 weeks and neurophysiological examinations were carried out. After oral acrylonitrile, animals developed behavioral sensitization characterized by salivation, locomotor hyperactivity, and moderately intense stereotypies. Rats dosed with 50 mg/kg developed hindlimb weakness associated with decreases in sensory conduction velocity (SCV) and in the amplitude of the sensory action potential (ASAP). Rats exposed to acrylonitrile by inhalation exhibited time- and concentration-dependent decreases in motor conduction velocity (MCV), SCV, and ASAP, which were partially reversible after 8 weeks of recovery. The authors

concluded that the nervous system of the rat appears to be a target following either oral or inhalation exposures of acrylonitrile. The NOAEL by inhalation for 24 weeks was 25 ppm.

Changes in electrophysiological parameters after 24 wks of exposure (Gagnaire *et al*., 1998)

Acrylonitrile	MCV (m/sec)	SCV (m/sec)	AMAP (mvolts)	ASAP (μvolts)
0 ppm	42.9 ± 0.9[a]	53.3 ± 1.0	17.8 ± 1.2	186 ± 8
25 ppm	41.6 ± 0.8	50.5 ± 0.8*	16.1 ± 0.8	164 ± 11
50 ppm	38.1 ± 0.9**	49.1 ± 0.5***	15.7 ± 1.0	159 ± 5*
100 ppm	38.5 ± 1.2**	48.4 ± 1.0***	17.4 ± 0.9	133 ± 11***

[a] Mean ± SEM; * $p<0.05$; ** $p<0.01$; ***$p<0.001$

In a developmental study, Murray *et al.* (1978) exposed rats to acrylonitrile vapors at 0, 40 ppm (87 mg/m^3), or 80 ppm (174 mg/m^3) for 6 hours/day during gestational days 6 to 15. In the 80 ppm exposed group, significant increases in fetal malformations were observed including short tail, missing vertebrae, short trunk, omphalocoele, and hemivertebra (Murray *et al.*, 1978). No differences in implantations, live fetuses, or resorptions were seen in the exposed (40 and 80 ppm) versus the control group. Maternal toxicity was observed as decreased body weight at both exposure levels. After adjustment to continuous exposure, this study identified a developmental NOAEL of 10 ppm and a LOAEL of 20 ppm (with maternal toxicity).

Saillenfait *et al*. (1993) studied the developmental toxicity of eight aliphatic mononitriles in Sprague-Dawley rats after inhalation exposure for 6 hr/day during days 6 to 20 of gestation. The range of exposure levels for acrylonitrile was 12, 25, 50, and 100 ppm; group sizes were 20-23 females. Embryolethality was observed after exposure to 25 ppm (54 mg/m^3) acrylonitrile in the presence of overt signs of maternal toxicity. Fetal weights were significantly lower at 25 ppm. Thus 12 ppm (26 mg/m^3) is a NOAEL for developmental toxicity using this study design.

VI. Derivation of Chronic Reference Exposure Level

Study	Quast *et al.*, 1980
Study population	Sprague-Dawley rats (100/sex/concentration)
Exposure method	Discontinuous whole-body inhalation exposures (0, 20, or 80 ppm)
Critical effects	Degeneration and inflammation of nasal respiratory epithelium; hyperplasia of mucous secreting cells
LOAEL	20 ppm
NOAEL	Not observed
BMC_{05}	1.5 ppm
Exposure continuity	6 hours/day, 5 days/week
Average experimental exposure	0.27 ppm for BMC_{05} (1.5 x 6/24 x 5/7)
Human equivalent concentration	0.067 ppm (gas with extrathoracic respiratory effects; RGDR = 0.25 based on MV = 0.33 m^3/day, SA(ET) = 11.6 cm^2)

Exposure duration	2 years
LOAEL uncertainty factor	Not needed in the BMC approach
Subchronic uncertainty factor	1
Interspecies uncertainty factor	3
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	30
Inhalation reference exposure level	0.002 ppm (2 ppb; 0.005 mg/m^3; 5 $\mu g/m^3$)

Sprague-Dawley rats (100/sex/concentration) were exposed 6 hours/day, 5 days/week for 2 years to 0, 20, or 80 ppm acrylonitrile (0, 43, and 174 mg/m^3, respectively). Significant degenerative and inflammatory changes were observed in the respiratory epithelium of the nasal turbinates at both exposure concentrations (20 and 80 ppm). This treatment-related irritation of the nasal mucosa appeared in the 20 ppm exposed male rats as either epithelial hyperplasia of the nasal turbinates, or as hyperplasia of the mucous secreting cells. In the 20 ppm exposed females it appeared as either focal inflammation in the nasal turbinates or flattening of the respiratory epithelium of the nasal turbinates. In 80 ppm exposed rats the effects were more severe, including suppurative rhinitis, hyperplasia, focal erosions, and squamous metaplasia of the respiratory epithelium. No treatment-related effects in the olfactory epithelium, trachea, or lower respiratory system were observed at either concentration. This study identified a LOAEL for pathological alterations in the respiratory epithelium of the extrathoracic region of the respiratory tract of 20 ppm (43 mg/m^3). The U.S. EPA (1994) based its RfC of 2 $\mu g/m^3$ on the same study but included a Modifying Factor (MF) of 10 for database deficiencies. The criteria for use of modifying factors are not well specified by U.S. EPA. Such modifying factors were not used by OEHHA.

OEHHA used a benchmark dose approach to determine the chronic REL for acrylonitrile. The cumulative gamma distribution model in the U.S. EPA's BMDS sotware was individually fit to the data on respiratory epithelium hyperplasia in the nasal turbinates in males, hyperplasia of the mucous secreting cells in males, focal inflammation in the nasal turbinates in females, and flattening of the respiratory epithelium of the nasal turbinates in females. The resulting BMC_{05} values (1.27, 1.33, 2.18, 1.35) were averaged to yield a value of 1.5 ppm. The RGDR adjustment and appropriate uncertainty factors were applied as indicated in the above table and resulted in a chronic REL of 5 $\mu g/m^3$.

For comparison, Gagnaire *et al*. (1998) found a NOAEL for nervous system effects at 24 weeks of 25 ppm, which is equivalent to a continuous exposure of 4.5 ppm. Use of the default RGDR of 1 for systemic effects, a subchronic UF of 3, an interspecies UF of 3, and an intraspecies UF of 10 results in an estimated REL of 45 ppb (100 $\mu g/m^3$). We were unable to derive a BMC from the neurotoxicity data due partly to the tendency of the animals in the 100 ppm group to yield values for two of the four endpoints measured closer to the controls than those in the 50 ppm group.

As another comparison, Saillenfait *et al*. (1983) found a 12 ppm (26 mg/m^3) NOAEL for fetal weight reduction (6 h/d exposure). This is equivalent to a continuous exposure of 3 ppm (on

days 6 to 20 of gestation). Use of the default RGDR of 1 for systemic effects, an interspecies UF of 3, and an intraspecies UF of 10 results in an estimated REL of 100 ppb (200 $\mu g/m^3$).

Finally, after adjustment to continuous exposure, Murray *et al*. (1978) identified a developmental NOAEL, adjusted to continuous exposure, of 10 ppm and a LOAEL of 20 ppm (with maternal toxicity at both levels). Use of the default RGDR of 1 for systemic effects, an interspecies UF of 3, and an intraspecies UF of 10 results in an estimated REL of 30 ppb (70 $\mu g/m^3$).

VII. Data Strengths and Limitations for Development of the REL

Significant strengths in the chronic REL for acrylonitrile include (1) the availability of chronic inhalation exposure data from a well-conducted study with histopathological analysis and (2) the demonstration of a dose-response relationship. Major uncertainties are (1) the lack of adequate human exposure data, (2) the lack of a NOAEL in the 2 year study, (3) lack of inhalation bioassay in a second species, and (4) lack of reproductive data for inhalation exposures when an oral study showed adverse reproductive effects

When assessing the health effects of acrylonitrile, its carcinogenicity must also be assessed.

VIII. Potential for Differential Impacts on Children's Health

The chronic REL is considerably lower than the comparison estimate based on developmental effects. Although neurotoxicity, an endpoint which is often associated with increased sensitivity of younger animals or humans, was evaluated as one of the alternative endpoints, the comparison reference level for this end point in adults was more than an order of magnitude higher that the REL based on histological changes in the upper respiratory tract. It is therefore considered that the REL is likely to be adequately protective of infants and children.

IX. References

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CHRONIC TOXICITY SUMMARY

BERYLLIUM and BERYLLIUM COMPOUNDS

(beryllium-9; glucinium; glucinum; beryllium metallic)
CAS Registry Number: 7440-41-7

(beryllium oxide; beryllia; beryllium monoxide)
CAS Registry Number: 1304-56-9

(beryllium hydroxide; beryllium hydrate; beryllium dihydroxide)
CAS Registry Number: 13327-32-7

(beryllium sulfate; sulfuric acid; beryllium salt)
CAS Registry Number: 13510-49-1

I. Chronic Toxicity Summary

Inhalation reference exposure level	**0.007 mg Be/m^3**
Critical effect(s)	Beryllium sensitization and chronic beryllium disease in occupationally exposed humans
Hazard index target(s)	Respiratory system; immune system
Oral reference exposure level	0.002 mg/kg-day
Critical efect	Small intestinal lesions in dogs
Hazard index target(s)	Gastrointestinal tract/liver

II. Physical and Chemical Properties Summary (ATSDR, 1993)

	Metallic beryllium	*Beryllium oxide*	*Beryllium hydroxide*	*Beryllium sulfate*
Description	Solid gray, hexagonal structure	White light, amorphous powder	White amorphous powder or crystalline	Colorless tetragonal crystals
Molecular formula	Be	BeO	$Be(OH)_2$	$BeSO_4$
Molecular weight	9.012 g/mol	25.01 g/mol	43.03 g/mol	105.07 g/mol
Solubility	Insoluble in water			Soluble
Conversion factor	Not applicable			

III. Major Uses and Sources

Beryllium is a metallic element mined as bertrandite and beryl mineral ores. As the lightest structural metal, beryllium is used in the space, aircraft, and nuclear industries in a variety of components including aircraft disc brakes, x-ray transmission windows, vehicle optics, nuclear reactor neutron reflectors, fuel containers, precision instruments, rocket propellants, navigational systems, heat shields, and mirrors. In addition to the four species listed, there are many other beryllium-containing compounds, including other salts, ores, and alloys (see, e.g., CRC, 1994). The annual statewide industrial emissions from facilities reporting under the Air Toxics Hot Spots Act in California based on the most recent inventory were estimated to be 2279 pounds of beryllium (CARB, 2000).

Beryllium alloys, especially the hardest alloy beryllium copper, are used in electrical equipment, precision instruments, springs, valves, non-sparking tools, and in molds for injection-molded plastics for automotive, industrial, and consumer applications. Beryllium oxide is used in high-technology ceramics, electronic heat sinks, electrical insulators, crucibles, thermocouple tubing, and laser structural components. Other beryllium compounds, including the chloride, nitrate, fluoride, and sulfate, are utilized as chemical reagents or generated from the refining of beryllium-containing ores.

Beryllium is naturally emitted into the atmosphere by windblown dusts and volcanic particles. However, the major emission source is the combustion of coal and fuel oil, which releases beryllium-containing particulates and ash. Other beryllium-releasing industrial processes include ore processing, metal fabrication, beryllium oxide production, and municipal waste incineration (ATSDR, 1993). Beryllium also occurs in tobacco smoke (0-0.0005 μg/cigarette) (Smith *et al*., 1997).

IV. Effects of Human Exposure

The respiratory tract is the major target organ system in humans following the inhalation of beryllium. The common symptoms of chronic beryllium disease (CBD) include shortness of breath upon exertion, weight loss, cough, fatigue, chest pain, anorexia, and overall weakness. Most studies reporting adverse respiratory effects in humans involve occupational exposure to beryllium. Exposure to soluble beryllium compounds is associated with acute beryllium pneumonitis (Eisenbud *et al.*, 1948). Exposure to either soluble or insoluble beryllium compounds may result in obstructive and restrictive diseases of the lung, called chronic beryllium disease (berylliosis) (Cotes *et al.*, 1983; Johnson, 1983; Infante *et al.*, 1980; Kriebel *et al.*, 1988a; Metzner and Lieben, 1961). The total number of beryllium-related disease cases has declined since the adoption of industrial standards (Eisenbud and Lisson, 1983; ATSDR, 1993).

Historically, beryllium pneumonitis has been associated with occupational concentrations over 0.1 mg Be/m^3, primarily as beryllium sulfate or beryllium fluoride (Eisenbud *et al.*, 1948). The atmospheric concentrations related to chronic beryllium disease have been more difficult to define, in part due to the lack of individual exposure estimates, especially in the studies derived from the berylliosis case registries (Infante *et al.*, 1980; Lieben and Metzner, 1959). However,

Infante and associates (1980) reported significantly increased mortality due to non-neoplastic respiratory disease in beryllium-exposed workers, and noted one case of chronic berylliosis in a worker following seven years exposure to $\leq$ 2 µg Be/m^3. In a 30-year follow-up study of 146 beryllium-exposed workers, Cotes *et al.* (1983) identified seven cases of chronic beryllium related disease. All the cases were exposed to beryllium oxide or hydroxide, but in a wide range of retrospectively estimated doses (over 3000 samples from 1952 to 1960). The estimated average daily exposure did not exceed 2 µg/m^3 for the ten site/process classifications, but 318 samples did exceed 2 µg Be/m^3 (and 20 samples were greater than 25 µg Be/m^3). No atmospheric samples were available after 1963, even though the exposure occurred through 1973. The LOAEL for occupationally induced berylliosis observed in this study was estimated from uncertain exposure data to be less than 2 µg Be/m^3.

One cross-sectional study (Kriebel *et al.*, 1988a; Kriebel *et al.*, 1988b) estimated beryllium exposure levels for 309 workers originally surveyed in 1977, with a median duration of exposure of 17 years (range 2 to 39 years). Historic plant levels were estimated to be as high as 100 µg Be/m^3, and, even as late as 1975, some job classifications exceeded 10 µg Be/m^3. The workers' median cumulative exposure was 65 µg Be/m^3-year (range 0.1 to 4400 µg Be/m^3-years); the median lifetime exposure estimate was 4.3 µg/m^3 (range 0.01 to 150 µg/m^3). Spirometric measurement of pulmonary function, chest x-rays, and arterial blood gas measurements were collected. Decrements in lung function, as defined by forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1), were associated with cumulative exposure up to 20 years prior to the health survey, even in workers with no radiographic abnormalities. Differences in alveolar-arterial oxygen gradient were associated with cumulative exposure in the 10 years prior to the study. These endpoints give a LOAEL of 39 µg/m^3-years (geometric mean cumulative exposure) for decrements in pulmonary function and changes in arterial blood gases.

Non-occupational beryllium-related chronic disease has been reported in individuals residing in the vicinity of beryllium manufacturing industries (Eisenbud *et al.*, 1949; Metzner and Lieben, 1961). An early cross-sectional study (Eisenbud *et al.*, 1949) described 11 cases of non-occupational berylliosis after x-ray and clinical examination of approximately 10,000 residents near a beryllium fabrication facility in Lorain, Ohio. Ten of the cases resided within 3/4 mile of the plant (up to 7 years duration), and five cases resided within 1/4 mile. The authors estimated a 1% disease incidence within 1/4 mile (500 individuals). Atmospheric sampling in 1947 identified an average level of 0.2 µg Be/m^3 at 1/4 mile decreasing to 0 µg Be/m^3 at 10 miles, but samples varied up to 100 fold over the 10 week sampling period. Utilizing current and historical exposure estimates based on discharge, process, inventory, and building design changes, this study estimated a chronic LOAEL in the range of 0.01 to 0.1 µg Be/m^3 for continuous exposure to beryllium compounds, based on the development of chronic berylliosis.

Metzner and Lieben (1961) also reported 26 cases of chronic berylliosis in a population of approximately 100,000, living within 7 miles of a refining and alloy fabrication plant (duration 6 to 19 years). Neighborhood exposure assessment conducted over 14 months during 1958 and 1959 identified a mean level of 0.0155 µg Be/m^3, with 10% of the samples registering over 0.03 µg Be/m^3. Limited measurements conducted earlier at the site were higher (1.0 to 1.8 µg Be/m^3 in 1953 and 0.91 to 1.4 µg Be/m^3 in 1954).

Chronic beryllium disease appears to involve a cell-mediated immune response, especially granulomatous reactions found in the lungs of sensitive individuals. Humans exposed to beryllium compounds have demonstrated increased T-cell activity (*in vitro*) and histological abnormalities of the lymph nodes (Cullen *et al.*, 1987; Johnson, 1983). Johnson (1983) described granuloma of lymph nodes and chronic interstitial pneumonitis in a small number of beryllium metal handling machinists (LOAEL = 4.6 μg Be/m^3). A second study identified granulomatous lung lesions, scarred lung tissue, and breathing difficulties in workers from a precious metal refining facility exposed to a mixture of beryllium and other metals (Cullen *et al.*, 1987). Also, altered proliferative responses of lymphocytes obtained by bronchoalveolar lavage indicated increased T-cell activity *in vitro*. Cullen *et al.* (1987) reported a mean exposure level of 1.2 μg Be/m^3 (range = 0.22 – 43 μg/m^3). USEPA (1998) and ATSDR (2000) considered 0.52 μg Be/m^3 to be the LOAEL for CBD from this study since this was the average concentration in the furnace area where 4 of the 5 CBD cases worked.

Sensitization to beryllium, as measured by the beryllium lymphocyte proliferation test (BeLPT), can occur in the absence of chronic beryllium disease (Kreiss *et al*., 1989). The authors hoped that the identification of sensitized individuals without disease might prevent clinical disease, presumably by removing the individuals from exposure to beryllium. Some beryllium-sensitized individuals progress to having clinical disease (Newman *et al*., 1992). Data obtained from a four-year survey conducted at beryllium-copper alloy manufacturing factories in Japan (Yoshida *et al*., 1997) indicated that the T cells of workers continuously exposed to more than 0.01 μg Be/m^3 were activated and that the cell-mediated immune (CMI) response was promoted. The BeLPT in workers exposed to less than 0.01 μg Be/m^3 was unaffected.

Genetic influences on development of CBD have been identified. CBD is associated with the allelic substitution of glutamic acid for lysine at position 69 in the HLA-DPB1 protein (Richieldi *et al*., 1993). Up to 97% of CBD patients may have the Glu69 marker, but only 30-45% of beryllium-exposed, unaffected individuals carry the same marker. Because CBD occurs in only 1-6% of exposed workers, Glu69 is not likely to be the only genetic factor influencing the development of CBD. Changes in other sequences of the HLA-DPB1 gene and in the copy number of Glu69 are also involved (Wang *et al*., 1999).

The Rocky Flats Environmental Technology Site in Colorado is part of the U.S. Department of Energy nuclear weapons complex. Operations using Be began in 1953, Be production operations began in 1957, and the first case of CBD was diagnosed in a machinist in 1984. Exposures could have occurred during foundry operations, casting, shearing, rolling, cutting, welding, machining, sanding, polishing, assembly, and chemical analysis operations. Since 1991, 29 cases of CBD and 76-78 cases of beryllium sensitization have been identified (Stange *et al*., 1996). Several cases appear to have had only minimal Be exposure, since the employees were in administrative functions, not primary beryllium operations. Personal air monitoring devices used over a period of 4 years showed a breathing zone level of 1.04 μg Be/m^3. ATSDR (2000) considered 1.04 μg Be/m^3 to be the LOAEL for this study. A recent case-control study of workers at Rocky Flats (Viet *et al.*, 2000) suggested that exposures of workers to lower Be levels might lower the future incidence of CBD, but not necessarily the incidence of sensitivity to Be.

Kreiss *et al.* (1996) investigated the prevalence of beryllium sensitization in relation to work process and beryllium exposure measurements in a beryllia ceramics plant that had operated since 1980. In 1992 they interviewed 136 employees (97.8% of the workforce), ascertained beryllium sensitization with the beryllium lymphocyte proliferation blood test (BeLPT), and reviewed industrial hygiene measurements. Eight employees were beryllium-sensitized (5.9%); six of the eight had granulomatous disease based on transbronchial lung biopsy. Machinists had a Be sensitization rate of 14.3% compared to 1.2% among other employees. Machining operations (drilling, dicing, centerless grinding, and/or surface grinding) had significantly higher general area and breathing zone measurements than other work processes during the time in which most beryllium-sensitized cases had started machining. Daily weighted average estimates of exposure for matching processes also exceeded estimates for other work processes in that time period (median daily weighted average = 0.9 $\mu g/m^3$). Daily weighted averages for the machining process accounted for the majority of exceedances of the 2.0 $\mu g/m^3$ OSHA Permissible Exposure Limit (PEL); 8.1% of machining daily weighted averages were above the PEL. The LOAEL from this study was 0.55 $\mu g/m^3$, the median exposure of the sensitized workers.

The facility was again surveyed in 1998 after some attempts were made to lower exposure to beryllium (Henneberger *et al*., 2001). The investigators separated the workers into 77 long-term workers hired before the 1992 screening and 74 short-term workers hired after 1992. Among 20 short-term workers exposed to the lowest mean Be level (0.05 to 0.19 $\mu g/m^3$), two showed Be sensitivity by the BeLPT test. Thus a fraction of workers appears to be exquisitely sensitive to beryllium.

Based on a review of this and other occupational studies Wambach and Tuggle (2000) have suggested that the workplace standard of 2 $\mu g/m^3$ be lowered to 0.1 $\mu g/m^3$. Some workers might still be sensitized to beryllium at this level (Yoshida *et al*., 1997).

V. Effects of Animal Exposure

Three chronic studies, two in rats (Vorwald and Reeves, 1959; Reeves *et al.*, 1967) and one in guinea pigs (Reeves *et al.*, 1970), observed adverse inflammatory and proliferative respiratory changes following inhalation exposure to beryllium compounds. Vorwald and Reeves (1959) observed inflamed lungs and fibrosis in rats exposed to 0.006 mg Be/m^3 (as BeO) for an unspecified duration. A later study exposed Sprague-Dawley CD rats for 72 weeks (7 hr/d, 5 d/wk) to 34.25 μg Be/m^3 from $BeSO_4$ (Reeves *et al.*, 1967). Gross and histological changes observed in exposed versus unexposed rats included increased lung weight, inflamed lungs, emphysema, arteriolar wall thickening, granulomas, fibrosis, and proliferative responses within the alveoli (LOAEL = 34.25 μg Be/m^3). Guinea pigs were exposed to 0, 3.7, 15.4, or 29.3 μg Be/m^3 (from the sulfate) for 6 hours/day, 5 days/week for up to 1 year (Reeves *et al.*, 1970). Respiratory alterations observed in the beryllium-exposed groups included increased tracheobronchial lymph node and lung wet weights, interstitial pneumonitis, and granulomatous lesions. These adverse respiratory effects were observed in all the beryllium dosed groups and indicated a chronic inhalation LOAEL of 3.7 μg Be/m^3.

Wagner *et al.* (1969) exposed monkeys, rats, and hamsters to 0.21 and 0.62 mg Be/m^3 as fumes from bertrandite or beryl ore, respectively, for 6 hours/day, 5 days/week for up to 17 months. Exposed animals displayed severe effects, including (1) bronchial lymphocytic infiltrates, abscesses, consolidated lobes, and granulomatous lesions after exposure to 0.21 mg Be/m^3 from bertrandite ore, and (2) inflamed lungs, fibrosis, and granuloma after exposure to 0.62 mg Be/m^3 from beryl ore. Lung inflammation was observed in the exposed monkeys, and a few granulomatous lung lesions were observed in the hamsters after similar exposure conditions (up to 23 months).

Immunological effects have been observed in a few subchronic studies (Schepers, 1964; Schepers *et al.*, 1957; Stiefel *et al.*, 1980). Schepers (1964) exposed monkeys (*Macacus mullata*) to three soluble forms of beryllium (BeF_2, $BeSO_4$, $BeHPO_4$) daily for 6 hours/day over 7 to 30 days. Increased lung weight, inflammation, emphysema, and fibrosis of the lung were observed after 17 days at 0.198 mg Be/m^3 (as $BeSO_4$). Histological examination found pleuritis, congestion, emphysema, consolidation, and edema of the lung. Immunological effects were seen as hyperplasia of the lymph nodes typical of immune activation after 7 to 18 days exposure to either 0.198 or 0.184 mg Be/m^3 as the sulfate or fluoride. A subchronic inhalation study reported immunological effects as increased, beryllium-specific stimulation of T-lymphocytes *in vitro* from Wistar rats and guinea pigs exposed daily (6 hours/day) over 10 weeks (LOAEL = 0.5 mg/m^3) (Stiefel *et al.*, 1980). However, a subchronic inhalation study in Wistar and Sherman rats (Schepers *et al.*, 1957) observed multiple lung alterations including granulomas (LOAEL = 35 µg Be/m^3) but did not find any accompanying immunological effects after 30 days discontinuous exposure (5-6 d/wk, 4-8 hr/d) to beryllium fumes from $BeSO_4$.

VI. Derivation of Chronic Reference Exposure Levels

Derivation of Inhalation Reference Exposure Level

Key study	Kreiss *et al*., 1996
Study population	8 beryllium-sensitized workers among 136 employees in a beryllia ceramics plant
Exposure method	Workplace
Critical effects	Beryllium sensitization (chronic beryllium disease)
LOAEL	0.55 µg/m^3 (median exposure of sensitized workers)
NOAEL	Not observed
Exposure continuity	Workplace
Average experimental exposure	0.2 µg/m^3 for LOAEL group (0.55 x 10/20 x 5/7)
Human equivalent concentration	0.2 µg/m^3
Exposure duration	6.1 years (5 mo – 10 yr)
LOAEL uncertainty factor	10 (low incidence but serious, irreversible chronic disease)
Subchronic uncertainty factor	1
Interspecies uncertainty factor	1
Intraspecies uncertainty factor	3 (sensitized may not be only sensitive subpopulation) (see below)
Cumulative uncertainty factor	30
Inhalation chronic REL	0.007 µg/m^3

Supportive study	Eisenbud *et al.* (1949)
Study population	Approximately 10,000 individuals within 2 miles of a beryllium manufacturing plant
Exposure method	Environmental exposure
Critical effects	Pulmonary berylliosis in 11 residents
LOAEL	0.03 µg/m^3 (geometric mean of range of measured exposures associated with berylliosis of 0.01 to 0.1 µg/m^3)
NOAEL	Not observed
Exposure continuity	Continuous
Average exposure	Estimated to be approximately 0.3 µg/m^3 (historical exposures estimated to be 10-fold higher than measured values) for LOAEL group
Human equivalent concentration	0.3 µg/m^3 for LOAEL group
Exposure duration	Up to 7 years
LOAEL uncertainty factor	10
Subchronic uncertainty factor	3
Interspecies uncertainty factor	1
Intraspecies uncertainty factor	3
Cumulative uncertainty factor	100
Inhalation chronic REL	0.003 µg/m^3

U.S. EPA (1998) developed an RfC of 0.02 μg/m^3 based on beryllium sensitization and progression to chronic beryllium disease (CBD) identified by Kreiss *et al*. (1996). The Kreiss *et al*. (1996) occupational exposure study identified a LOAEL for beryllium sensitization in workers of 0.55 μg/m^3 (median of average exposure concentrations of the 8 Be sensitized workers). The Eisenbud *et al*. (1949) study, which U.S. EPA used as a co-principal study and which in U.S. EPA's opinion used relatively insensitive screening methods, suggested a NOAEL of 0.01-0.1 μg/m^3 in community residents living near a beryllium plant. U.S. EPA used the LOAEL from the Kreiss *et al*. (1996) study for the operational derivation of the RfC, because the screening method used in the Eisenbud *et al*. (1949) study was considered to be less sensitive than the method used in the Kreiss *et al*. (1996) study. The LOAEL was time adjusted to 0.2 μg/m^3, then a total UF of 10 was used to obtain the RfC of 0.02 μg/m^3. The UF of 10 was comprised of a UF of 3 to account for the sensitive nature of the subclinical endpoint (beryllium sensitization) and a database UF of 3 to account for the poor quality of exposure monitoring in the Kreiss *et al*. and Eisenbud *et al*. studies. Poor exposure monitoring was also a problem in other epidemiology studies that assessed the incidence of beryllium sensitization. The U.S. EPA did not explicitly apply a LOAEL to NOAEL uncertainty factor. Thus implicitly the factor is 1.

OEHHA prefers to use the methodology for assignment of UFs, which is described in OEHHA (2000) and used in our derivation of the REL for beryllium, including use of a LOAEL to NOAEL Uncertainty Factor of 10. Since chronic beryllium disease (CBD) is serious, chronic, disabling, usually irreversible, and often fatal (Newman *et al*., 1997), it is difficult to justify use of a LOAEL to NOAEL factor of only 3. OEHHA has not used database deficiency UFs since the criteria for use of such factors are not well specified by U.S. EPA. The people who get CBD are likely that part of the population who are by nature more sensitive to beryllium, for example those with the human leukocyte antigen (HLA) class II marker HLA-DP Glu69 (Richeldi *et al*., 1993; Saltini *et al*., 1998). Although it is likely that the effects are seen in a "sensitive subpopulation," OEHHA applied an intraspecies uncertainty factor (UF_H). OEHHA used an intermediate UF_H of 3, since 1) there may be other population factors involved in being sensitive, such as immature lungs, and 2) all the diseased were initially healthy adult workers.

For comparison the LOAEL from guinea pigs of 3.7 μg Be/m^3 (Reeves *et al.*, 1970) is equivalent to a continuous exposure of 0.66 μg/m^3. Division by UFs of 10 for intraspecies, 10 for interspecies (since HEC adjustments are not available yet for guinea pigs), and 10 for use of a LOAEL results in a REL of 0.0007 μg/m^3

VII. Data Strengths and Limitations for Development of the REL

The major strength of the inhalation chronic REL for beryllium is the use of human data from persons occupationally exposed. The major uncertainties are the lack of a NOAEL observation in the key study, the lack of long-term exposure data, the difficulty of estimating exposures, and the lack of chronic exposure data.

VIII. Potential for Differential Impacts on Children's Health

No evidence to support a differential effect of beryllium on infants or children was found in the literature. However, children have developed beryllium disease from metal brought home on the parents' work clothes and by living near a facility using beryllium. Unfortunately the number of children and their ages were not published (Eisenbud *et al*., 1948).

Derivation of Chronic Oral Reference Exposure Level

In addition to being inhaled, airborne beryllium can settle onto crops and soil and enter the body by ingestion. Thus an oral chronic reference exposure level for beryllium is also required for conducting Air Toxics Hot Spots risk assessments.

Study	Morgareidge *et al*., 1976
Study population	Male and female dogs (5/sex/group)
Exposure method	Diet containing 0, 1, 5, 50 or 500 ppm Be as beryllium sulfate tetrahydrate
Critical effects	Small intestinal lesions
LOAEL	500 ppm
NOAEL	50 ppm (1.2 mg/kg bw-day)
Exposure continuity	Continuous
Exposure duration	Up to 3 years, 4 months
Average experimental exposure	1.2 mg/kg bw-day (males, 1.1; females, 1.3)
BMD_{05}	0.244 mg/kg-day
LOAEL uncertainty factor	Not needed in BMD approach
Subchronic uncertainty factor	1
Interspecies uncertainty factor	10
Intraspecies factor	10
Cumulative uncertainty factor	100
Oral reference exposure level	0.002 mg/kg-day

Morgareidge *et al*. (1976) conducted a long-term feeding study in which beagle dogs (aged 8 to 12 mo) were fed diets (for 1 h per day) containing 0, 5, 50, or 500 ppm Be for 172 weeks. The 500 ppm group was terminated at 33 weeks because of overt signs of toxicity, and an additional group was added to the study and fed a diet containing 1 ppm Be (for 143 weeks). The 1, 5, 50, and 500 ppm concentrations corresponded to doses of 0.023, 0.12, 1.1, and 12.2 mg/kg-day for males and 0.029, 0.15, 1.3, and 17.4 mg/kg-day for females. All animals in the 500 ppm group showed fairly extensive erosive (ulcerative) and inflammatory lesions in the gastrointestinal tract. These occurred predominantly in the small intestine and to a lesser extent in the stomach and large intestine, and were considered treatment related. All animals with stomach or large intestinal lesions also had lesions in the small intestine, except for one animal (whose stomach lesions were very localized and not very severe). Lesions in the small intestine (4/5 males and 5/5 females) were considered to be treatment-related and included desquamation of the epithelium, edema, fibrin thrombi, acute inflammation, subacute/chronic inflammation, necrosis and thinning/atrophy of the epithelium, and ulceration. High-dose animals also showed

moderate to marked erythroid hypoplasia of the bone marrow, which the authors also considered treatment related. (Bile stasis and vasculitis in the liver, acute inflammation in the lymph nodes, and kidney occurring in these animals was attributed to a likely systemic bacterial invasion through the damaged intestinal mucosa.) In the 50 ppm group, one female dog, which died after 70 weeks of treatment, showed gastrointestinal lesions, which were less severe, but occurred in the same locations and appeared to be the same types of lesions as those in dogs administered 500 ppm. The observation that beryllium is poorly absorbed by the gastrointestinal tract (Owen, 1990; ATSDR, 2000) probably explains why lesions were not seen outside the gastrointestinal tract. In addition the predominance of lesions in the small intestine may have been partly due to precipitation of beryllium phosphate there due to the slightly alkaline pH (Reeves, 1965). Thus 500 ppm was a LOAEL and 50 ppm was a NOAEL (statistically) for gastrointestinal lesions.

USEPA used the same study to derive its RfD of 0.002 mg/kg-day. The U.S. EPA stated its confidence in the RfD as: study - medium; database – low to medium, and RfD - low to medium. USEPA used a BD_{10} approach and included a database UF of 3. OEHHA used a BD_{05} approach (specifically a Weibull model in the USEPA's BMDS software) and did not include a database UF since the criteria for use of modifying factors such as this are not well specified by U.S. EPA. However, the final value for the oral chronic REL was the same as the USEPA's RfD.

This RfD and the oral REL are limited to soluble beryllium salts. Data on the teratogenicity or reproductive effects of beryllium are limited. Beryllium has been reported to produce terata and increased mortality in chick embryos.

When assessing the health effects of beryllium, its carcinogenicity must also be assessed.

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CHRONIC TOXICITY SUMMARY

CHLOROPICRIN

(trichloronitromethane; nitrochloroform; nitrochloromethane)

CAS Registry Number: 76-06-2

I. Chronic Toxicity Summary

Inhalation reference exposure level	**0.4 µg/m^3** (0.05 ppb)
Critical effect(s)	Nasal rhinitis and bronchiectasis in mice
Hazard index target(s)	Respiratory system

II. Chemical Property Summary (from HSDB (1996) except as noted)

Description	Colorless to faint yellow liquid
Molecular formula	CCl_3NO_2
Molecular weight	164.4 g/mol
Boiling point	112°C
Melting point	–64°C (CRC, 1994)
Vapor pressure	5.7 torr @ 0°C (Fries and West, 1921); 3.2 kPa (24 torr) @ 25°C (Tomlin, 1994)
Solubility	1.6 g/L water @ 25°C; 2.272 g/L water @ 0°C 1.9 g/L water @ 20°C; miscible with benzene, ethanol, carbon disulfide, ether, carbon tetrachloride, acetone, methanol, acetic acid
Conversion factor	6.72 µg/m^3 per ppb at 25ºC

III. Major Uses and Sources

Chloropicrin is used primarily as a preplant soil fumigant against insects and fungi; it also kills weed and grass seeds when applied to soil. Chloropicrin is occasionally used as a fumigant in grain elevators and storage bins (HSDB, 1996). Chloropicrin is used as an indicator chemical in other fumigants such as methyl bromide because of its potent irritant properties. Chloropicrin was used in World War I as a chemical warfare agent because of its potent activity as a lachrymator. Chloropicrin has a minor use in the chemical synthesis of methyl violet. Chloropicrin can also form in drinking water as a result of chlorination processes (Duguet *et al.*, 1985; Merlet *et al.*, 1985). The annual statewide industrial emissions from facilities reporting under the Air Toxics Hot Spots Act in California based on the most recent inventory were estimated to be 1507 pounds of chloropicrin (CARB, 2000). This does not include emissions from its major use as a preplant soil fumigant, either alone or in combination with other fumigants, because agricultural field applications are not covered under the Air Toxics Hot Spots

program. Approximately 3,630,000 lbs. of chloropicrin were used in agriculture in California in 1999 (DPR, 2000).

IV. Effects of Human Exposure

No studies are available which describe toxic effects to humans from chronic exposure to chloropicrin. Human exposures to concentrations less than 1 ppm for very short periods of time are extremely irritating (ACGIH, 1992; Fries and West, 1921). The threshold of odor detection in humans is approximately 1 ppm (ACGIH, 1992).

V. Effects of Animal Exposure

Burleigh-Flayer and Benson (1995) conducted a chronic inhalation bioassay with CD rats (50-60 per sex per dose) exposed discontinuously to 0 (air), 0.1, 0.5, or 1.0 ppm 99.6% pure chloropicrin vapor 6 hours/day for 5 consecutive days/week over 107 weeks. Clinical signs (such as hypoactivity and decreased startle response) were increased in both sexes, primarily at 1.0 ppm. Increased mortality was noted in males at 0.5 and 1 ppm and in females at 1 ppm. Absolute and relative increased lung and liver weights and increased nasal rhinitis were reported in both sexes at the 1 ppm level. However, no effects were seen at 0.1 ppm. Thus this study yielded a NOAEL of 0.1 ppm (0.67 mg/m^3) for chronic non-cancer effects in rats.

Results from chronic inhalation of chloropicrin in rats (Burleigh-Flayer and Benson, 1995)

Chloropicrin	Lung wt., m	Lung wt., f	Rhinitis, m	Rhinitis, f	Mean survival, m
0	2.086 g	1.574 g	20/50	18/50	696 d
0.1 ppm	2.089 g	1.464 g	24/50	17/50	669 d
0.5 ppm	2.202 g	1.460 g	21/50	26/50	672 d*
1.0 ppm	2.448 g	1.633 g	35/50**	23/50	647 d**

*$p<0.05$; **$p<0.01$

A similar study in mice (Burleigh-Flayer *et al*., 1995) resulted in the same NOAEL. CD-1 mice (50/sex/dose) were exposed to chloropicrin (99.6% pure) vapor at 0 (air), 0.1, 0.5, or 1.0 ppm for 6 hours/day, 5 days/week for at least 78 weeks. Body weights and body weight gains were significantly decreased in both sexes at ≥ 0.5 ppm. Food consumption was decreased in males at 1.0 ppm and in females at ≥ 0.5 ppm. Absolute and relative lung weights were increased in a dose-related manner in both sexes at ≥ 0.5 ppm. Changes in pathology observed macroscopically in the 1.0 ppm males included increased numbers of lung nodules and increased numbers of kidney cysts. In females lung masses and kidney cysts were seen at 0.5 ppm. Microscopic pathology changes included increased nasal cavity lesions (including serous exudate, hyaline epithelial inclusions, rhinitis, olfactory and epithelial atrophy) and lung lesions (including alveolar protein deposits, alveolar histiocytosis, hemorrhage, peribronchiolar lymphocytic infiltrate, bronchiectasis, bronchial submucosal fibrosis, peribronchiolar smooth muscle hyperplasia), in addition to kidney cysts at ≥ 0.5 ppm (CDPR, 2000).

Results from chronic inhalation of chloropicrin in mice (Burleigh-Flayer *et al*., 1995)

Chloropicrin	Rhinitis, m	Rhinitis, f	Bronchiectasis, m	Bronchiectasis, f	
0	6/50	3/50	0/50	0/50	
0.1 ppm	7/50	6/50	3/50	5/50	
0.5 ppm	17/50**	18/50**	28/50**	28/50**	
1.0 ppm	35/50**	32/50**	41/50**	44/50**	

**p<0.01

Yoshida *et al*. (1987) exposed groups of 12 male Fischer 344 rats intermittently to 0, 0.37, 0.67, 1.58, or 2.93 ppm chloropicrin vapor 6 h/day, 5 days/week for 13 weeks. Mean body weights were reduced in the highest 2 exposure groups, and red blood cell count, hematocrit, and hemoglobin concentration were significantly increased in the 2.93 ppm group. The treatment-related histological lesions reported were degeneration and necrosis of the bronchial and bronchiolar epithelia at 2.93 ppm and hypertrophy of these epithelia at 1.58 ppm. Thus the primary target organ was the respiratory tract and the subchronic NOAEL was 0.67 ppm (4.5 mg/m^3). (Eyelid closure and decrease in motor activity were seen in all exposure groups only during exposure. No morphological changes were seen at 0.67 ppm, so the authors deemed the behavior changes minor and not toxicologically important.)

Male Swiss-Webster mice (group numbers ranging from 16-24) were exposed by inhalation to a single level of different sensory irritants including chloropicrin for 6 hours/day for 5 days; unexposed control groups had 8-10 mice (Buckley *et al.*, 1984). The exposure level for chloropicrin was 7.9 ppm, which approximated the level sufficient to cause a 50% decrease in respiratory rate in mice (RD_{50}) (Kane *et al.*, 1979). Half the exposed mice and half the control animals were terminated immediately after the exposures and the other half 72 hours after the last exposure. All were examined for respiratory tract lesions. Body weights of chloropicrin exposed animals were reduced 10-25% below controls, but increased to normal levels during the recovery period. Nasal exudate and distention of the abdomen were observed. "Moderate" lesions, characterized by exfoliation, erosion, ulceration, or necrosis, were observed in the respiratory and olfactory epithelium, and minimal inflammation and squamous metaplasia were observed in the respiratory epithelium alone. Moderate to severe damage to the lower respiratory tract was described as "fibrosing peribronchitis and peribronchiolitis". Exfoliation, hyperplasia, and squamous metaplasia were also noted.

Condie *et al.* (1994) conducted a study of the toxicity of chloropicrin by oral exposure in Sprague-Dawley rats. Ten and ninety-day studies were conducted by dosing animals daily with chloropicrin in vehicle (corn oil) at a volume of 1 ml/kg. Groups of 10 rats/sex/group were dosed with 0, 10, 20, 40, and 80 mg/kg for the 10-day study and with 0, 2, 8, and 32 mg/kg for the 90-day study. Parameters examined included mortality, body weight, food and water consumption, hematology, serum clinical chemistry, and gross pathology and histology of organs. Only the high-dose group and the control group animals from the 90-day study were examined histopathologically. In the 90-day study, 6 males and 2 females in the 32 mg/kg dose group and 1 male and 3 females in the 8 mg/kg dose group died before the scheduled termination time. The authors noted signs of pulmonary complications (inflammation and congestion) in the dead animals. Previously, the animals had shown signs of respiratory distress, including wheezing and dyspnea. The deaths were considered to be exposure related and most likely due

to aspiration of chloropicrin. Among the survivors, mean body weight, hemoglobin levels, and hematocrits were significantly reduced in males in the 32 mg/kg dose group. Absolute thymus weights were reduced in female rats at 32 mg/kg, and female rats in the 8 mg/kg dose group showed decreased white blood cell count. Most animals in the 32 mg/kg dose group (>60%) showed histopathological changes in the forestomach including chronic inflammation, acantholysis, and hyperkeratosis. The authors considered the NOAEL to be 8 mg/kg/day.

VI. Derivation of Chronic Reference Exposure Level (REL)

Study	Burleigh-Flayer and Benson (1995)
Study population	CD-1 mice (60 per sex per dose)
Exposure method	Discontinuous inhalation (0, 0.1, 0.5 or 1.0 ppm)
Critical effects	Nasal rhinitis; bronchiectasis
LOAEL	0.5 ppm
NOAEL	0.1 ppm
Exposure continuity	6 hours/day, 5 days/week
Exposure duration	107 weeks
BMC_{05}	0.042 ppm
Average experimental exposure	0.0075 ppm at the BMC_{05} (0.042 x 6/24 x 5/7)
Human equivalent concentration	0.0016 ppm at the BMC_{05} (gas with extrathoracic respiratory effects, RGDR = 0.21 based on MV = 0.044 L/min and SA(ET) = 3 cm^2)
LOAEL uncertainty factor	not needed in the BMC approach
Subchronic uncertainty factor	1
Interspecies uncertainty factor	3 (since RGDR adjustment was made)
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	30
Inhalation reference exposure level	0.05 ppb (0.4 $\mu g/m^3$)

The data on bronchiecstasis incidence in male and female mice were combined and the chronic REL for chloropicrin was developed using the BMC approach. Of the several models tested, the Gamma MultiHit Model gave the best fit to the combined bronchiecstasis data (p = 0.9750). The MLE_{05} was 0.070 ppm and the BMC_{05} was 0.042 ppm. Use of time extrapolation to equivalent continuous exposure, an RGDR adjustment for the area of the respiratory tract affected, and a total uncertainty factor of 30 resulted in a chronic REL of 0.05 ppb (0.4 $\mu g/m^3$).

The chronic study in mice (Burleigh-Flayer *et al*., 1995) yielded the same NOAEL of 0.1 ppm as the chronic study in rats (Burleigh-Flayer and Benson, 1995). Use of the mouse data with the NOAEL/UF approach led to a cREL estimate of 0.1 ppb. Use of the rat data yielded a chronic REL estimate of 0.2 ppb by the NOAEL/UF approach.

As another comparison, the study of Yoshida *et al*. (1987) found a NOAEL in rats of 0.67 ppm for intermittent exposure for 13 weeks. This is equivalent to a continuous exposure of 120 ppb.

Use of an RGDR of 0.25 for rats and a total uncertainty factor of 100 (3 for subchronic, 3 for interspecies, and 10 for intraspecies) results in a REL estimate of 0.03 ppb (0.2 $\mu g/m^3$).

VII. Data Strengths and Limitations for Development of the REL

Significant strengths in the REL for chloropicrin include the duration of exposure (lifetime) in the key study, the multiple dose study design with adequate sample sizes, and the demonstration of a NOAEL in rats and mice. Major areas of uncertainty are the lack of adequate human exposure data, limited reproductive toxicity data, and the appropriateness of time extrapolation of concentrations that cause irritative effects such as rhinitis.

VIII. Potential for Differential Impacts on Children's Health

Chloropicrin is a respiratory irritant. Respiratory irritants often have steep dose-response curves. Thus use of the human intraspecies factor of 10 should result in a REL that adequately protects children. Exacerbation of asthma, which has a more severe impact on children than on adults, is a known response to some respiratory irritants. However, there is no direct evidence in the literature to quantify such a response to chloropicrin, or to quantify a differential effect of chloropicrin on infants or children. We are currently evaluating our risk assessment methodologies, in particular the intraspecies uncertainty factor (UF_H), for adequacy in protecting infants and children. While we have not so far identified any indications that the currently used UF_H of 10 might be less than adequate to protect infants and children, this possibility should be considered in evaluating any exposure situation involving chronic exposures of infants or children to chloropicrin.

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Response to Comments on the October 1997 Draft of the

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

Responses to Comments on the Methodology and the First Forty Chemicals

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Allied Signal - Naphthalene

Allied Signal Chemicals of Morristown, New Jersey, submitted comments on December 15, 1997 regarding the draft chronic reference exposure level for **naphthalene** presented in the OEHHA Technical Support Document for the Determination of Noncancer Chronic Reference Exposure Levels. The proposed chronic REL was based on a 2-year NTP study (1992) with mice. Olfactory epithelial metaplasia and respiratory epithelial hyperplasia were noted in most (>95%) exposed animals at the lowest concentration (10 ppm) tested but not in any of the control animals. Adjustment for discontinuous exposure and a cumulative 1000-fold uncertainty factor for interspecies differences, intraspecies variability, and lack of a NOAEL resulted in a proposed REL of 9 $\mu g/m^3$ (2 ppb).

Comment 1. In general, additional details of the study should be provided, such as species used, methods of administration, and all results (not just selected findings).

Response. The presentation of research findings has been reviewed and additional details have been added where warranted.

Comment 2. In addition, the results of an unpublished 13-week inhalation study in rats (Coombs, D.W., Kiernan, P.C., Hardy, C.J., Crook, D., Lewis, D.J., and Gopinath, C. Naphthalene: 13-Week Inhalation Study in Rats, Huntingdon Research Centre Ltd., England, Report No. LDA 2/930704, April 28, 1993) is not mentioned.

Response. The document cited has been requested from the study authors and, if a copy of this unpublished study is obtained, a review will be added to the naphthalene section of the OEHHA document.

Comment 3. The summary of the chronic inhalation bioassay in $B6C3F_1$ mice (NTP, 1992) should also include the results/conclusion for carcinogenicity, a primary objective of this study. The lesions mentioned in this summary should be identified as "nonneoplastic" lesions.

Response. The potential carcinogenicity of naphthalene was evaluated separately by OEHHA. OEHHA does not currently consider naphthalene to be a carcinogen, thus any lesions mentioned would be noncarcinogenic. The Technical Support Document focuses on noncancer endpoints as noted in the Introduction.

Comment 4. The data presented in Table 1 do not appear accurate, as the incidence for 0 ppm is for female mice and the incidences for 10 and 30 ppm are for male mice. It seems that the table should include consistent data for both sexes in order to be complete.

Response. OEHHA thanks the commentator for pointing out errors in the table. Corrections have been made.

Comment 5. The draft OEHHA document does not include results from an unpublished subchronic inhalation toxicity study in male and female Sprague-Dawley rats which was conducted by Huntingdon Research Centre Ltd., and then reviewed and found acceptable by the U.S. EPA (Coombs et al., 1993). Rats were exposed to naphthalene vapor for 13-weeks (snout only, 6 hours/day, 5 days/week) at nominal concentrations of 0, 2, 10 or 60 ppm. Compared to controls, treatment-related effects were observed in all groups. In the low-dose group (2 ppm or 0.01 mg/L), male and female rats had minimal degenerative changes and proliferative lesions in the nasal passages. In the mid-dose group (10 ppm or 0.052 mg/L), moderate degenerative and proliferative nasal passage lesions were produced, along with hypertrophy of the respiratory epithelium and decreased body weight gain and food consumption (males only). In the high-dose group (60 ppm or 0.315 mg/L), marked degenerative and proliferative nasal passage lesions were produced, as well as degenerate fibers in the spinal cord and sciatic nerve in one male, and decreased body weight gain and food consumption. Based on this information, the systemic NOEL for both sexes was estimated to be < 2 ppm (0.01 mg/L).

Response. As noted previously, OEHHA thanks the commentator for providing information about this unpublished study. OEHHA is attempting to obtain a copy for review. Based on the data summary provided by the commentator, the results obtained in this 13-week are consistent with those observed in the 104 week NTP bioassay.

Comment 6. The summary of the Shopp et al. study (1984) focuses only on a single finding for which the toxicological significance is not clear (dose-related inhibition of liver aryl hydrocarbon hydroxylase activity in both sexes). The summary should include results of all other parameters evaluated. At a daily dose level of up to 1/4 the LD50 (133 mg/kg) for 90 days, there was no treatment-related mortality, no significant effects on body weight, and no significant changes in organ weights, with the exception of reduced spleen weights in females at 133 mg/kg. Although an organ (spleen) associated with immune function showed decreased weight, there was no evidence of immunotoxicity in any treatment group of either sex. No treatment-related effects were seen in serum enzyme and electrolyte levels. A screen of the effects of the 90-day naphthalene treatment on various aspects of the liver drug metabolizing system indicated no alterations, with the exception of the specific dose-related inhibition of aryl hydrocarbon hydroxylase activity.

Response. Text has been added describing these additional findings of the study of Shopp and associates.

Comment 7. The summary of the Navarro et al. study (1991) does not mention the species used, the method of oral administration, or the number of days the animals were dosed. However, this information can be derived from the reference title. Pregnant female Sprague-Dawley CD rats were administered naphthalene (0, 50, 150, or 450 mg/kg/day) by gavage during gestational days 6-15. The adverse maternal effects observed at the low dose (50 mg/kg/day) consisted of transient clinical signs indicative of CNS depression. By the third day of dosing the dams

acquired a tolerance to the low dose and did not show maternal toxicity thereafter. However, the maternal toxicity (including CNS depression, reduced body weight, and altered food & water consumption) in dams receiving 150 and 450 mg/kg/day was greater and longer lasting.

Response. OEHHA thanks the commentator for this clarifying comment. Additional text has been added to the document.

Comment 8. The summary of the Harris et al, study (1979) does not indicate the method of administration of naphthalene or the species of animal used. Sprague-Dawley rats were administered naphthalene by ip injection.

Response. Clarifying details of this study have been added to the document.

Comment 9. The reference (U.S. EPA, 1986a or b) is confusing in the last two summaries (NZ white rabbit developmental study and rat dermal application study). The rabbit developmental study and the rat dermal application study are listed separately in the reference section as U.S. EPA, 1986 and U.S. EPA, 1986b, respectively.

Response. OEHHA thanks the commentator for noting this error; corrections have been made to the document.

Comment 10. It is our opinion that the use of an interspecies uncertainty factor of 10 and intraspecies uncertainty factor of 10 in the calculation of the REL for naphthalene (9 $\mu g/m^3$) is overly conservative and unrealistic based on the endpoint of upper respiratory system irritation. Rats and mice are far more susceptible to upper respiratory irritation than humans "based on (1) physiological differences in mode of breathing (obligate nasal for rat; oronasal for humans); (2) differences in overall geometry of the nasal passages, including the turbinate profiles; (3) the enormous difference in relative nasal cavity surface areas between rats and humans; (4) differences in the proportion of nasal cavity surface area covered by different epithelia; (5) differences in mucociliary clearance routes, especially in the anterior portion of the nasal cavity; and (6) differences in the inspiratory airflow routes. In rodents, almost 100% of a volatile chemical is absorbed or trapped in the tissues of the nasal passages.

Response. The data on naphthalene effects in the respiratory system suggest that the observed effects are <u>not</u> due to direct irritancy, but rather due to absorption and activation to a reactive metabolite. Thus interspecies comparisons of responses to direct acting irritants is not helpful. Naphthalene has low reactivity and low water solubility. Necrosis of olfactory epithelium (Plopper CG, Suverkropp C, Morin D, Nishio S, Buckpitt A, 1992, Relationship of cytochrome P-450 activity to Clara cell cytotoxicity. I. Histopathologic comparison of the respiratory tract of mice, rats and hamsters after parenteral administration of naphthalene, J Pharmacol Exp Ther 261(1):353-63) and of bronchial Clara cells (O'Brien et al., 1989, Tolerance to multiple doses of the pulmonary toxicant, naphthalene, Toxicol. Appl. Pharmacol. 99(3):487-500) have been noted

in rodents following intraperitoneal injection of naphthalene. Respiratory epithelial cells, as well as liver, appear to be major sites of activation of naphthalene to toxic intermediates.

Comment 11. For example, 10 ppm of naphthalene vapor, which is the NIOSH 10-hour TWA value recommended to protect humans from exposure to naphthalene vapor in the work place, produced an incidence of 96% and 100% nasal effects in male and female mice, respectively in the NTP study (1992). Furthermore, ACGIH recommends an 8-hour TLV TWA value of 10 ppm in view of the fact that irritation is experienced in humans at 15 ppm and that continued exposure at that concentration may result in fairly serious eye effects. (See American Conference Governmental Industrial Hygienists (ACGIH). Documentation of the Threshold Limit Values (TLVs) for Chemicals in the Work Environment, 5th Ed., 1986).

Response. Comparison of the REL with an occupational standard is not particularly informative. OEHHA agrees with the recommendations of USEPA and ACGIH itself that the occupational exposure limits such as NIOSH RELs and ACGIH TLVs are not an appropriate basis for the derivation of RELs to protect the general public, including sensitive subgroups, from exposures over a lifetime.

Comment 12. Taking into account the well documented interspecies differences with respect to nasal or upper respiratory irritation, an interspecies uncertainty factor of 3 is recommended as a more realistic uncertainty factor to use in the calculation of the REL. In fact one could easily justify an uncertainty factor of one.

Response. As noted previously, the data on naphthalene effects in the respiratory system suggest that the observed effects are <u>not</u> due to direct irritancy, but rather due to absorption and activation to a reactive metabolite. It is true that a default interspecies uncertainty factor of 3 was used by OEHHA for most chemicals for which a human equivalent concentration (HEC) was estimated. However, in the case of naphthalene, a factor of 3 was considered to be inadequate, because the major effects noted in human populations exposed to naphthalene, namely hemolytic anemia and cataracts, were not noted in animal studies. Thus available animal studies may underpredict human risks because of the relative insensitivity of rodents to these effects. Therefore a 10-fold interspecies uncertainty factor was used.

Comment 13. In addition, it is thought that the intraspecies uncertainty factor of 10 is much too conservative with materials that are irritants. The distribution from normal to sensitive populations is generally approximately 3-fold. (See Rotman, H.H., Fliegelman, M.J., Moore, T., Smith, R.G., Anglen, D.M., Kowarski, C.J. and Weg, J.G. Effects of low concentration of chlorine on pulmonary function in humans. J. Appl. Physiol. 54: 1120-1124, 1993).

Response: As noted in the previous response, since the mechanism of naphthalene respiratory toxicity differs from that for direct irritants, the variability in human responses to such irritants is not relevant to assessing the variability in human response to naphthalene exposure. In addition, the range of interindividual response may be broad for some irritants (e.g., formaldehyde).

Comment 14: In summary, a more practical REL of 0.022 ppm (~100 μg/m^3) is calculated when an uncertainty factor of 3 is used for both interspecies and intraspecies variability. Considering that only marginal effects were seen in a subchronic inhalation study at 2 ppm in rats, a sensitive species for nasal irritants, 0.022 ppm would clearly represent a safe level for chronic exposure to the general population.

Response: As described above, OEHHA can not support the changes suggested by the commentator in this case. Recently USEPA developed an inhalation reference concentration (RfC) for naphthalene. The USEPA RfC is in fact 3-fold *lower* than that proposed by OEHHA. USEPA used the same study, endpoint, and uncertainty factors as those proposed in 1997 by OEHHA. USEPA, however, added an additional 3-fold database uncertainty factor because of the lack of a two-generation reproductive toxicity study and chronic data for additional species.

Allied Signal – Allied Engineered Materials

Comments on the methodology used in the chronic REL TSD were made by Dr. George Rusch of Allied Signal – Allied Engineered Materials in a letter dated December 19, 1997.

Comment 1. I have reviewed the Technical Support Document dated October 1997, pages 1 - 46. In my judgement, it is well thought out and clearly presents the process to be used for the calculation of RELs. The consideration given to existing guidelines such as the RfDs, ADI and various occupational exposure guidance levels is well described as is the utilization of both toxicology and epidemiology studies. Again, in the area of risk assessment, the utilization of NOAELs and LOAELs are well described. I strongly support the use of variable uncertainty factors which take into consideration the type and severity of the effects observed and their relevance to man. Table 2 on page 21 is most informative. Utilization of all the considerations described in Section 3.2 - 3.6 on pages 22 -31 can lead to robust risk assessments. Table 7 presents a valuable, flexible approach in the calculation of uncertainty factors.

It is, however, important in reviewing the data on specific chemicals that uncertainty factors be carefully selected to most precisely estimate the true uncertainty. There can be a tendency, when looking at multiple uncertainties, to treat each in a conservative fashion such that the combined uncertainty factors is not reflective of the true uncertainty.

Response. The issue of treatment of multiple areas of uncertainty is an area of ongoing evaluation by both OEHHA and US EPA. Multiplying several uncertainty factors could yield unnecessarily conservative exposure guidelines. Thus US EPA has set the maximum uncertainty factor at 3,000 to partially offset such concerns. On the other hand, there are numerous areas of uncertainty not specifically addressed with conventional uncertainty factor approaches. Analysis of data on human variability, including genetic variability, by Dale Hattis and others indicate that human interindividual variability may be much greater than 10-fold for some chemicals. A factor of 10 for intraspecies variability will not be adequate for those chemicals. If an animal model is insensitive to a certain chemical, such as the rabbit model was to thalidomide, the standard interspecies uncertainty factor of 10 would also not protect humans. These uncertainties have been considered to potentially offset any over-conservatism arising from aggregation of multiple uncertainty factors. OEHHA's goal is to develop better data-based approaches in the future, but such methods are time-consuming and data-intensive.

Comment 2. It is also important, in the selection of key studies as the basis for the REL, that the most significant studies be given the greatest consideration. Again, there can be a tendency to select studies with low NOAELs over others that may be of higher quality and greater relevancy to the endpoint being evaluated. Focusing on key studies of good scientific quality will result in meaningful, valuable risk assessments. In contrast, risk assessments that use poor data and large or unsupported uncertainty factors, lack credibility and ultimately are of limited value for protecting the public.

Response. OEHHA agrees that human relevance and data quality are key issues. Human relevance was emphasized and human exposure data were used wherever possible. In numerous cases the key study did not involve the lowest exposure concentration for which adverse effects

have been claimed. In one case a chemical under review was dropped from the document because the scientific database was judged to be inadequate. Numerous other chemicals of concern to California air quality agencies were not included in the current document because of the poor quality of the scientific database. The need for large uncertainty factors can best be addressed by the development of better data. Most toxicity studies have been designed to acquire data for purposes other than health risk assessment and thus are not optimal for that purpose. But by the same token, failing to address potential health impacts because there are limitations in the scientific database would be imprudent public health policy.

Comment 3. My concern is based in part on a brief review of the "Proposed OEHHA Chronic Inhalation REL Summary" which lists RELs for many chemicals. Many of the actual values presented in this table appear to be very conservative. For example, the value of 100 $\mu g/m^3$ for ammonia, a normal biological metabolite, is well below the odor and irritation threshold; that for fluoride is an order of magnitude below the typical dose received by ingestion; and the level for dichlorodifluoromethane is one thousand times below the occupational exposure limit and over 50 thousand times below even marginal effect levels. I would suggest that those conducting the risk assessments review the guidance in the Technical Support Document and reconsider their calculations and approach where the values do not appear supported by the data. This will greatly increase the value of these guidance levels.

Response. The use of uncertainty factors was judicious and compares favorably with those used by US EPA in the derivation of Reference Concentrations (Table 9 of the Chronic Reference Exposure Level TSD). Occupational exposure limits (OELs) were by design not incorporated into this document. This is in accord with the developers of the OELs, who have cautioned against use of such values for protection of the general public. OEL values lack a consistent basis, are designed for healthy workers, and frequently approximate more closely a LOAEL rather than a NOAEL. In addition, frank toxic effects occur in some workers at some TLVs.

The ammonia RfC was adopted as the proposed chronic REL because the US EPA evaluation was considered adequate by OEHHA.

In the case of fluoride, differences in toxicity by route of exposure are known for several chemicals. For example, nickel, chromium VI, beryllium, and cadmium are much more toxic by the inhalation route than by the oral route.

In the case of dichlorodifluoromethane, OEHHA used the maximum uncertainty factor of 3,000 because staff based the REL on a LOAEL from an animal 90-day study (defined by USEPA as a “subchronic study” in rats and mice). To use different UFs we would have to change the default procedure in some way such as considering a guinea pig 90 day experiment to be chronic (and thus using a lower UF) or to have evidence that humans were not more sensitive to dichlorodifluoromethane than animals or that there was limited intraspecies variability to dichlorodifluoromethane. If we had the latter type of information, we would probably also have human data on which to base the chronic REL.

California Mining Association

Comments on the chronic REL for **hydrogen cyanide** were made by Denise M. Jones, Executive Director of the California Mining Association. The proposed chronic REL for HCN is the USEPA RfC of 3 $\mu g/m^3$.

Comment 1. Based on our review of this document, the California Mining Association strongly recommends against adoption of the proposed Chronic Reference Exposure Level (REL) for hydrogen cyanide (HCN). Several of CMA's member companies use dilute sodium cyanide solutions as an essential component of their ore extraction processes. Potential emission sources include heap leach pads, leaching tanks, solution retention ponds, carbon circuit tanks, and electrowining processes. The results of numerous studies investigating potential HCN emissions from the preceding sources are regulated by the Mine Safety and Health Administration (MSHA) at 10 ppm or less in the work place. The MSHA HCN exposure limit is based on peer-reviewed data and was ratified during a formal rulemaking process.

Response. The proposed chronic REL for HCN is the USEPA RfC of 3 $\mu g/m^3$, which has been in use since 1994. All USEPA Reference Concentrations (RfCs), available when the Technical Support Document (TSD) on chronic Reference Exposure Levels was drafted in October 1997, are being used as chronic RELs. RfCs are already used by the USEPA and by California's Department of Toxic Substances Control and were earlier incorporated by reference in Appendix F of the Emissions Inventory Criteria and Guidelines for the Air Toxics "Hot Spots" Program for use in screening risk assessments in the Hot Spots Program. These Guidelines were effective July 1, 1997. The Risk Assessment Advisory Committee (RAAC) recommended that CalEPA harmonize where possible with USEPA on risk assessment. Governor Wilson's Executive Order W-137-96 concerned the enhancement of consistency and uniformity in risk assessment between Cal EPA and USEPA. Use of RfCs as chronic RELs was one action that OEHHA took to address the RAAC recommendation and to implement the Executive Order. RfCs released after October 1997, including ones that are revisions of those in the October 1997 draft, will be evaluated for use in the Hot Spots program by reviewing the scientific basis of each RfC when it becomes available and by determining whether the scientific literature cited in the RfC is appropriate. Appropriate RfCs will be submitted yearly to the SRP for their review and possible endorsement.

The MSHA HCN level is for healthy workers exposed during a normal work-week. The chronic REL is for continuous ambient exposure for the entire population including sensitive individuals, such as infants, children, the elderly, and the respiratory impaired. The MSHA HCN value is not relevant for such exposure, other than to indicate that the chronic REL should be lower than it. OEHHA staff note that the ACGIH has a STEL (ceiling limit) of 5 ppm (5.5 mg/m^3) for HCN, somewhat lower than the MSHA value of 10 ppm.

Comment 2. OEHHA has proposed adoption of the U.S. EPA reference concentration (RFC) for HCN, as published in the IRIS database. Supporting documentation provided for the proposed HCN Chronic REL indicates that U.S. EPA's RFC is based on only one study, performed in Egypt and published in 1975. The Egyptian study evaluated 36 male electroplating

workers in three factories using a mixture of chemical compounds containing cyanide. Based on our review of available literature, and our members considerable experience in the evaluation of the potential health effects of chronic compounds used in the mining industry, the U.S. EPA adopted the HCN RFC without sufficient scientific study. The following summarizes our specific concerns regarding the Egyptian study and U.S. EPA's RFC. No NOAEL was identified. It is uncertain as to whether HCN exposure levels were accurately characterized. No information was supplied to evaluate potentially conflicting factors, such as food supply, lifestyle or working conditions. As a result of the preceding issues, it is not possible to objectively determine whether OEHHA's proposed Chronic HCN REL is more protective of human health than the existing HCN REL. In conclusion, based on our review of available data, no compelling scientific evidence has been supplied by U.S. EPA or OEHHA to justify adoption of the proposed HCN chronic REL. As a result, we strongly recommend against adoption of the proposed HCN chronic REL.

Response. As stated above the chronic REL is for ambient exposure of the general population. The comment points out some of the problems with using human data. Although the REL is based on a single study of 36 exposed humans, hydrogen cyanide is a known metabolic poison and needs a chronic REL. However the commentator does not suggest an alternative study for the development of the REL. The existing animal studies would likely result in a much lower chronic REL due to their subacute/subchronic duration and to the HCN levels tested. OEHHA would be pleased to review any superior study and would also encourage USEPA to do the same.

Chemical Manufacturers Association (CMA) - Ethylene Glycol Panel

Comments on the chronic REL for **ethylene glycol** were received from the Ethylene Glycol Panel of the Chemical Manufacturers Association (CMA). Panel members include BASF Corporation, the Dow Chemical Company, Eastman Chemical Company, Huntsman Corporation, Occidental Chemical Corporation, Shell Chemical Company, and Union Carbide Corporation. OEHHA staff developed a chronic REL of 400 $\mu g/m^3$ based on a 37 day inhalation exposure of prison volunteers to ethylene glycol.

Comment 1. The technical support document provides an ethylene glycol chronic inhalation reference exposure level (REL) of 400 $\mu g/m^3$. However, the Panel notes that the calculations used to derive the REL are flawed. In addition, the uncertainty factors used in the ethylene glycol assessment are overly conservative and should be lowered. As outlined below, using the appropriate values in the calculations and more appropriate uncertainty factors, the chronic inhalation REL for ethylene glycol should be set at 730 $\mu g/m^3$, or higher.

In the technical support document, there appears to be an error in the formula used to derive "ppm" exposure values from "mg/m^3"values. For example, the document indicates that the proposed REL of 0.2 ppm ethylene glycol would be equivalent to 400 $\mu g/m^3$. However, based on the appropriate formula, indicated below, 0.2 ppm ethylene glycol would actually be equivalent to 0.508 mg/m^3, or 508 $\mu g/m^3$.

$$mg/m^3 \text{ at } 25\text{`C and } 760 \text{ mm Hg} = \frac{\text{ppm x molecular weight (EG = 62.07)}}{24.45}$$

$$1 \text{ ppm} = 2.53865 \text{ } mg/m^3$$

$$0.2 \text{ ppm} = 0.508 \text{ } mg/m^3 \text{ or } 508$$

Response. The formula used to convert ppm to mg/m^3 in the document is correct. The human equivalent concentration of 16.7 ppm was divided by a UF of 100 to get an REL of 0.167 ppm or 423 $\mu g/m^3$. Unfortunately both values were subsequently rounded separately to 0.2 ppm and 400 $\mu g/m^3$. When the 0.167 ppm is rounded first to 0.2 ppm, the equivalent value is 508 $\mu g/m^3$, which is rounded to 500 $\mu g/m^3$. Based on this comment OEHHA staff will revise the chronic REL to 500 $\mu g/m^3$.

Comment 2. The exposure levels used as the basis for the REL are inappropriately reported in the technical support document. According to the support document, the basis of the REL is the Wills *et al.* (1974) study, with the REL calculated from the average exposure level from the No Observed Adverse Effect Level (NOAEL). The Wills study, "Inhalation of Aerosolized Ethylene Glycol by Man," is a human study that was conducted by NASA to evaluate the irritant and systemic effects from continuous exposure to ethylene glycol aerosols. During the main study, "twenty volunteers were exposed during 20 to 22 hours per day to aerosolized ethylene glycol in mean daily concentrations between 3 and 67 mg/m^3." However, in its review of the Wills study, the technical support document indicated that the upper end of the exposure concentrations was only 49 mg/m^3 (reported as 20 ppm in the technical document), rather than 67 mg/m^3 (or 26.4 ppm).

Using the correct NOAEL value of 67 mg/m^3 in the derivation equation and the appropriate conversion factor between "mg/m^3 and "ppm", the calculated human equivalent concentration should be 22 ppm. (See footnote 2.)

Response. OEHHA staff used the highest mean value of 49 mg/m^3 (20 ppm) as the No-Observed-Adverse-Effect-Level (NOAEL), not the highest high value of 67 mg/m^3 (rounded from 66.8). (See Table 1 from Wills et al. below.) OEHHA staff believe that 49 mg/m^3 is the appropriate NOAEL.

Table 1. Concentrations of Ethylene Glycol in the Air within the Exposure Chamber

	Concentration of ethylene glycol in air, mg/m^3		
Days	Low	High[a]	Mean
1-7	3.6	75.0	37
8-14	18.8	44.8	29
15-21	0.8	41.6	17
22-28	3.5	49.2	23
29-35	20.6	**66.8**	**49**
36-37	14.4	39.0	31

[a] This column does not include the very high concentrations maintained for comparatively brief periods.

Comment 3. The subchronic uncertainty factor should be reduced from 10 to 3. EPA's IRIS database states that an uncertainty factor "of 3 is used for extrapolation from subchronic to chronic duration due to limited progression between short-term and subchronic exposure and due to rapid metabolism." Ethylene glycol has been shown to have rapid metabolism. Moreover, ethylene glycol respiratory irritation response is due to short-term exposure and does not appear to worsen at subchronic exposure duration, which is supported by the observation in the Wills study with humans exposed up to 30 days.

Response. OEHHA staff consider 30 days to be too short to be considered for a factor less than 10. This length of 30 days is considered by OEHHA staff to be subacute for humans. It is only 0.12% of the 70-year human life span versus 4.2% of a rodent's 2-year life span. Although respiratory irritation might not worsen, the factor of 10 protects against other known systemic effects that may occur over long-term exposure to ethylene glycol in the other 99+% of the human life span.

Comment 4. In addition, it should be noted that the American Conference of Governmental Industrial Hygienists (ACGIH) also considered the Wills study when recommending an occupational exposure level for ethylene glycol. Because of the reported irritation of the upper respiratory tract at 140 mg/m^3 (the LOAEL), ACGIH selected 100 mg/m^3 as the ethylene glycol TLV ceiling value. To the Panel's knowledge, no systemic toxic or irritant effects have been reported in humans from inhalation of ethylene glycol at concentrations less than 100 mg/m^3.

With the corrected human equivalent concentration and the appropriate uncertainty factors applied, the chronic inhalation REL for ethylene glycol should be at least 730 $\mu g/m^3$ (0.287 or 0.3 ppm).

Response. Comment noted. The TLV is for healthy workers and may not protect sensitive individuals in the general population. Furthermore, as stated above, OEHHA staff do not consider 30 days to be a subchronic exposure for humans, although respiratory irritation might not worsen with longer exposure.

Comment 5. The summary section indicates that the critical effects include eye irritation in humans. However, the Wills study did not report any eye irritation, but only respiratory irritation.

Response. The Wills et al. (1974) study did not report any eye irritation. OEHHA staff will delete the reference.

Comment 6. SECTION III - MAJOR USES AND SOURCES: The Panel is concerned with some of the listings in this section which appear to be incorrect, and potentially, dangerously misleading. For example, the technical support document indicates that ethylene glycol is used as a vehicle in some pharmaceutical preparations or as a flavoring, which are inappropriate and certainly not uses recognized by the Panel members. Attached is an information sheet developed by the Panel that provides an overview of recognized uses of ethylene glycol.

Response. This information is from the ethylene glycol file in HSDB and is based on the 1965 edition of Ethel Browning's Toxicology and Metabolism of Industrial Solvents. The file was reviewed by a scientific review panel in 1990. The Ethylene Glycol Panel should make its information available to the National Library of Medicine, maintainers of the HSDB.

Comment 7. SECTION IV - EFFECTS OF HUMAN EXPOSURE. The technical support document includes a review of the Laitinen *et al* study (1995). Attached is the Panel's critique of the Laitinen study. As you will note, given the concerns raised on the clinical chemistry and the analytical methodology; and the findings of ethylene glycol in the control samples, the findings of this study would have to be considered questionable at best. The Panel is also providing a copy of its recent information sheet, "Ethylene Glycol: Research Shows that Normal Skin Contact Is Not Expected to Cause a Health Hazard", which provides an overview of available dermal data on ethylene glycol. In fact, the American Conference of Governmental Industrial Hygienists concluded that a "skin notation", a designation referring to potential exposure by the dermal route, was not necessary for ethylene glycol, given its negligible absorption through the skin

Response. Laitinen et al. made a tentative conclusion from their study of 10 car mechanics: "Therefore, it seems that ethylene glycol is absorbed by skin contact." The study was published in a respected occupational journal and may be questioning the accepted belief about skin

absorption. The point is not critical to the development of the chronic REL. The critique should be sent to the authors of the article or to the journal *Occupational Medicine (Oxford)*.

Comment 8. SECTION V - EFFECTS OF ANIMAL EXPOSURE. The first paragraph of this section includes a review of the DePass study, which indicates that the exposure levels for both rats and mice were 0, 0.04, 0.2, or 1 g/kg/day, and that there were no effects observed in mice. Therefore, the NOAEL for mice would be 1 g/kg/day (1000 mg/kg/day), and not 40 mg/kg/day, as reported in the last sentence.

Response. OEHHA staff regret the error and will change the sentence.

Comment 9. The fourth paragraph of this section includes a review of the Tyl mouse nose-only inhalation study. The technical support document indicates that the NOAEL for maternal effects in this study was 500 mg/m^3, based on increased kidney weights. However, the significance of the kidney weight change has been questioned. The study author herself has concluded "The absence of any treatment-related maternal renal lesions is not unexpected since the mouse appears resistant to ethylene glycol-induced nephrotoxicity after short term exposure, especially since the systemic exposure in the present study is lower than that previously employed (see for example, Price et al., 1985). There is no apparent explanation for the increased maternal kidney weights observed at 1000 and 2500 mg/m^3 by nose-only exposure, in the absence of any microscopic lesions." The Panel believes that the control values were abnormally low in this study. There were no statistically significant differences for relative kidney weights at 1000 mg/m^3 and there were no absolute or relative weight differences in three other inhalation studies at concentrations as high as 2500 mg/m^3. Given that there were no microscopic lesions in the kidneys, that the findings have not been reproduced, and that the author has indicated no apparent explanation for the findings, the kidney weight change should not be used as the basis for the maternal NOAEL in the Tyl study.

Response. Comment noted. OEHHA staff will review the Tyl study in mice, especially the data on controls. However, the true NOAEL for the Tyl study in mice will not influence the chronic REL, which is based on a NOAEL of 50 mg/m^3 (20 ppm) found in a study of respiratory tract irritation in people. The Tyl study also will not influence the respiratory irritation endpoint.

Chemical Manufacturers Association – Isopropanol Panel

Comments on the chronic REL for **isopropanol** (IPA) were made by the Isopropanol Panel of the CMA in a letter from Courtney M. Price dated January 29, 1998. The IPA Panel includes all major U.S. manufacturers of IPA, including: Exxon Chemical Company, BP Chemical Company, ARCO Chemical Company, Shell Chemical Company and Union Carbide Corporation. OEHHA developed a chronic REL of 2,000 $\mu g/m^3$ based on a subchronic (13 week) inhalation study in mice and rats by Burleigh-Flayer et al. (1994).

The Panel believes that IPA should not be listed as an air toxic. Accordingly, the Panel has filed a petition with the California Air Resources Board requesting that IPA be removed from the California list of air toxics. The petition explains that an extensive database exists for IPA and demonstrates that this chemical poses low toxicological concerns. Indeed, IPA is not regulated by the federal government under any environmental statute based on toxicity concerns. A copy of the petition is attached to the comments.

The Panel further asserts:

- OEHHA's chronic toxicity summary for IPA omits discussion of the results of the rat and mouse chronic inhalation studies, which, along with numerous other studies, were conducted by the Panel pursuant to a test rule under Section 4 of the Toxic Substances Control Act (TSCA).

- Any chronic REL for IPA should be derived from the rat chronic inhalation study. This study was of chronic duration by the most relevant route of exposure and demonstrates the lowest "critical toxic effect" of the IPA studies - exacerbation of chronic progressive nephropathy - with a NOAEL of 500 ppm. Applying OEHHA's REL methodology to this NOAEL results in an REL of 7.3 mg/m^3 (3.0 ppm).

- The toxicity summary as currently written bases the critical effect for the chronic REL on changes that are not adverse or relevant to human health. Specifically, OEHHA relies on hyaline droplets in the kidneys of male rats, although the toxicity summary states that these effects are not relevant to humans, and on increased relative liver weights in female mice, although the summary states that this effect may be considered more of a metabolic response than a toxic effect.

- The toxicity summary also credits several questionable findings that the Panel believes should not be included in the toxicity summary. Specifically, the IPA chronic toxicity summary lists three indicators of chronic adverse effects: the development of tolerance of narcosis, blood chemistry changes and reduced fetal body weights. The Panel, however, questions the relevance of the first two effects and the validity of the third effect. The Panel therefore believes that OEHHA should remove references to these questionable findings from its chronic toxicity summary for IPA.

The following Appendices were included:

APPENDIX A. OECD SIDS Dossier for Isopropanol
APPENDIX B. OECD SIDS Initial Assessment Report (SIAR) for Isopropanol
APPENDIX C. Petition of the CMA Isopropanol Panel to Remove Isopropanol from the California List of Air Toxics, Submitted to the California Air Resources Board January 29, 1998
APPENDIX D. Kapp *et al.,* (1996). Isopropanol: Summary of TSCA Test Rule Studies and Relevance to Hazard Identification. *Regulatory Toxicology and Pharmacology* 23: 183-192.
APPENDIX E. Burleigh-Flayer, H., Garman, R., Neptun, D., Bevan, C., Gardiner, T., Kapp, R.,. Tyler, T., and Wright G. (1997). Isopropanol vapor inhalation oncogenicity study in Fischer 344 rats and CD - 1 mice. *Fundam. Appl.* Toxicol., 36:95-111.

Comment 1. Under a Toxic Substances Control Act (TSCA) test rule, Panel members have sponsored extensive studies of IPA, including chronic inhalation studies in rats and mice. All of these studies have been published in the peer-reviewed literature. In addition, the Panel recently worked collaboratively with the United States Environmental Protection Agency (EPA) to prepare a SIDS dossier and SIDS Initial Assessment Report (SIAR) for IPA. Copies of the SIDS dossier and SIAR are attached to these comments as Appendices A and B, respectively.

IPA should not be regulated as an air toxic. The California Air Toxic "Hot Spots" Program lists over 400 chemicals, including IPA, as air toxics for which emissions must be reported and a risk assessment may be required. The Panel believes, however, that IPA is not properly listed as an air toxic. An extensive database exists on the toxicity of IPA and demonstrates that this chemical poses low toxicological concerns. Indeed, IPA is not regulated by the federal government under any environmental statute based on toxicity concerns. IPA is not listed as a federal hazardous air pollutant (HAP), nor is it listed as a "hazardous waste" under the Resource Conservation and Recovery Act (RCRA), a "hazardous substance" under the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA), or a "toxic chemical" under Section 313 of the Emergency Planning and Community Right-to-Know Act (EPCRA). 2 IPA's workplace exposure limits (OSHA permissible exposure limit of 400 ppm) confirm that it is relatively non-toxic.

Moreover, IPA has relatively low photochemical reactivity and has been approved as a substitute for ozone-depleting substances (ODSs). Thus, the removal of IPA from the California air toxics list would facilitate pollution prevention efforts in California, while its retention on that list merely results in unnecessary and wasteful expenditures. Because no toxicological basis exists for listing IPA as an air toxic, and because its listing may have an adverse effect on pollution prevention efforts in California, the Panel has submitted a petition to the California Air Resources Board (CARB) requesting that IPA be removed from the air toxics list. A copy of that petition is included as Appendix C. At a minimum, however, OEHHA should revise its chronic toxicity summary and REL for IPA as described below.

As described in the Panel's petition to remove IPA from the California list of air toxics, EPA has determined that IPA does not meet the criteria for listing under Section 313 of EPCRA; only "isopropyl alcohol (manufacturing - strong acid process") is included on this list. However, the strong acid process is no longer used in the United States.

Response. Isopropanol is currently listed as a Hot Spots chemical and therefore a chronic REL is being proposed. If isopropanol is delisted in California as a Toxic Air Contaminant, then it would likely be removed from the Hot Spots list and the chronic REL would be withdrawn.

Comment 2. The chronic toxicity summary for IPA should discuss the chronic inhalation studies in mice and rats. Because of the extensive studies of IPA conducted by the Panel under a TSCA Section 4 test rule, IPA's human health hazard potential has been extremely well-characterized. The studies that were included in this testing program are identified in Table 1. A review article, which includes citations to several publications of individual studies, is attached as Appendix D.

The EPA's Office of Pollution, Prevention and Toxics (OPPT) has already carefully reviewed all of these studies, and the Agency's assessment of these studies is reflected in a risk management (RM 1) review of IPA, as well as in the SIDS Initial Assessment Report (SIAR) prepared by the Panel and approved by EPA as part of the OECD SIDS program. Moreover, the Panel has striven to ensure that all data produced from its studies are published in the peer-reviewed literature.

TABLE 1. Health Effects Testing for IPA TSCA Section 4 Test Rule Studies

	Test Submission Of Final Report
Mutagenicity Study: Mammalian Cells in Culture	06/90
Developmental Toxicity Studies in Rats and Rabbits	12/90
Subchronic Inhalation Toxicity Studies in Rats and Mice	03/91
Mutagenicity Study: In Vivo Cytogenetics: Micronucleus	03/91
Acute and Subchronic Neurotoxicity Studies in Rats	03/91
Oral and Inhalation Pharmacokinetics Studies in Rats and Mice	03/91
Developmental Neurotoxicity Study in Rats	08/91
Reproductive Toxicity Study in Rats	05/92
Chronic Studies in Rats and Mice	06/94

OEHHA's chronic toxicity summary discusses several of these studies but fails to include the chronic inhalation studies conducted on rats and mice. Indeed, the summary states that a "weakness of the data base for" IPA is that "[n]o long-term studies, spanning a majority of the life span of the test animal, have been performed with isopropyl alcohol." OEHHA's incorrect statement, coupled with its failure to include a discussion of the most recent and relevant studies in the IPA chronic toxicity summary, creates the misleading impression that IPA is a high-production volume chemical that has not been adequately tested. That impression is wrong and should be corrected. In the end, the risk assessments conducted under the Hot Spots program will only be as good as the underlying assumptions and chemical-specific data on which OEHHA relies. It is critical that the most accurate and reliable health hazard information be used. The Panel therefore believes strongly that, if IPA is included in the Hot Spots program, then the technical support document should utilize the chronic studies sponsored by the Panel under TSCA Section 4.

Response. OEHHA prefers to base its RELs on peer-reviewed articles that have been published in the medical and toxicological literature. The chronic study appeared in the peer-reviewed literature after staff had completed its literature review. A summary of the chronic study has been added to the section on Effects of Animal Exposure. The chronic study has been used as the basis of a revised chronic REL.

Comment 3. Any chronic REL for IPA should be derived from the rat chronic inhalation study conducted under TSCA Section 4. Because OEHHA apparently was unaware of the chronic studies of IPA, the proposed IPA REL was calculated using a subchronic inhalation study. Clearly, however, the recent chronic inhalation studies in mice and rats (Burleigh-Flayer et al., 1997), which were conducted in accordance with EPA test guidelines, are more suitable for calculating a chronic REL than the subchronic studies. The results of the chronic studies are summarized below. [OEHHA staff have omitted the commentator's summary of the (negative) results about carcinogenicity since they are not relevant to the chronic REL.]

With regard to systemic chronic toxicity, Burleigh-Flayer *et* al. report that equivocal minimal to mild kidney effects, including renal tubular dilation, were observed in mice. The incidence of renal tubular proteinosis was generally significantly increased for all male and female treatment groups relative to controls; however, the majority of affected animals showed minimal degrees of tubular proteinosis *(i.e.,* only a few tubules affected), there was no concentration-related gradient in either the frequency or severity of this change, and there was no corresponding evidence of alterations to the glomeruli. Mild to moderate degrees of tubular dilation were observed in a small number of females in the 2500 and 5000 ppm groups, but were significantly increased only for the 5000 ppm group. Moreover, this finding was not duplicated in male mice (a significant increase was seen only for the 500 ppm group, but not at the higher dose levels), nor was it accompanied by evidence of tubular cell degeneration or urinary outflow obstruction.

Kidney effects also were observed in the rat following chronic exposure. These effects included some organ weight changes and an exacerbation of chronic progressive nephropathy that occurred in both male and female rats at 2500 and 5000 ppm. Chronic progressive nephropathy is a spontaneous kidney disease of unknown etiology that occurs commonly in aged rats. Although the human health relevance of this condition is unknown, the study researchers considered the effect to be treatment-related and adverse to the rat. (It was considered to be the likely cause of early mortality in some male rats). Exposure to 500 ppm IPA did not produce any effects on the kidney, and is considered the NOAEL for this study.

The Panel believes that rat chronic inhalation study (Burleigh-Flayer *et al, 1997)* should be considered the "critical study" for derivation of an REL for IPA. The study was of chronic duration (two years), by the most relevant route of exposure (inhalation) and demonstrates the lowest "critical toxic effect" of the IPA studies - the exacerbation of chronic progressive nephropathy that occurred in both male and female rats at 2500 and 5000 ppm. This effect should be considered the "critical toxic effect" because it was the likely cause of early mortality in some rats and the study researchers considered the effect to be treatment-related and adverse.

As described above, equivocal effects to the kidney (tubular proteinosis and dilation) were also reported in mice following chronic exposure to IPA vapor. However, it was not clear whether these effects were treatment-related, nor was it clear whether they were adverse effects. Accordingly, the Panel does not consider these effects to be as appropriate for consideration as the "critical toxic effect."

As noted above, OEHHA has generally adopted EPA's RfC methodology for calculating chronic RELs. *See* EPA, *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry*, EPA/600/8-90/066F (October, 1994).

As described above, at 2500 and 5000 ppm, the rats experienced chronic progressive nephropathy. Thus, 2500 ppm should be considered the LOAEL for kidney effects, and 500 ppm can be considered the NOAEL. The NOAEL then must be converted into mg/m , and dosimetrically adjusted to provide a human equivalent concentration (HEQ NOAEL, accounting for the non-continuous duration of the dosing in the inhalation study. Id. at 4-2 1.

Critical Study:	IPA Chronic Rat Inhalation Study (Burleigh-Flayer *et al* 1997)
Critical Toxic Effect:	Chronic progressive nephropathy
Study NOAEL (ppm):	500 ppm
Study NOAEL (mg/m3):	500 ppm x 60.11 */24.45 = 1229 mg/m^3
NOAEL[ADJ]:	1229 x 6/24 x 5/7 = 220 mg/m^3
NOAELWCI:	NOAEL[ADJ] x [b:a lambda(a)/b:a lambda(h)]**
	220 mg/m^3 x 1 = 220 mg/m^3

The molecular weight of IPA is 60.11. For water-soluble compounds such as IPA, a factor of one is used.

Consistent with EPA's RfC methodology, OEHHA's methodology involves the application of uncertainty factors to the NOAELWC1 to arrive at an REL that is designed to be protective of the general population receiving repeated daily exposures over the course of a lifetime. Uncertainty factors can range from one (no uncertainty) to ten (the highest value), with a median of three, for five separate categories of uncertainty: (1) protection of sensitive human subpopulations; (2) extrapolating from animal data to humans; (3) extrapolating from subchronic to chronic exposure levels; (4) extrapolating from a LOAEL to a NOAEL; and (5) accounting for an incomplete data set. [According to EPA, however, a composite (maximum) uncertainty factor involving four areas of uncertainty would be 3,000, reflecting the fact that these factors are interdependent.]

An uncertainty factor of 10 typically is used to protect sensitive human subpopulations. For extrapolation from animal data to humans, EPA recommends, and OEHHA has used, an uncertainty factor of three when relying on default dosimetric adjustments in deriving a NOAEL [HEC] from the NOAEL. The Panel has applied these default adjustments to the chronic IPA study. No uncertainty factor is necessary to extrapolate from a LOAEL to a NOAEL, as a clear NOAEL was identified in the IPA study and was used in these calculations.

Similarly, the inhalation study was of chronic duration, so no uncertainty factor is necessary to extrapolate from subchronic to chronic. [Nor is an uncertainty factor needed to account for an incomplete database. As identified in these comments, and generally described in OEHHA's chronic toxicity summary for IPA, a large database exists for IPA, covering a broad range of endpoints and routes of exposure.] Accordingly, an uncertainty factor of 30 would be applied to the NOAEL [HEC, to derive an REL for IPA.

$$\text{REL} \quad 220 \text{ mg/m}^3 / 30 = 7.3 \text{ mg/m}^3 \text{ (3.0 ppm)}$$

Response. OEHHA agrees with the commentator that the 1997 chronic inhalation study in rats and mice by Burleigh-Flayer et al., which became available too late to be included in the October 1997 draft, is superior to the 1994 subchronic study originally used. OEHHA has based a revised chronic REL for isopropanol on the 1997 study and arrived at the same REL calculated by the commentator. The critical effects occurred in the kidney. Therefore we are revising our document accordingly.

Comment 4. OEHHA should remove references to questionable findings from its chronic toxicity summary for IPA. For the reasons discussed above, the Panel believes that, if an REL is to be derived for IPA, OEHHA should use the chronic inhalation study. However, the Panel also believes that modifications to the IPA chronic toxicity summary are necessary to ensure that the document accurately describes the potential human health effects of IPA. As noted above, the chronic toxicity summary should include a discussion of the chronic inhalation studies. In addition, the Panel believes that the toxicity summary as currently written bases the critical effect for the chronic REL on changes reported in the subchronic inhalation study that OEHHA itself has acknowledged are not adverse or relevant to human health. The toxicity summary also credits several questionable findings from the subchronic inhalation and other studies that the Panel believes should not be included in the toxicity summary. OEHHA derived its chronic REL for IPA from a subchronic inhalation study in rats and mice (Burleigh-Flayer *et al.* 1994). OEHHA states that the critical effects are increased relative liver weight (10 percent over controls) in female mice and hyaline droplets in the kidneys of male rats. Elsewhere in the toxicity summary, however, OEHHA states that the "hyaline droplets found in kidneys of male rats has been shown to be a male rat-specific phenomenon and is not considered to be relevant to human risk assessment." The toxicity summary also states: “Many studies also noted increased liver and kidney weights in exposed animals but with no observable relevant pathology. This change may be considered more of a metabolic response, rather than a toxic effect, of the alcohol.”

The Panel agrees that the kidney effect (hyaline droplets) is not relevant to humans, and that the increased liver weights (and kidney weights in other studies) are more properly considered a metabolic response to exposures to high doses of the alcohol. Because of their equivocal nature, the Panel believes that the increased liver weights and hyaline droplets should not be listed as critical effects for derivation of the chronic REL for IPA.

The toxicity summary also discusses results of some studies that the Panel believes are of questionable validity. Specifically, the IPA chronic toxicity summary lists three sensitive

indicators of IPA chronic adverse effects: the development of tolerance to narcosis, blood chemistry changes and reduced fetal body weights. The Panel, however, questions the relevance of the first two effects and the validity of the third effect, and therefore believes that these effects should not be discussed in the summary.

The first effect, tolerance to narcosis, is questionable as an indicator of chronic adverse effect. Narcosis is clearly adverse, but the diminishing of this effect following repeated exposure (likely through enzyme adaptation) would appear to be a positive adaptation for the animal and not an adverse effect. The second effect, hematological changes (anemia) reportedly was observed in the cited studies, Burleigh-Flayer *et al* (1994) and USEPA/OTS (1986) (actually a BIBRA study). However, anemia was not observed in the IPA chronic study, even though the chronic study involved concentrations as high as that at which the effect was observed by Burleigh-Flayer *et al.* (1994) and the higher equivalent concentration that produced the effect in USEPA/OTS (1986). The fact that the chronic study did not corroborate this finding calls into question the reliability of the anemia effect as an indicator of chronic toxicity.

Response. As indicated above, a summary of the chronic inhalation study has been added to the section on Effects of Animal Exposure. The summary notes the lack of anemia in the chronic study, although it occurred in the subchronic study. OEHHA has reviewed the chronic REL summary for other possible revisions.

Comment 5. The third effect, reduced fetal body weight, is an appropriate indicator of chronic adverse effects. Nonetheless, the conclusion in the toxicity summary that this effect occurred at doses lower than those that caused maternal toxicity is questionable when the data are examined as a whole. Specifically, the OEHHA chronic toxicity summary concludes that the LOAEL for fetal body weight effects in the Tyl *et* al. (1994) study was 400 mg/kg. The data presented in the manuscript do not support this conclusion, however, showing statistically significant changes in fetal body weight only at 800 and 1200 mg/kg, doses which also produced maternal lethality. There was no effect on fetal body weight at 400 mg/kg; thus, this dose level should be considered the NOAEL.

Moreover, although Nelson *et* al. (1988) reported reduced fetal weights at all vapor concentrations (3500, 7500, 10000 ppm) and effects on maternal body weight at only the top two vapor concentrations, this study's assessment of maternal toxicity is suspect given that the recent subchronic and chronic inhalation toxicity studies clearly identified narcotic effects in animals (non-pregnant) at 2500 ppm (Burleigh-Flayer *et* al., 1994, 1997). Nelson may have simply missed these narcotic effects in his study. Although Nelson *et* al. (1988) reported a very slight reduction in fetal weight in the 3500 ppm fetuses (approximately 3%), the study researchers discounted this finding in their discussion as not selective developmental toxicity.

However, except for a small but statistically significant decrease in fetal weight in the case of isopropanol, no effect was detected with either solvent at 3500 ppm. These data indicate that neither of these alcohols is a selective developmental hazard to the developing conceptus.

Similarly, in the two BIBRA studies (reported by OEHHA as US EPA/OTS studies), maternal toxicity also apparently was present at the dose levels at which reduced fetal body weights were reported.

The OEHHA toxicity summary further cites Beyer (1992) (or Bevan *et al.,* 1995) as showing a LOAEL for developmental effects at a dosage that did not produce parental toxicity (1000 mg/kg). In fact, however, several parental effects were observed in this study at 1000 mg/kg, including increases in body weights in females, increases in liver weights without structural changes in females, increases in liver weights with hepatocellular hypertrophy in a few males, and increases in kidney weight and structural changes in males. Nonetheless, OEHHA's interpretation may be correct in that these effects may not be adverse to the animal such that fetal effects were seen in this two-generation reproductive toxicity study in the absence of clear parental toxicity. It should be noted, however, that the developmental toxicity study in rats (Tyl *et al.,* 1994) found clear maternal toxicity (lethality, decreased body weight) at only a slightly higher dosage than was used in Beyer (1200 mg/kg).

(The Panel has access only to abstracts of these studies, rather than to the studies themselves. Thus, it is difficult to interpret the study results and assess fully the adequacy of the studies. Nonetheless, the abstracts report that in both studies, animals had reduced food and water intake at the middle and high dose levels (1.0 and 2.0, and 1.25 and 2.5 percent IPA in drinking water in the reproductive and teratogenicity studies, respectively). The reproductive and embryotoxicity study reports decreased body weights in the middle and high dose female animals, while the teratogenicity study reports decreased body weights only in the high dose females. These results are somewhat surprising in that the middle dose animals in the teratogenicity study were exposed to higher concentrations of IPA than the middle dose animals in the reproductive and embryotoxicity study.)

The Panel believes that a weight-of-the-evidence evaluation of these studies leads to a conclusion that IPA may produce only equivocal minimal selective toxicity to the developing fetus at high doses, but that delays in development generally occur only at levels that produce parental toxicity. The Panel requests that OEHHA reevaluate its discussion on developmental toxicity in light of these comments. The Panel further requests that OEHHA revise its final toxicity summary for IPA to remove references crediting questionable findings to ensure that the public is not misled about the potential human health effects of IPA exposure.

Response. As indicated above, a summary of the chronic inhalation study has been added to the section on Effects of Animal Exposure. OEHHA has reviewed the chronic REL summary for possible revisions. The chronic REL has been revised and the critical effect for the revised REL is kidney lesions as described in the 1997 chronic inhalation study.

In regard to developmental studies, especially fetal body weight effects, OEHHA is very concerned about the possible biological importance of even small weight decrements in (small) animal fetuses, even when the decrements may not be statistically significant. In humans, the logarithm of infant mortality (death before the infant's first birthday) increases linearly as birth weight decreases from 3500 to 1000 grams (Hogue *et al*., 1987; Rees and Hattis, 1994). This log-linear relationship exists on both sides of the birthweight of 2500 g conventionally used as a

cutoff defining low birth weight. There is no evidence for a threshold or break in the curve in this region. Thus any reduction in human birth-weight is a cause for concern since it increases the risk of infant mortality. (Hogue CJ, Buehler JW, Strauss LT, Smith JC. Overview of the National Infant Mortality Surveillance (NIMS) project--design, methods, results. Public Health Rep 1987 Mar-Apr;102(2):126-138; Rees DC, Hattis D. Chapter 8. Developing Quantitative Strategies for Animal to Human Extrapolation. In: Principles and Methods of Toxicology. Third Edition. AW Hayes, editor. New York: Raven, 1994). In the absence of certainty, OEHHA staff take the health protective approach that the reduced weight effect in animal fetuses may be biologically significant and may have import for humans. Tyl et al. (1994) used Dunnett's test to show statistically significant diffrerences between the controls and the 800 and 1200 mg/kg dosed animals (Table 1 of Tyl et al., 1994). Analysis of the data by a trend test showed a highly statistically significant trend ($p<0.001$). In each comparison of rat fetal weight (combined, males only, females only) the fetuses in the 1200 mg/kg dosed group weighed less than those in the 800 mg/kg group, which in turn weighed less than the 400 mg/kg fetuses, which weighed less than the controls. Based on the Hogue et al. results, OEHHA considers the 400 mg/kg group to set a biological LOAEL even if not statistically a LOAEL by a test such as Dunnett's.

Similar to the commentator, OEHHA staff have difficulty when faced with reviewing only the abstracts of studies. It is difficult to base a REL on a one paragraph abstract.

Comment 6. (CONCLUSION). For the reasons set forth in these comments, the Panel believes that IPA should be removed from the list of "air toxics" subject to the "Hot Spots" program. At a minimum, however, OEHHA should derive a chronic REL for IPA using the chronic rat inhalation study, rather than the subchronic study. OEHHA also should remove language from its chronic toxicity summary for IPA that suggests that this chemical has not been adequately studied, and should remove references crediting questionable findings from this document.

Response: OEHHA appreciates the thoroughness of the comments. OEHHA presently has no authority to remove IPA from the Hot Spots list. However, OEHHA has revised its chronic REL for IPA using the rat chronic inhalation study, as suggested by the comment. OEHHA has also reviewed the chronic REL summary and made possible revisions. For example, since a chronic inhalation study is now available, OEHHA included a summary of the study and deleted the statement that no long-term chronic study was available.

Chemical Manufacturers Association - Ketones Panel

The Chemical Manufacturers Association (CMA) Ketones Panel submitted comments on January 28, 1998 in response to the draft chronic reference exposure level (REL) for **methyl ethyl ketone (MEK)**. In the draft TSD OEHHA proposed use of the USEPA Reference Concentration (RfC) of 1,000 $\mu g/m^3$ (0.3 ppm) as the chronic REL. The RfC is based on decreased mean fetal body weight in mice.

Comment 1. OEHHA should re-calculate the REL for MEK using current EPA methodology for deriving inhalation reference concentrations (RfCs). Using current EPA methodology, the REL should be 3.3 mg/m^3 (slightly greater than 1 ppm). The uncertainty factor for MEK for interspecies extrapolation should be 3 and not 10. In the Technical Support Document, OEHHA states that the RELs were developed using the United States Environmental Protection Agency's (EPA) methodology for deriving RfCs. EPA's RfC calculation for MEK is reported in the Integrated Risk Information System (IRIS), an EPA on-line database containing health risk and EPA regulatory information. OEHHA thus based its REL calculations for MEK on the methodology reflected in IRIS. EPA derived the RfC for MEK using a developmental toxicity study (Schwetz et al.; Mast et. al. 1989). RfCs are calculated by applying various "uncertainty factors" (UFs) to account for the uncertainty of applying results from animal testing to humans and for any lack of unequivocal data. The RfC calculation listed in IRIS for MEK was performed in 1992, and uses a default UF of 10 for interspecies extrapolation. In 1994, EPA published new guidance for deriving RfCs. *See* EPA Office of Research and Development, "Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry," EPA No. 600/8-90/066F (Oct. 1994). The new guidance states that, if standard default dosimetric adjustments have been made, an UF of 3 should be used for interspecies extrapolation rather than an UF of 10. Since the 1994 RfC Guidance was issued, the Agency has used this approach for setting a number of RfCs in the IRIS database. The IRIS database clearly indicates that default dosimetric adjustments were made in the case of MEK. However, because the RfC was established before the 1994 RfC Guidance was adopted, an UF of 10 for interspecies extrapolation, rather than an UF of 3, was used to derive the RfC that is currently listed in IRIS. Using the UF of 3 for interspecies extrapolation reduces the total uncertainty factor from 3,000 to 900, and produces a corrected RfC value of 3.3 mg/in^3 (slightly greater than 1 ppm).

Response. All USEPA Reference Concentrations (RfCs), available when the Technical Support Document (TSD) on chronic Reference Exposure Levels was drafted in October 1997, are being proposed as chronic RELs. RfCs are already used by the USEPA and by California's Department of Toxic Substances Control and were earlier incorporated by reference in Appendix F of the Emissions Inventory Criteria and Guidelines for the Air Toxics "Hot Spots" Program for use in screening risk assessments in the Hot Spots Program. These Guidelines were effective July 1, 1997. The Risk Assessment Advisory Committee (RAAC) recommended that CalEPA harmonize where possible with USEPA on risk assessment. Governor's Executive Order W-137-96 concerned the enhancement of consistency and uniformity in risk assessment between Cal EPA and USEPA. Use of RfCs as chronic RELs was one action that OEHHA took to address the RAAC recommendation and to implement the Executive Order. RfCs released after October 1997, including ones that are revisions of those in the October 1997 draft, will be evaluated for

use in the Hot Spots program. OEHHA staff will review the scientific basis of each RfC when it becomes available and determine whether the scientific literature cited in the RfC is appropriate. Appropriate RfCs will be submitted to the SRP for their review and possible endorsement.

In the case of the MEK RfC, OEHHA agrees that the use of a 10-fold intraspecies factor in this case differs from the method more recently supported by USEPA.

Comment 2. This corrected RfC should be considered a conservative value because it is designed to allow continuous exposure for a lifetime of 70 years without adverse effect. Moreover, in the case of MEK, a modifying factor of 3 for incomplete database probably is excessive. A 2-generation reproductive effects study in rats using 2-butanol, which is rapidly converted metabolically to MEK, has been conducted and in fact was used by EPA to derive an oral reference dose (RfD) for MEK. Further, experience with other compounds shows that an UF of 10 for lack of a chronic study usually is higher than necessary (Dourson, M.L. and Stara, L.F., 1983, "Regulatory history and experimental support of uncertainty (safety) factors", *Regulatory Toxicology and Pharmacology*, 3: 224-238).

Response. OEHHA agrees that there is reason to eliminate a modifying factor of 3 for incomplete database. OEHHA has not used modifying factors in the development of its chronic RELs.

Comment 3. EPA has not revised the MEK IRIS data since 1992, and therefore has not re-calculated the RfC for MEK using the 1994 Guidance methodology. The IRIS database RfC for MEK, as a result, is outdated and inaccurate. Because OEHHA used an UF of 10 for MEK in its calculations for interspecies extrapolation, it appears that OEHHA relied on the outdated RfC methodology as reflected in IRIS. The 1994 Guidance clearly dictates that the correct UF for interspecies extrapolation for MEK should be 3. OEHHA should therefore re-calculate the REL for MEK using an UF of 3 for interspecies extrapolation.

Response. OEHHA reevaluated the RfC and proposed REL, which were derived from the data of Schwetz and associates (1991). Using slight differences in approach preferred by OEHHA, a chronic REL value of 10 ppm (30,000 $\mu g/m^3$) was derived. However, this reanalysis presents a situation where the short-term exposure study of Schwetz is no longer the most appropriate study to evaluate potential chronic health effects, since the 90 day inhalation study of Cavender and associates (1983) reported adverse effects at levels close to that reported by Schwetz. From the Cavender study a revised chronic REL of 4 ppm (10,000 $\mu g/m^3$) was derived (table below).

OEHHA revised chronic REL

Study	Cavender *et al*., 1983
Study population	Rats
Exposure method	Inhalation for 90 days
Critical effects	Increased liver weight and relative kidney weight in males and females
LOAEL	5,041 ppm
NOAEL	2,518 ppm
Exposure continuity	6 hours/day; 5 days/week
Average experimental exposure	449.6 ppm for NOAEL group
Human equivalent concentration	449.6 ppm for NOAEL group (gas with systemic effects, based on RGDR = 1.0 using default assumption that lambda (a) = lambda (h))
Exposure duration	90 days
LOAEL UF	1
Subchronic UF	3
Interspecies UF	3
Intraspecies UF	10
Cumulative UF	100
Chronic inhalation reference exposure level (REL)	4 ppm (4,000 ppb; 10 mg/m^3; 10,000 $\mu g/m^3$)

Chemical Manufacturers Association (CMA) - Metal Catalysts Panel

Comments on the Determination of Chronic Toxicity Reference Exposure Levels were received from the Metal Catalysts Panel of the Chemical Manufacturers Association (CMA) in a letter dated January 29, 1998. The CMA Metal Catalysts Panel represents firms manufacturing, using, or reprocessing metal-bearing catalysts, including nickel and nickel compounds. Member firms were Akzo Nobel Chemicals Inc., CRI International, Inc., Criterion Catalyst Co., LP, Crosfield Catalysts, Engelhard Corporation, Gulf Chemical & Metallurgical, Haldor Topsoe, Inc., OM Group, Inc., United Catalysts Inc., and W.R. Grace & Co.

The Panel supported comments separately submitted on the Guidelines and proposed REL for **nickel** by the Nickel Development Institute, the Nickel Producers Environmental Research Association, and Inco United States, Inc (see below). OEHHA proposed a chronic REL of 0.05 $\mu g/m^3$ for nickel based on respiratory system and immune system toxicity.

Chemical Manufacturers Association - Olefins Panel

Comments on the chronic REL for **propylene** were received from Courtney M. Price, on behalf of the Olefins Panel of the Chemical Manufacturers Association (CMA), in a letter dated January 29, 1998.

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

OEHHA developed a chronic inhalation REL of 3,000 $\mu g/m^3$ for propylene based on an inhalation study in rats.

Comment 1. The OEHHA summary for propylene should emphasize the minimal severity and species-specificity of the nasal effects and the NOEL of 10,000 ppm in a 14-week study. The observed nasal effects for propylene are minimal, reversible, and have been observed in only one species. OSHA does not regulate propylene inhalation, and ACGIH has classified propylene as a simple asphyxiant [ACGIH 1997, p.34] -- that is, an essentially inert gas that can cause asphyxiation at high levels due to dilution of oxygen in the atmosphere, but which otherwise does not have significant physiologic effects [ACGIH, 1997]. The nasal effects in the rat provide a basis for deriving a chronic REL simply because they are the only observed adverse effects. OEHHA should emphasize to users of the REL document, however, the minimal severity of the effects and the fact that they have been reported only for one species in one study.

Quest *et al*. (1984; NTP, 1985) reported the appearance of nasal cavity changes in rats following chronic exposure to both the low exposure level of 5,000 ppm and the high exposure level of 10,000 ppm, while there were no such effects observed in mice exposed to the same levels. Based on a review of these data, it is clear that chronic exposure to 5,000 ppm propylene can cause some minimal effects in the nasal cavity of rats (but not mice). These effects include increased incidence of inflammation, not otherwise specified (NOS), with no obvious dose-response relationship, and of squamous metaplasia, again with no obvious dose-response relationship; and increased incidence of epithelial hyperplasia in females only. The lack of a clear dose-response effect complicates the interpretation of the significance of these observations, in particular for inflammation, NOS, where the high exposure level incidences were similar to control values. In addition, epithelial hyperplasia, which was observed in one sex only, generally is reversible upon cessation of treatment.

Overall, the minimal severity of these effects, the general reversibility of epithelial hyperplasia, and the lack of dose-response relationship for the other effects indicate that 5,000 ppm represents a borderline LOAEL/NOAEL. In addition, the 14-week subchronic exposure data (NTP, 1985) demonstrated a clear NOEL of 10,000 ppm, with no effects in nasal cavity of rats, at either 5,000 or 10,000 ppm exposure levels, thus emphasizing the minimal response following chronic exposure to 5,000 ppm. The Panel believes that the OEHHA summary for the propylene REL should emphasize these points.

Response. OEHHA staff agree with the commentator that the effects observed at 5000 ppm in rats, as reported by Quest *et al.*, are of low severity. Staff also agree that the lack of a clear dose-response for some of the observed toxic effects (e.g., squamous metaplasia and inflammation) complicates the interpretation of those particular findings. However, it is important to note that with the squamous metaplasia, a statistically significant response was obtained at the low dose in both sexes and at the high dose in females, therefore a propylene-related effect cannot be ruled out. In addition, while the inflammatory lesions were statistically significant only for low-dose male rats, the incidence among high-dose males was of similar magnitude, suggesting that a plateau effect had occurred over the range of concentrations tested.

OEHHA acknowledges that the toxicity effects observed by Quest *et al.* are of low severity, both in the text of OEHHA's document and in the calculation of the REL, where an uncertainty factor of 3 is used instead of the usual 10 to account for the magnitude of the effect observed at a LOAEL compared with a NOAEL. In regards to epithelial hyperplasia, it may be generally reversible upon cessation of exposure. This is consistent with the determination that this LOAEL is of lower severity. However, in the Quest/NTP study, animals were not observed following exposure, so it is unclear what would have happened in this case. It is important to note that chronic RELs are based on continuous life-time exposures, where reversiblity of tissue damage upon cessation of exposure would not come into play.

The study by Quest/NTP, conducted in rats and mice, was the only chronic inhalation toxicity investigation found for propylene. There are no data on toxic responses from chronic inhalation to propylene from any other species, including humans. While the results of this study do suggest that a species difference exists between rats and mice in response to the inhalation of propylene, the authors also suggest that the difference could be due to a better compensatory reflex apnea defense mechanism, as documented in B6C3F1 mice exposed to formaldehyde. If so, the mice may not have taken in as much of the compound into the respiratory tract, thereby resulting in less tissue damage and a lesser degree of respiratory tract toxicity than that observed in rats.

In regards to OSHA and ACGIH, these organizations develop guidance for healthy workers exposed to chemicals during a normal workweek. The chronic REL is intended to protect against continuous lifetime ambient exposure for the entire population, including those individuals who may be more sensitive to the toxic effects of airborne chemicals. Those individuals include infants, children, the elderly, and those with compromised respiratory systems.

Comment 2. OEHHA should calculate the Human Equivalent Concentration based on the total respiratory tract surface area. OEHHA calculated a Human Equivalent Concentration (HEC) by using a calculated regional gas dosage ratio (RGDR) of 0.21, based on extrathoracic respiratory surface area and a minute volume derived from body weight. The Panel believes that using an RGDR is a plausible method to estimate an equivalent human exposure, but that the RGDR should be based on total respiratory tract surface area, not just on extrathoracic respiratory tract surface area.

The nasal cavity effects seen in rodents are expected to be, in large part, due to the fact that rats are obligate nose-breathers. Humans, however, are not obligate nose-breathers, and generally are mouth- and nose-breathers. The equivalent target tissue for irritation effects in humans would be the entire respiratory tract. Therefore, the Panel believes that if one is to estimate an HEC with an RGDR, the RGDR should be calculated using the surface area for the entire respiratory tract to better approximate the conditions of dose to humans. Thus, based on the methodology described in the Technical Support Document, the calculation of an RGDR for a gas with respiratory effects would be as follows:

$$RGDR = \frac{(\text{Minute volume})_{rat}/(\text{Minute volume})_{human}}{(\text{Surface area})_{rat}/(\text{Surface area})_{human}}$$

The values used by EPA for minute volumes of rats and humans are 2.3996×10^{-4} m^3/min and 0.0138 m^3/min, respectively (EPA, 1994). Using the values cited in the OEHHA Technical Support Document, the total respiratory tract surface areas are 3,440 cm^2 and 543,400 cm^2, for rat and human, respectively. Thus, the calculation for the RGDR would be:

$$\frac{(2.3996 \times 10^{-4})/(0.0138)}{(3{,}440/543{,}400)} = \frac{.017388406}{.006330512} = 2.746761399$$

Use of this factor (2.75) would imply that the exposure level in humans required to result in an equivalent dose per surface area is higher than the exposure level in rats. This is logical as the surface area for the human respiratory tract is much larger than the rat one, about 158 times larger, compared with the 59-fold difference in minute volume. Therefore it would take a much higher exposure concentration in humans than in rats to result in an equivalent dose per surface area for humans. However, to be conservative, the Panel recommends that OEHHA use a factor of 1 to convert the rat LOAEL to a human equivalent concentration.

Response. OEHHA staff determined that the critical effects in the Quest et al. (1984) report were in the extrathoracic portion of the respiratory system, especially the nasal cavity. Thus staff made the HEC adjustment for a gas with extrathoracic respiratory effects and thus calculated a RGDR of 0.21. Staff then used an interspecies UF of 3 since some of the uncertainty/variability in the interspecies extrapolation was subsumed in the HEC correction. That "the equivalent target tissue for irritation effects in humans would be the entire respiratory tract" is possible but since there are no data in humans it is only a guess. In the absence of human data OEHHA staff take a public health protective approach and assume that the target tissue is the same one seen in animals, the nasal epithelium, and use the suggested approach for such an effect.

Comment 3. OEHHA should consider eliminating some uncertainty factors and should acknowledge the conservatism of the propylene REL. Using the foregoing recommendations to derive a chronic inhalation REL for propylene would result in the following values:

Study	Quest *et al.*, 1984; NTP, 1985
Study population	50 rats/group/sex, 300 total

Exposure method	Discontinuous whole body inhalation exposure (0 or 4,985 or 9,891 ppm)
Critical effects	Respiratory tract irritation: species-specific, non-dose-related squamous metaplasia (males and females); epithelial hyperplasia (females only); non-dose-related inflammation (males only) of nasal cavity.
LOAEL/NOAEL	4,985 ppm
NOEL 14-week	10,000 ppm
Exposure continuity	6 hr/d, 5 d/wk
Exposure duration	2 years
Average experimental exposure	890 ppm
Human equivalent concentration	890 ppm (based on entire respiratory tract surface area comparison)
LOAEL uncertainty factor	3 (minimal effects, low severity, reversible or non-dose related)
Subchronic uncertainty factor	1
Interspecies uncertainty factor	3
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	100
Inhalation reference exposure level	8.9 ppm

This value is very conservative. OEHHA applied an uncertainty factor of 3 for use of a low severity LOAEL. The Panel believes that the minimal effects noted at the borderline LOAEL/NOAEL exposure level of 5,000 ppm, the reversibility of the epithelial hyperplasia, and the lack of dose-response for effects such as squamous metaplasia, would support a lower uncertainty factor than the factor of 3 for use of a LOAEL uncertainty factor. Indeed, OEHHA has noted the need to develop a more sophisticated method to address low severity effects. In the case of propylene, the Panel believes that application of the LOAEL uncertainty factor is very conservative.

Furthermore, OEHHA applied an uncertainty factor of 3 for interspecies variation, in addition to the adjustment of the exposure level to a human equivalent concentration. As discussed above, however, the Panel believes an appropriate rat to human conversion would give a HEC that is higher than the rat LOAEL by a factor of 2.75. Thus, use of a factor of 1 for the HEC is already conservative.

The cumulative effect of these uncertainty factors provides an extremely conservative REL. The Panel believes that OEHHA should consider eliminating the uncertainty factors for the LOAEL and for interspecies variation. If OEHHA nevertheless persists in using uncertainty factors of 3 for these parameters, then the REL discussion should point out the very conservative nature of the propylene REL.

Response. OEHHA has used a modified LOAEL to NOAEL uncertainty factor of 3. A factor of 1 would indicate no effect while the data clearly show some effect. OEHHA acknowledges the

need for additional research in order to implement a more sophisticated approach than what we are doing at present. This is stated in our document.

The lower interspecies UF of 3 is used in those cases where an HEC adjustment has been applied since part of the interspecies adjustment involves different configurations of the respiratory system.

The chronic REL must address uncertainties in the available data. Unfortunately, there are very limited data available on the toxicity of propylene. No long-term human toxicologic or epidemiologic studies were located in the literature. No reproductive/developmental data for humans or animals are available. If a better study becomes available, we will use it as the basis for a better health value.

Chemical Manufacturers Association - Phenol Regulatory Task Force

Comments on the chronic REL for **phenol** were made by the CMA's Phenol Regulatory Task Group (Task Group) in a letter dated January 29, 1998. The Task Group is comprised of the major domestic manufacturers of phenol that represent approximately 95 percent of United States production of the chemical. Task Group members include: Allied Signal Inc., Aristech Chemical Corporation, Dakota Gasification Company, Dow Chemical Company, Georgia Gulf Corporation, GE Plastics, GIRSA, Inc., JLM Industries, Inc., Kalama Chemical, Inc., Merichem Company; Shell Chemical Company; and Texaco Refining & Marketing. Associate members are: Borden Inc. and Procter & Gamble. OEHHA proposed a chronic REL of 600 $\mu g/m^3$ for phenol based on reports of systemic effects in mice, rats and monkeys inhaling phenol.

The Task Group urges OEHHA to withdraw its draft chronic toxicity summary and proposed reference exposure level (REL) for phenol. The studies on which OEHHA has relied are inadequate to derive a REL, and the draft chronic toxicity summary does not reflect accurately phenol's potential health effects. All data bearing on phenol's chronic health effects, including data recently generated by members of the Task Group, should be reviewed before OEHHA publishes its chronic toxicity summary or issues a final REL. In restricting its comments to the toxicity summary and related REL, however, the Task Group does not endorse the risk assessment practices, policies, and methods set forth in those Guidelines in whole or in part. Moreover, the Task Group reserves the right to challenge OEHHA's use of the Guidelines to assess or regulate any chemical, including phenol. OEHHA staff provide detailed responses to the appended comments below.

Comment 1. *The studies on which OEHHA relies are not adequate to derive a REL*. OEHHA has based its proposed REL of 0.2 parts per million (ppm) (600 micrograms per cubic meter ($\mu g/m^3$)) for phenol on the findings of two subchronic inhalation studies performed in animal species: Sandage (1961) and Dalin and Kristofferson (1974). These studies are an inadequate basis for deriving a REL. The Sandage (1961) study in rhesus monkeys, rats, and mice detected no adverse effects following continuous exposure to phenol at 5 ppm for 90 days.

The Dalin and Kristofferson (1974) study in rats exposed continuously to phenol concentrations of 26 ppm reported some signs of neurological impairment, but the signs did not last during the whole exposure period and therefore were not considered to be severe. Moreover, the results are inconsistent with those of Deichmann et al. (1944). In the Deichmann et al. study involving inhalation exposure to 26 to 52 ppm phenol, no overt neurological signs were found in mice or rats after 88 and 74 days of exposure. For these reasons, the Task Group believes, that studies on which OEHHA relies are not adequate to derive a REL for phenol, and the proposed REL should be withdrawn.

Even if the studies on which OEHHA relies were an adequate basis for deriving a REL, the approach OEHHA uses to estimate risk does not accurately reflect phenol's potential chronic inhalation hazard. Using the no observed adverse effect level (NOAEL) of 5 ppm

referenced in its draft summary, a comparable human equivalent concentration of approximately 28 ppm would be derived, which, in turn, gives rise to a REL of approximately 1.0 ppm (using the identical uncertainty factors employed by OEHHA).

Moreover, based upon the available toxicity database for phenol, the occupational Safety and Health Administration (OSHA) has established an exposure limit of 5 ppm 8-hour time-weighted average. Identical standards have been established by the National Institute for Occupational Safety and Health (NI0SH) and the American Conference for Governmental Industrial Hygienists (ACGIH). Adjustment of the occupational exposure standard of 5 ppm for continuous rather than workday exposure would derive a REL of 1.0 ppm - a value which is, the Task Group believes, far more defensible than the standard of 0.2 ppm proposed by OEHHA.

REL calculations using human equivalent concentrations are appended as Attachment 1. The Panel notes that OEHHA has computed an HEC of 5 ppm, which is equivalent to the NOAEL. Because OEHHA has not set forth its HEC calculations, the Panel is unable to comment upon these calculations or their effect on that HEC.

Accordingly, RELs derived using existing occupational standards, or animal studies together with appropriate human equivalent concentrations, would yield roughly the same value - one that is considerably higher than that proposed by OEHHA. The Task Group believes that OEHHA's proposed REL is not supported by the data on phenol's toxicity, and will mislead the public about the health significance of exposure to low levels of phenol in the ambient air.

Response. OEHHA staff do not understand the basis for the commentator converting the animal NOAEL of 5 ppm into an HEC of 28 ppm. OEHHA determined that phenol is a gas with systemic effects. We used an RGDR of 1 using default assumptions. Thus the Human Equivalent Concentration (HEC) is the same as the average animal exposure concentration, in this case 5 ppm. The methodology is explained in the introductory chapter of the Technical Support Document and in the 1994 document U.S. Environmental Protection Agency Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry (EPA/600/8-90/066F. Office of Research and Development, Washington, DC). With this methodogy it is rare for the HEC to be greater than the average animal exposure.

In regard to TLVs and PELs, neither USEPA nor OEHHA use work-place standards to calculate RfCs and RELs. In regard to the TLV of 5 ppm, time adjustment to continuous exposure from 40 to 168 hours would result in a value of 1.2 ppm. However, TLVs are usually not NOAELs. They are usually LOAELs and in some cases FELs (Frank Effect Levels) for healthy workers. In the case of phenol the TLV is based on a study of 8 human volunteers who were exposed to from 1.6 to 5.2 ppm phenol by face mask for 8 hours on one day (Piotrowski, 1971). The study did not report any irritation of the eyes, nose and throat. Thus based on this experiment 5.2 ppm (20,002 $\mu g/m^3$) is a NOAEL for an acute exposure. OEHHA used this study as the basis of its acute REL for phenol. For a chronic REL, allowances for extrapolating from a 1 day acute exposure to chronic exposure (for which

precedents are lacking) and for exposing sensitive individuals such as infants, children, asthmatics and the elderly would need to be made.

Other human studies have reported workplace levels of 3.3 ppm phenol (Ohtsuji and Ikeda, 1972), 4 ppm phenol (Connecticut Bureau of Industrial Hygiene, undated), and 1.22-4.95 ppm phenol (Ogata *et al*., 1986). The studies do not mention adverse health effects or years of exposure. For comparison with the REL proposed, assume, for example, that 4 ppm is a human chronic NOAEL. A worker inhales 10 cubic meters of air per workday, so the level of phenol averaged over 7 days would be 1.43 ppm (4 x 10/20 x 5/7). Applying an uncertainty factor of 10 to account for variability in sensitivity in the human population results in a REL of 143 ppb or 550 $\mu g/m^3$, in good agreement with the 600 $\mu g/m^3$ REL derived from animal studies. The comment time-adjusted the TLV of 5 ppm to 1 ppm (3,850 $\mu g/m^3$) but did not make any allowance for variability in sensitivity in the human population. Thus OEHHA is still proposing 600 $\mu g/m^3$ as the chronic REL for phenol.

Comment 2. *Before publishing its chronic toxicity summary and REL, OEHHA must consider all information on phenol's health effects including data being generated by task group members*. The California Toxic Air Contaminant Program provides that OEHHA "shall evaluate the health effects of and prepare recommendations regarding ... toxic air contaminants." In conducting its evaluation, OEHHA must "consider all available scientific data," including, but not limited to, data provided by state and federal agencies, private industry, and public health and environmental organizations. The evaluation must include an assessment of the availability and quality of data on health effects, including potency, mode of action, and other biological factors. OEHHA's Guidelines are intended to help implement this statutory requirement. OEHHA's draft toxicity summary does not, however, review and evaluate all available information on phenol's health effects. Studies or information not reviewed by OEHHA include:

Argus Research Laboratories (1997): In this study conducted in rats exposed by gavage to high levels of phenol, which has been provided to OEHHA by the Non-Prescription Drug Manufacturers Association (NDMA) the only evidence of developmental toxicity observed was a decrease in fetal body weight and an increased incidence of one minor skeletal variation at the high dose level (360 mg/kg/day) only, a dose level associated with serious maternal toxicity. No developmental toxicity was observed at 60 or 120 mg/kg/day, despite the occurrence of significant maternal toxicity at the 120 mg/kg/day level.

ATSDR Toxicological Profile for Phenol (Sept. 1997): OEHHA's chronic toxicity summary for phenol relies heavily on an eight-year old ATSDR toxicological profile. OEHHA apparently has not reviewed, and does not reference, the updated profile for phenol, which was released by ATSDR for public comment in September 1997. The1997 draft profile summarizes a large number of studies addressing phenol's potential health effects that are not included in the 1989 profile.

CMA Pharmacokinetic Study: In this study, provided to EPA by Task Group members in *1994,* no phenol was detected in the blood of rats exposed to phenol in the ambient air at concentrations of 25 ppm, or in drinking water at concentrations of 5,000 ppm. This study demonstrated that, under both exposure conditions, phenol is readily conjugated and detoxified.

The Task Group also urges OEHHA not to publish its chronic toxicity summary, or issue a final REL for phenol, until after it has reviewed additional data generated recently by Task Group members, as well as data that are being generated and which will be available soon. The most recent schedule for completing these data is appended as Attachment 3. These studies are being conducted pursuant to an enforceable consent agreement entered into between the United States Environmental Protection Agency (EPA) and some members of the Task Group to satisfy certain testing proposed by EPA. The testing is intended to characterize phenol's potential for subchronic neurotoxicity, developmental toxicity, reproductive toxicity, and respiratory toxicity and will provide additional data upon which to base a REL. Data completed to date, pursuant to the ECA, include the following:

Subacute Rat Inhalation Study: No toxic effects were detected in the respiratory system of rats exposed to phenol concentrations up to 25 ppm for two weeks. A copy of this study is appended as Attachment 3.

Subchronic Drinking water Study in the Rat: No neurotoxic effects were reported in rats exposed to phenol in drinking water at doses up to 5,000 ppm.

Task Group members also are conducting a two generation reproductive toxicity study in the rat. In its chronic toxicity summary, OEHHA commented that "[n]o multi-generational studies evaluating reproductive or developmental effects under chronic exposure conditions could be identified. " The ongoing CMA study will provide definitive data on this endpoint. CMA is also conducting a neurotoxicity study. These studies will be available no later than, and October 17, 1998, respectively. The Task Group urges OEHHA to defer publishing the chronic toxicity summary, or issuing a final REL for phenol, until it has received and reviewed the data. Publication of the summary and REL at this time would be contrary to the intent embodied in the Health and Safety Code that OEH11A use all available information to characterize toxic air contaminants.

Response. OEHHA appreciates the additional information on phenols. But their relevance to developing a chronic inhalation REL is limited.

Argus Research Laboratories (1997). This is not an inhalation study but a recent gavage study (not yet published in the peer-reviewed literature), that addresses developmental endpoints. It would appear to have limited relevance to developing a chronic inhalation REL.

ATSDR Toxicological Profile for Phenol (Sept. 1997). The chronic REL Technical Support Document was released in October 1997 and thus staff did not have the opportunity to

thoroughly review the ATSDR profile. However, OEHHA did its own literature searches for phenol and referred to ATSDR as a convenient summary document.

CMA Pharmacokinetic Study. In this unpublished study, no phenol was detected in the blood of rats ex posed to phenol in air at 25 ppm, or in drinking water at 5,000 ppm. This study indicates that phenol is readily conjugated and detoxified, but it is not applicable to developing a chronic inhalation exposure level.

Subacute Rat Inhalation Study. No toxic effects were detected in the respiratory system of rats exposed to phenol concentrations up to 25 ppm for two weeks. This result is consistent with the results of the subchronic studies OEHHA staff used to develop the chronic REL.

Subchronic Drinking Water Study in the Rat. It is not clear how a subchronic drinking water study in the rat is relevant to the chronic REL especially since the length of the study is not specified.

Task Group's two generation reproductive toxicity study in the rat due June 17, 1999. OEHHA staff is not willing to delay release of the chronic REL until this report is released. However, we will be happy to review it when it is released to determine if the chronic REL should be revised.

Task Group's a neurotoxicity study due October 17, 1998. As of February 1999 OEHHA staff have not received a copy of this study. However, we will be happy to review it when it is released to determine if the chronic REL should be revised.

Comment 3. *OEHHA should revise its draft toxicity summary to describe more accurately phenol's potential chronic health effects*. The Task Group urges OEHHA to revise its draft chronic toxicity summary for phenol to characterize accurately phenol's potential chronic health effects. In particular, OEHHA has not accurately described phenol's potential developmental and reproductive effects. In its summary, OEHHA reviewed two studies conducted by Jones-Price et al. (1983) ("Teratologic evaluation of phenol in CD-1 rats" and "Teratologic evaluation of phenol in CD-1 mice. Research Triangle Institute) and notes that, in the first study, pregnant rats dosed with 0, 30, 60, and 120 mg/kg/day phenol on gestation days 6-15 exhibited reduced fetal body weight in a dose-related manner. The second study notes that in the fetus, reduced growth, decreased viability, and an increased incidence of cleft palate was also observed at the highest dose.

The Jones-Price et al. (1983a) study does not support the conclusion that phenol causes developmental /reproductive toxicity, for the following reasons.

- EPA has expressed "low confidence" in the Jones-Price et al. studies in its Integrated Risk Information System (IRIS) database because of the gavage nature of dosing.

- A seven percent decrease in fetal body weight (the only endpoint apparently affected in the study, which evaluated dozens of endpoints) is close to the limits of statistics to discern a significant decrease in body weight in a study of this type (five-six percent is the limit). Thus, the effect is at the border of being detectable.

- A seven percent decrease in fetal body weight may not be biologically significant. Decreases in fetal body weight of this small magnitude are usually readily reversible and of no functional consequence.

The average fetal body weight of the control group in this study was high compared to historical controls. This observation calls into question whether the apparent decrease in fetal body weight at the high dose was real and repeatable. The authors did not consider the historical control data in their interpretation of the fetal body weight data.

The authors did however consider historical control data in the interpretation of malformation data. The incidence of malformations was also unusually high in the controls in this study. Based on the comparison with historical controls, the authors concluded phenol had no significant effect on malformation data. A similar comparison with historical controls would show that phenol had no significant effect on fetal weight.

The preliminary range-finding study for the NCTR (1983) rat study showed no effect on fetal body weight at much higher doses. Although the statistical power of the preliminary study was less than that of the full study, one would expect to see some indication of a reduction in fetal weight at the higher doses.

A statistically significant difference was observed at the high dose only. Thus, a clear dose-response relationship was not demonstrated.

The litter size was 12 percent greater in the high dose group than in the control group. An inverse relationship between fetal weight and litter size is well recognized. While a 12 percent increase in litter size is not normally sufficient to explain a significant decrease in fetal weight, given that the decrease was at the limit of statistical significance, one cannot rule out the possibility that increased litter size may have played some role in the difference in fetal weight. Additionally, the combination of the heavier weight control group, plus the increased litter size, may have been sufficient to result in a statistically significant (although minimal) decrease in fetal weight.

Response. In regard to fetal weight differences, the weight decrement of 7% was statistically significant. A weight difference of 7% may be biologically meaningful in a very small, developing animal. The weight decrement of 7% might not be biologically significant if the loss is generally distributed. If it were specific to some organ or system, it could be. In the absence of certainty, OEHHA takes the health protective approach that the effect may be biologically significant. However, the difference in fetal body weights between the experiment cited and historical controls could mean that there was really no difference. Also, as pointed out in the comment, the increase in litter size may also have affected the fetal body

weight. OEHHA prefers to use articles from the peer-reviewed scientific literature to develop RELs since such discrepancies are often noticed by peer reviewers. USEPA's low confidence in the study is a conclusion of their peer review.

A further concern with fetal weight reduction is that in humans the logarithm of infant mortality (death) increases linearly as birth weight decreases from 3500 to 1000 grams (Hogue *et al*., 1987; Rees and Hattis, 1994). This log-linear relationship exists on both sides of the weight (2500 g) conventionally used as a cutoff defining low birth weight. There is no evidence for a threshold. Thus any reduction in fetal weight is a cause for concern. (Hogue CJ, Buehler JW, Strauss LT, Smith JC. Overview of the National Infant Mortality Surveillance (NIMS) project--design, methods, results. Public Health Rep 1987 Mar-Apr;102(2):126-138; Rees DC, Hattis D. Chapter 8. Developing Quantitative Strategies for Animal to Human Extrapolation. In: Principles and Methods of Toxicology. Third Edition. AW Hayes, editor. New York: Raven, 1994)

Comment 4. The chronic toxicity summary should also be revised to correct or clarify the following: *Include Phenol Exposure Levels for End-Points*: In the section of the toxicity summary entitled Effects of Animal Exposures, OEHHA describes a number of subchronic and chronic studies conducted with phenol and concludes that their findings indicate pulmonary damage, liver damage, renal damage, neurological effects, as well as various other chronic effects. The introductory paragraph does not, however, reference the exposure at which these findings were induced. Absent these data, the public cannot accurately assess whether phenol presents any health risk. OEHHA should revise its discussion of the animal studies to indicate levels of exposure at issue and thereby provide a more meaningful and less misleading summary of phenol's potential health effects.

Response. Many toxicological effects occur at fairly high concentrations. OEHHA staff look for the most sensitive toxic endpoint in humans or in an animal that is considered to react like humans to the chemical. Thus, the concentrations used or estimated in the key study are regularly included as well as our estimate of what the LOAEL and NOAEL are. In addition phenol concentrations are given for many of the other studies cited. In OEHHA's chronic toxicity summary for phenol the concentrations used in many of the studies are specifically mentioned.

Comment 5. *OEHHA's Conclusion About the Greater Toxicity of Inhalation Exposure is Not Borne Out by CMA's Study:* OEHHA states that "[c]omparison of the three routes of exposure found that oral exposure was less effective at producing systemic toxic effects possibly due to the rapid metabolism of phenol to sulfate and glucuronide conjugates by the gastrointestinal tract," and that "inhalation is a sensitive route of exposure for laboratory animals." Data from CMA's pharmacokinetic study, however, indicate that under either oral or inhalation exposure, phenol is readily conjugated and detoxified. No phenol was detected in the blood of rats at inhalation concentrations of 25 ppm or after drinking water exposure to concentrations of 5,000 ppm. The Task Group therefore urges OEHHA to revise its

conclusion regarding phenol's purported greater sensitivity through the inhalation route to reflect the findings of CMA's study.

Response. OEHHA based its conclusion on the publications of Deichmann et al. (1944) and NTP (1980) concerning toxic effects of phenol. The comment does not state whether in the CMA study toxic effects were seen in rats ex posed to phenol in air at 25 ppm or in drinking water at 5,000 ppm. The CMA study itself does not state adverse effects by these routes. In fact 25 ppm was probably chosen for inhalation since Deichmann et al. reported no effects at 26 ppm. The CMA study did find transient muscle twitching in rats administered phenol by a third route, gavage, at 150 mg/kg phenol. In any case two free standing NOAELs for different routes of exposure are not an adequate basis to conclude that the routes do not differ in effects. Although other organ systems are more sensitive, phenol would be irritating to the respiratory system at high levels, an effect not likely to be ameliorated by rapid sulfation or glucuronidation. The phenomenon of irritancy would not be tested by measuring phenol concentrations in the blood. There is no indication given that objective measures of irritancy were taken in the CMA rat study. It is difficult to know when a laboratory animal is experiencing irritation until it is rather pronounced.

Comment 6. *OEHHA Should Provide a Statistical Analysis of Study Endpoints:* OEHHA does not apply any statistical analyses of study endpoints, or otherwise describe the strength of the association between exposure to phenol and the relevant effect. Absent such information, the public cannot properly assess the predictive power of the study and its relevance to human exposure.

Response. It has not been customary to provide a statistical analysis of all study endpoints and to mention all concentrations used. Usually an endpoint is mentioned only if it has been adversely affected consistently in exposures to the chemical under study. The toxicity summaries are brief summaries of the literature. It would not be useful to entertain statistical analyses of every study mentioned.

Comment 7. *Correct the Reference to the Jones-Price et al. (1983b) Study:* OEHHA states that increased mortality was detected in rats in this chronic developmental effect study. The study in which increased maternal mortality was detected was conducted with mice, not rats, and the draft should be corrected accordingly.

Response. OEHHA has changed the animal from rats to mice in the summary of the Jones-Price et al. (1983b) study.

Chemical Manufacturers Association – Phthalate Ester Panel

Comments on the chronic REL for **diethylhexylphthalate** (DEHP) were made by the Phthalate Ester Panel of the Chemical Manufacturers Association in a letter dated January 29, 1998. OEHHA proposed a chronic REL for DEHP of 10 $\mu g/m^3$ based on a rat subchronic inhalation study by Klimisch et al. (1992) which found increased liver weight plus the appearance of lung alveolar thickening and foam-cell proliferation.

Comment 1. D*iethylhexylphthalate***.** OEHHA should adjust the DEHP REL to reflect the known greater sensitivity of the rat and should revise its discussion of the effects of DEHP.

Response. OEHHA staff are not aware of available data useful in assessing the relative susceptibility of humans and rats to inhaled DEHP. The commentator does not specify any. It has been the practice of OEHHA as well as USEPA and other authoritative bodies to consider the most sensitive species when estimating potential human health risks based on animal data.

Comment 2. DEHP has very low vapor pressure, so that the study (Klimisch *et al*., 1992) used to derive the REL was performed using a specially-generated aerosol. OEHHA should make that distinction clear to readers.

Response. OEHHA agrees that the vapor pressure of DEHP is low. However air contaminants, such as DEHP, that exist mostly or entirely as particulates rather than vapors may still be present at levels hazardous to human health. The low vapor pressure of DEHP was indicated or reflected at several locations in the document. (1) Mass concentration units ($\mu g/m^3$) were not converted to volume concentration units (ppb) in the Chronic Toxicity Summary (p. A-186). (2) The vapor pressure is reported in the Physical and Chemical Properties Summary (p. A-186). (3) The particulate nature of DEHP administered by Klimisch and associates (1992), as well as by Schmezer and colleagues (1988), was described in the experimental summary (p. A-187). The review of the study of Merkle and associates (1988) did not specifically mention the particulate nature of the administered DEHP. Text is being added at several locations in the document to emphasize the particulate nature of DEHP at concentrations experimentally studied.

Comment 3. OEHHA also should emphasize that the effects observed in Klimisch, et al., were reversible upon cessation of treatment.

Response. The apparent resolution of adverse findings after an eight-week post-exposure period was noted in the document (A-187). Additional text is being added to "Section VI. Derivation of Chronic Reference Exposure Level" to clarify this point. However, it should be noted the OEHHA chronic reference exposure levels specifically address the potential health effects from continuous lifetime exposures. Issues specific to

intermittent or less-than-lifetime exposures such as resolution of adverse effects over time are not addressed in this document.

Comment 4. OEHHA has incorrectly identified liver weight increase as a critical effect in this study, and should list only the lung effects as a critical effect. In addition, OEHHA has incorrectly characterized other studies as demonstrating a potential for DEHP inhalation to cause pulmonary effects. OEHHA should revise its discussion to correct these mischaracterizations.

Response. Relative liver weights were significantly increased in males and females at the LOAEL dose in the Klimisch et al. (1992) study, and absolute liver weights were significantly increased at that dose. No histopathological evidence of liver toxicity was noted, and the authors considered the effects secondary to toxicity at other sites. The text in the document is being changed to emphasize that the primary adverse effects observed at the LOAEL dose were increased lung weights, accompanied by foam-cell proliferation and alveolar septi thickening.

Comment 5. OEHHA should not apply an interspecies uncertainty factor to derive the REL. Extensive data demonstrate that primates are far less susceptible to DEHP effects than the rat. Indeed, OEHHA should adjust the REL by a factor of 0.2 to account for the known difference between primates and rats.

Response. The existing database of relative toxicity of substances toward different species does not support assuming species more closely linked evolutionarily will respond to chemical exposures more similarly than distantly related species. Among the two most commonly studied rodent species, rats and mice, large differences in susceptibility have frequently been reported. Also relative species susceptibility observed for oral exposures may differ from that observed for inhalation exposures, in part because of large species difference in lung anatomy.

Chemical Manufacturers Association (CMA) - Propylene Glycol Methyl Ether Panel

Comments on the chronic REL proposed for **propylene glycol methyl ether** (PGME) were received from the Propylene Glycol Methyl Ether Panel of the Chemical Manufacturers Association (CMA). The proposed chronic REL is the USEPA RfC of 2,000 $\mu g/m^3$ based on neurotoxicity.

Comment 1. The TSD proposes an REL for PGME of 2,000 $\mu g/m^3$ (0.6 ppm) by explicitly accepting U.S. EPA's Reference Concentration (RfC) for the compound. EPA derived this RfC by applying an uncertainty factor of 300 (factors of 10 each for the absence of a chronic study and intraspecies variability, and a factor of 3 for interspecies differences) to the 1,000 ppm No Effect Levels (NOEL's) in the Landry (1983) rat and rabbit 13-week inhalation studies. The observed effects of note at 3,000 ppm were

transient sedation in both species that resolved after the first one-two weeks of exposure and an adaptive hepatocellular swelling in rats with no evidence of degenerative changes.

Response. USEPA Reference Concentrations (RfCs), available when the chronic REL TSD was drafted in October 1997, are being used as chronic Reference Exposure Levels (RELs). RfCs are already in use by California's Department of Toxic Substances Control and by the USEPA and were earlier incorporated by reference in Appendix F of the Emissions Inventory Criteria and Guidelines for the Air Toxics "Hot Spots" Program for use in screening risk assessments in the Hot Spots Program. These Guidelines were effective July 1, 1997. The RfCs were recommended for use by OEHHA by the Risk Assessment Advisory Committee (RAAC) and used in response to Governor Wilson's Executive Order W-137-96 which concerned the enhancement of consistency and uniformity in risk assessment. RfCs released after October 1997 will be evaluated for use by reviewing each new RfC as it becomes available. Acceptable RfCs will be submitted yearly to the SRP for review and possible endorsement.

Comment 2. The Panel has recently completed lifetime studies of PGME in rats and mice exposed to 0, 300, 1,000 or 3,000 ppm PGME vapor for two years. As in the Landry study, sedation was observed at 3,000 ppm for both species, but, again, the effects had resolved by the second week of the study. PGME did not cause a dose-related increase in tumors in males or females of either species. Lifetime NOELs of 300 ppm were determined for both rats and mice.

We recommend employing this chronic study in the REL determination to eliminate the need for a subchronic vs. chronic uncertainty factor of 10 in the RfC/REL calculation. Because this study has just recently been completed, the final laboratory report has not yet been issued. However we will send the full report to you as soon as possible.

Response. Staff appreciates receiving the documentation of a chronic study of exposure to PGME and looks forward to the full report. A lifetime NOEL of 300 ppm from an exposure continuity of presumably 6 hours per day, five days per week results in an average experimental exposure of 54 ppm and a human equivalent concentration (HEC) of 54 ppm. Applying a total uncertainty factor of 30 (3 for interspecies UF and 10 for intraspecies UF) to the HEC results in a REL of 1.8 ppm, 3-fold higher than the RfC of 0.6 ppm. Staff will reconsider the proposed REL when the study is finalized. OEHHA staff encourage the commentator to submit the study to a peer-reviewed journal in order to increase the acceptability of the results.

Comment 3. The Panel has also recently completed a two-generation reproduction study of PGME in rats. We enclose that study report. As you will see, the NOEL for fertility and reproductive effects was 1,000 ppm; no effects were seen in the parents at 300 ppm. Decreased female fertility and reproductive effects were found at the highest concentration tested, 3,000 ppm PGME. These effects were associated with general toxicity and apparent resultant nutritional stress by the mothers and offspring at this high

concentration of PGME and not thought to be due to direct toxicity to reproductive organs.

Response. Staff appreciates the information on these endpoints. Both the proposed REL/RfC and a REL based on the chronic study described above should be protective against adverse reproductive effects.

Chemical Manufacturers Association – Hydrocarbon Solvents Panel (Xylenes)

Comments on the chronic REL for **xylenes** were made by the Hydrocarbon Solvents Panel of the Chemical Manufacturers Association. The Panel's members include: CITGO Petroleum Company, Exxon Chemical Company, Koch Chemical Company, Mobil Chemical Company, Phillips 66 Chemical, Shell Chemical Company, and Sun Company. OEHHA developed a chronic REL of 700 $\mu g/m^3$ from a study of 175 xylene-exposed factory workers by Uchida et al. (1993). Critical effects were nervous system effects as well as irritation of the eyes, nose and throat.

Comment 1. The Chemical Manufacturers Association (CMA) Hydrocarbon Solvents Panel has reviewed the Reference Level (REL) proposed for xylenes. We find the human study upon which that value is based seriously flawed and urge California not to establish an REL based on that study. We also include comments on the Technical Support Document's (TSD's) discussion of animal developmental studies of xylenes.

Response. Responses to the substantive issues are provided below.

Comment 2. THE PROPOSED REL. California proposes an REL of 0.05 ppm (200 $\mu g/m^3$) for xylenes. That value is derived from the Uchida et al. (1993) study of factory workers, which OEHHA interprets as finding a Lowest Observed Adverse Effect Level (LOAEL) of 14.2 ppm and no NOAEL. The critical effects specified are increases in the prevalence of eye irritation, sore throat, floating sensation and poor appetite. OEHHA converts the reported average 14.2 ppm workplace exposures to a continuous lifetime exposure of 5.1 ppm and then applies an uncertainty factor of 100 (10 for the absence of a NOAEL and 10 for intraspecies difference) to obtain the 0.05 ppm REL.

SIGNIFICANT FLAWS IN THE UCHIDA STUDY. The Uchida study suffers from a number of serious deficiencies and limitations in the design and reporting that render it unreliable for risk assessment.

Absence of Well-Documented Health Effects Data. First, Uchida, *et al.* used a subjective symptom questionnaire to assess health effects and thus did not obtain well-documented or reliable data on health effects. Symptom questionnaires may be substantially influenced by response bias and are therefore not reliable indicators of adverse health effects. The authors reported no control for such a potential bias (e.g., blinded interview), nor any validation of the subjective survey (e.g., a neurobehavioral or irritancy assessment).

Response. As noted by the comment, the subjective reports are not objectively verified by other measures. We agree that such verification would provide additional confidence in the subjective reports. The Uchida et al. (1993) article does not indicate whether the survey was blinded. We also agree that blinded interviews reduce the likelihood of inadvertent bias; the comment therefore raises a substantial potential limitation of this study. Here, the simplicity of the task and of the questions mitigates the potential for

such bias. Furthermore, and more importantly, the overall prevalence of subjective symptoms during work was greatly increased in the workers exposed to xylene as compared to the controls (19.2% versus 4.0%). With respect to many individual symptoms (e.g., eye irritation, nasal irritation, sore throat, floating sensation, and headache) the differences between exposed and unexposed workers were as great or greater than the overall prevalence. The magnitude of the observed differences makes such bias an unlikely explanation. The magnitude of the response differences also reduces concerns regarding the lack of an objective validation of the subjective complaints.

Comment 3. Other apparent problems with the symptom survey are an inherent bias to irritation and CNS symptoms (especially Part 1) and a duplication of like symptoms (e.g., dizziness, floating sensation, drunken feeling). This problem may have resulted in inflated prevalence results in the exposed workers.

Response. The comment asserts that there was an inherent bias toward irritation and CNS symptoms in the questionnaire. The sensory and subjective symptoms of Part 1 of the questionnaire (unusual smell, unusual taste, and face flushing aside) solely relate to irritative and CNS depressant effects. The Part I survey results are therefore experimentally limited to finding only effects related to irritancy and CNS depression. This limitation is not a bias that would affect the validity of the results as to the health effects covered by the survey. This limitation was appropriate given the known ability of many solvents to cause irritation and CNS depression. However, the absence (except for facial flushing) from the list of other symptoms not associated with the known health effects of xylene exposure is of some relevance. The presence of other unrelated symptoms on the list could have served as an internal control for false positive results. Here, the prevalence of the likely unrelated facial flushing symptom was not increased. In addition, the prevalence of the drunkenness symptom (the most severe symptom of CNS depression) was not increased.

As the comment points out, the duplication of like symptoms in the questionnaire has the potential to inflate the <u>overall</u> prevalence rates. However, this duplication is substantially mitigated by the means of calculating prevalence rates which takes the number of questions into account. The prevalence rate for a group is calculated by dividing the number of affirmative answers by the group by the number of people in the group and dividing that result by the number of questions asked.

Here, the key question is whether or not the inflation in overall prevalence rates could have biased the results so as to produce a false positive rate for the study as a whole. This clearly is not the case. If one considers only those workers who report no symptoms, duplicative symptoms would not be an issue. For symptoms during work, the great majority of controls (189 out of 241 unexposed workers or 78%) report no symptoms; by contrast only a very small percentage of the exposed workers (37 out of 175 or 21%) report no symptoms. Although the overall prevalence rates at issue here include unusual smell and unusual taste as symptoms, OEHHA would not consider these

sensations as symptoms of toxic injury. However, the individual results for these two 'symptoms' suggests that they do not importantly contribute to the overall prevalence rates. Nevertheless, while the overall prevalence rates are positive, our draft document did not base its analysis on the overall prevalence rates alone. Uchida et al. (1993) also presented the prevalence results for each individual symptom that was significantly elevated. Our conclusions were also based on those data. Duplication of like symptoms does not affect those prevalence rates.

Comment 4. Odor may also have contributed to the subjective response results of the exposed workers. Dalton et al. (1997) recently demonstrated that both perceived odor and cognitive expectations about a chemical can significantly affect the reporting of health symptoms.

Response. In Dalton et al. (1997) subjects with a *positive* bias (having been told that the test substance was beneficial) reported less irritation from short-term exposures to acetone (800 ppm) or phenylethyl alcohol. However, subjects with a *negative* bias (having been told the substances were harmful over the long term) evinced no consistent differences from subjects with a neutral bias (having been given no health hazard information). The Uchida et al. (1993) study participant biases are likely either neutral or negative. The comment is not clear as to the source of the cognitive expectations regarding xylene or as to which symptoms they would be relevant. To the extent those expectations are based upon the actual experience of workers, they are of much less concern with respect to confounding.

The Dalton et al. (1997) analysis also posited that, if irritancy is primarily a function of both odor intensity and cognitive expectations, then odor intensity should be a predictor of irritancy. With respect to acetone, the test compound, this correlation held up. However, Dalton et al (!997) could not well control for the possibility that the irritancy of acetone (at a test concentration of 800 ppm) affected the reports of its odor intensity.

Interestingly, Doty et al. (1977) (cited in Dalton et al. (1997)) tested p-xylene for its ability to intranasally stimulate the trigeminal nerve in anosmic subjects. Trigeminal nerve stimulation relates to the irritancy or pungency of a compound as opposed to its odor. These anosmic subjects rated p-xylene on average as a 3.69 in overall intensity (the intensity scale ranged from very weak which had a value of one to very strong with a value of nine) as measured along several attributes (strength, pleasantness, warmth, safety). Thus, when p-xylene was actually tested, odor was not necessary to detect the trigeminal response to p-xylene.

The relationship between odor and pungency is apparently a complex one. Cometto-Muniz et al. (1990) (cited in Dalton et al. (1997)) reported that the odor threshold and pungency threshold for eight aliphatic alcohols (methanol to octanol) varied from 23-fold to 10,000-fold.

Furthermore, in Uchida et al. (1993), the subjective complaints of the workers over the prior three months were also elevated. While odor may arguably have contributed to the subjective responses of the exposed workers, odor is much less likely to account for the symptoms experienced while workers are not on the job. In addition, as to on-the-job complaints, the sensation of unusual smell was not reported to be significantly increased.

Comment 5. Limited Exposure Data. Second, the Uchida study's assessment of worker exposures is similarly problematic. The study relied on a single point estimate, one 8-hour air sample (time-weighted average, TWA), to characterize "chronic" solvent exposure. The TWA concentrations of xylene did not indicate maximum concentrations, which the authors admitted might have influenced the subjective symptom prevalence.

Also, no evaluations for other non-solvent exposures were included, although workers may have been exposed to such materials in rubber boot production (e.g., adhesives), plastic-coated wire production (e.g., metals), or printing work (e.g., pigments).

Response. For each exposed worker in the study, Uchida et al. (1993) assessed exposure over the period of an entire shift. The LOAEL of 14.2 ppm is based upon the geometric mean of 175 such exposure measures taken on the day before the questionnaire was administered. The measurements and survey instruments are therefore very close in time. We therefore have high confidence in the representativeness of those measurements.

With respect to the prevalence of symptoms on the job, the comment presents a substantial uncertainty as to the interpretation of the findings. Acute exposures to xylene can cause irritation of the eyes and respiratory tract as well as CNS depression. Therefore, with respect to the prevalence of symptoms reported on the job, there is uncertainty whether some of the symptoms with a potentially quick onset (eye irritation) relate to the peak exposures as much as to the 8-hour average exposures. Other symptoms (e.g., sore throat, headache) may not be as responsive to peak concentrations. With respect to symptoms outside of work, short-term variations in xylene exposure are much less a concern and the 8-hour time weighted average is more clearly a reasonable measure of exposure.

The comment suggests that perhaps other exposures could have accounted for the observed results. The study specifically addressed the potential for confounding by a variety of other solvents, which could produce a similar spectrum of effects. The spectrum of effects found here parallel closely with those previously reported for xylene; it seems improbable therefore that this same spectrum of relatively typical effects would be due to a confounding agent. Furthermore, with respect to subjective symptoms at work, very few of the exposed workers were without symptoms. Thus, each of the three workplaces studied would have to have been independently subject to such confounding. This appears particularly unlikely.

Comment 6. Failure to Assess Exposure Variations and Worker Hygiene Practices. Third, the relationship of duration of exposure to health effects was not specifically assessed, as the authors did not attempt to differentiate acute from chronic effects through evaluation of changes in symptom magnitude over time. Variations in an individual's length of time on the job or changes in work assignments over time could have resulted in differences in exposure that would have affected interpretation of chronic health effects.

Response. As noted in the comment, the Uchida et al. (1993) study does not well differentiate whether the observed adverse effects are the result of a long-term chronic exposure or are simply short term effects repeatedly occurring as the result of daily repeated exposures. The characterization of the effects as chronic or something much less than chronic is therefore uncertain.

It is not likely that symptoms away from the job, as compared to symptoms while at work, relate to peak exposures on any given day. Symptoms away from the job more likely relate to the prior cumulative exposure/duration and not peak concentrations.

The comment is correct that the available information does not distinguish whether any given symptom is more closely related to the prior shift's average exposure, the prior week's average exposure, or the prior year's average exposure. If we assume that only the prior day's exposure contributed to the observed symptoms, then the dose response analysis below would suggest the daily REL which would be protective of health. If we assume, at the opposite extreme, that the prior annual exposure accounts for the observed symptoms, the dose response analysis below provides the annual (chronic) REL value that would be protective of public health. The difference in the magnitude of these two RELs is small. Their principal practical difference relates to the time frame for which they would be applied. A daily REL of 0.07 ppm would result in a hazard index greater than one if exposures exceeded that level for any given day in a year. A chronic REL of 0.05 ppm would allow prolonged excursions above the 0.07 ppm level providing that they were balanced by exposure periods equally below 0.05 ppm such that the ground level concentration divided by the REL would be less than one.

	Daily Exposure	Annual Exposure
LOAEL:	14.2 ppm	14.2 ppm
Average exposure concentration*	7.1 ppm	5.1 ppm
LOAEL uncertainty factor	10	10
Subchronic uncertainty factor	1	1
Intraspecies uncertainty factor	10	10
Cumulative uncertainty factor	100	100
Inhalation reference exposure level	0.07 ppm	0.05 ppm
Applicable period	Daily	Annually

*For daily exposure, the standard continuity adjustment factor of 10/20 was applied. For annual exposure, the standard factors of 10/20 x 5/7 were applied.

Thus, with respect to dose response assessment, knowing whether or not the observed effects are subacute or chronic (or something in between) is not essential, in this context, to derive a reasonable and health protective chronic REL.

Comment 7. Finally, the authors did not comment on the workers' hygiene practices at the factories, specifically whether the workers wore gloves or instead had dermal contact with multiple solvents and other chemicals. Substantial dermal exposure would have complicated an accurate estimation of the worker exposure.

Response. One of the symptoms reported to be increased in both men and women was rough skin. This symptom would be consistent with solvent dermatitis and would therefore indicate the likelihood of skin contact. Thus, as noted in the comment, dermal absorption is a potential confounding effect. However, in a companion paper, Uchida et al. (1993) have extensively analyzed the relationship between urinary metabolite measurements and the actual xylene air levels for these same workers. Their analyses showed a very strong correlation between the measured air levels and the urinary metabolite levels. The parameters of the curve relating urinary metabolite levels to these air concentrations indicated that at the reported median air concentration of 14.2 ppm, the great bulk of the urinary metabolite levels would be predicted by the air concentration data. Thus, use of the air concentration data as the estimate of exposure is appropriate. Furthermore, dermal exposure relates much more to systemic effects than to such site-of-contact effects as eye and respiratory tract irritation.

Comment 8. There are a number of other less serious problems in the study. These problems, however, cannot be critically assessed because of a lack of sufficient detail given in the report. Taken together, the above problems in the health and exposure assessments of the Uchida study do not permit definitive conclusions of causality of adverse health effects associated with xylene exposure. This study should not be used for risk assessment of xylenes.

Response. The study’s subjective symptom survey does have limitations. The principal limitation, for our purposes, is that the key study data comes only from the results of a subjective symptom questionnaire. However, the magnitude of the differences observed for prevalence rates for many of the on-the-job symptoms reported to be increased in exposed workers as compared to unexposed workers (e.g., eye irritation: 25.1% v. 6.6%; nasal irritation: 40.6% v. 9.1%; sore throat: 31.4% v. 4.6%; floating sensation: 49.7% v. 8.3%; and headache: 22.9% v. 6.6%) strongly supports their use. For several of the symptoms while not at work over the past three months, there were also substantial differences in symptom prevalence in both men and women and in combination (forgetfulness: 33 v. 18%; nightmare: 40% v. 19%; anxiety: 12% v. 3%; inability to concentrate: 12% v. 3%). (These numerical values are estimated from graphical data in

Uchida et al. (1993), figure 2.) Given the potential for xylene to affect the CNS system in other studies, these symptoms are also of concern.

The temporal relationship between effects and exposure is not known. For some of the effects (eye irritation, nasal irritation), very short-term exposures may be more relevant than the longer term exposure history. For effects while not on the job, this concern is not as great. However, for the purposes of protecting the public health, this uncertainty as to the relevant exposure time frame is not a practical barrier to use of the study.

The exposure information itself is strong. Each of the 175 exposed subjects exposures were monitored on the day before their survey was conducted. The companion paper indicates that dermal exposure was not a major contributor to dose. The lack of complete industrial hygiene therefore is a minor limitation.

For these reasons, the study is suitable for use in deriving a chronic REL.

Comment 9. MISCHARACTERIZATION OF DEVELOPMENTAL EFFECTS. The TSD's discussion of the xylene animal developmental toxicity database does not include a critical and complete review of the xylene developmental toxicity studies. It thus suggests the erroneous conclusion that xylenes cause adverse developmental effects. There are substantial experimental design and data interpretation flaws in the cited studies that must be considered, and the well-conducted Biodynamics (1983) study, which did not find xylene to be a developmental toxicant, is not even cited. If you would like a copy of the Biodynamics study, as referenced, please contact Barbara Francis at (703)741-5609.

Response. The documentation for xylene devoted one paragraph in the TSD to its potential developmental toxicity. OEHHA did not purport to develop and provide an overall weight-of-the-evidence determination as to the potential developmental toxicity of xylene in one paragraph. The document itself offers no conclusion of its own regarding the overall weight of the evidence as to the potential developmental toxicity of xylene. The document does however put the reader on notice as to the existence of a substantial body of evidence that bears on the developmental toxicity of xylene.

The document quotes the 1995 ATSDR review, Toxicological Profile of Xylenes, thusly: "ATSDR concluded that the body of information available for the developmental effects are consistent with the hypothesis that xylene is fetotoxic and many fetotoxic responses are secondary to maternal toxicity." The paragraph then went on to briefly summarize some of the findings of the major studies bearing on the question of developmental toxicity. A principal purpose of the document is to provide background information relevant to the selection of the key study for dose response purposes. As with other health effects, the developmental toxicity data for xylene are presented with dose response information to make clear the margin of exposure between the proposed REL and other reported adverse effects.

Any inference that OEHHA inappropriately failed to cite the Biodynamics (1983) study would be incorrect. The ATSDR addressed the Biodynamics (1983) study in its review and did not find that it indicated the absence of an adverse effect on development. The ATSDR rather included the Biodynamics (1983) study in a group of studies which "had limitations that made them difficult to assess." (ATSDR p. 56). As a general rule, OEHHA prefers information published in the peer reviewed literature.

While OEHHA does not purport to offer a complete and comprehensive review of the developmental toxicity literature in this one paragraph, OEHHA has critically examined the available scientific literature. The summary is not in error as to the findings it presents. OEHHA did not offer an overall interpretation of those findings. Those findings, on their face, however, do provide evidence tending to support a conclusion that exposure to xylene may have adverse effects on development, perhaps at levels associated with maternal toxicity.

Yet, as the comment points out, there are some animal studies that did not find substantial adverse effects on fetal development. OEHHA agrees with the comment that this important and complicated subject matter merits more detail. We will therefore expand the treatment at issue. However, it is still not OEHHA's objective to develop an overall conclusion as to the weight of the evidence bearing on the developmental toxicity of xylene.

Comment 10. Inadequate Study Design. The first serious problem with the cited studies is inadequacies in study design. Unusual exposure durations were used (e.g., oral dosing of 3 times per day; continuous 24-hour exposures), suggesting excessive handling of the animals and possible stress-induced changes that could affect body weight gain/loss and food consumption (Marks et al., 1982). Continuous treatment in 24-hour exposures generally results in a higher incidence of growth and retardation characterized by decreased mean fetal body weights (Hudak and Ungvary, 1978).

Response. In general, all experimental manipulations of laboratory animals have an assumed potential to affect the study results. Therefore, it is necessary to have controls that match the experimental group, save for the alteration in one condition, so as to allow a contrast to be made on the one altered condition. In the Marks et al. (1982) study, the potential effect of the experimental manipulation (thrice daily doses by gavage) of the animals can not be denied. However, since Marks et al. (1982) included a vehicle control group in their study, this potential source of confounding was eliminated.

Hudak and Ungvary (1978) did not report that continuous treatment in 24 hour exposures generally results in a higher incidence of growth and retardation characterized by decreased mean fetal body weights. There, the untreated controls had fetal weight outcomes essentially the same as the air controls subjected to the exposure chamber manipulations. Furthermore, Hudak and Ungvary (1978) found 230 ppm xylene to have

no effect on mean fetal weight. In that study, xylene increased the incidence of skeletal anomalies and provided some evidence for retarding skeletal development.

Thus, the study design concerns raised by the comment are not a serious problem in the two example studies offered by the comment.

Comment 11. Unreliable Exposure Information. Second, in many of the studies (i.e., Hudak and Ungvary, 1978; Haas and Jacobsen, 1993), test atmospheres were not monitored continuously, and thus the exposure data provided are not reliable. Exposure test atmospheres should be monitored continuously and the method of generation should be well-documented.

Response. These comments relate potential limitations affecting some of the studies. However, the limitations bear mostly on the question of dose response and not hazard identification. OEHHA did not use the studies in its quantitative dose response assessment.

Comment 12. Species-Specific Problems. Third, the test species utilized in some of the studies may have also influenced the test results. Rabbits are known to show inherent erratic body weight gain and loss during gestation; therefore, the effects observed in the studies with this animal (e.g., Ungvary and Tatrai, 1985) must be interpreted cautiously. Some of the studies were also conducted with mice, a species known to show more variable types and incidences of spontaneous malformations compared to rats or rabbits. It is doubtful that the laboratories conducting these studies possessed the considerable experience that is necessary to work with the evaluations on the small fetus of a mouse.

Response. With respect to species differences in the variation associated with an experimental measure, increased variability within one species reduces the statistical power of experiments with that species and therefore increases the likelihood of a null result for such experiments. Thus, in the face of such increased variability, it is particularly the null result that needs to be appraised with caution.

It is difficult to respond to the comment's declaration: "It is doubtful that the laboratories conducting these studies possessed the considerable experience that is necessary to work with the evaluations on the small fetus of a mouse." However, it seems improbable that <u>all</u> the laboratories that utilized the mouse as the test species fell below a reasonable competency standard.

Regardless, poor technique is more likely to produce false null results than false positive ones. With respect to whether or not a given laboratory possessed the requisite skill to conduct studies in the mouse, poor execution of an experimental procedure may affect the accuracy or precision of an observation. Where poor precision occurs, the variance of the measures is increased and the power to discern an affect is reduced. Thus, poor precision would reduce experimental power and tend toward the null result. Where

poor accuracy is alternatively alleged, all of the measures tend to be skewed in the same way. Thus, as the exposed and control groups would be inaccurate in the same way, the differences between them would still be informative.

The blinding of experimental procedures provides further insurance as to the validity of the experimental results. Typically, the experimenters in these studies were blinded and did not know the treatments received by the test animals at the time of observation. Thus, to the extent (if any) the experimental procedures were poor, it is unlikely that the differences would reflect poor technique compounded by a subjective bias.

Comment 13. Improper Statistical Analyses. Fourth, the appropriateness of the statistical analyses employed in the cited studies is a major concern. The statistical analyses for the majority of the studies considered only the number of fetuses affected. Reproductive toxicologists now consider the litter the appropriate independent unit for statistical evaluation (USEPA, 1991).

Response. The comment is correct. The litter is the preferred unit of analysis for statistical comparisons between groups. The unit of analysis is a factor to be considered in evaluating each study's findings. It is possible that, if most or all of the adversely affected fetuses were in one or a few litters, the statistical comparison of control and experimental groups on the basis of individual fetuses would be misleading. Where the differences between experimental and control groups are sufficiently large, or where the findings have been replicated between studies, or within parts of studies, or where there is evidence of dose response, the opportunity to be misled (as to either a false positive or a false null) is much reduced.

Comment 14. Incorrect Interpretation of Certain Variants and Malformations. Finally, OEHHA's interpretation of the data from these studies is flawed. In several of the studies (e.g., Haas and Jacobsen, 1993; Hudak and Ungvary, 1978; Ungvary et al., 1980), skeletal variants (e.g., rudimentary ribs, fused sternebrae) were observed. Skeletal variations are not adverse developmental effects and, in rats, they have been found to be reversible (Chernoff, et al., 1991; Harris and De Sesso, 1994; Kimmel and Wilson, 1973). Skeletal variants such as rudimentary ribs and fused sternebrae should not be considered biologically significant in the absence of other conventional signs of embryotoxicity (e.g., increased malformations, increased embryolethality or decreased fetal weight). These variants are usually not regarded as harmful developmental toxic effects, but instead may be indicative of non-test-material-related stress due to the exposure regimen. They would only be considered toxic effects if a significant dose-related increase above controls (historical and concurrent) were observed.

Response. OEHHA did not interpret, but only presented, the available scientific information.

Comment 15. In addition, certain malformations such as cleft palate often occur spontaneously in mice as a result of environmental changes during critical stages of development. Thus, the biological significance of increased incidence of cleft palate in teratology studies must be evaluated carefully.

Response. Comment noted. The biological significance of any malformations must be carefully addressed in their interpretation. Where unexposed controls and exposed experimental groups are compared, the spontaneously occurring adverse effects should be of similar magnitude and incidence in each group. However, we agree with the comment that the mechanism of any increase in malformations in the experimental group should be evaluated carefully, especially with respect to extrapolating any findings to humans. Whether or not a malformation or other adverse effect represents a direct action upon reproduction or is secondary to a general maternal toxicity bears more upon the characterization of the toxic insult than its practical meaning. Yet, if the mechanism of the developmental insult in the test species is well understood and not thought likely to be relevant to humans, it would be inappropriate to regard the exposure on that basis alone as a potential human developmental toxicant.

The ATSDR quotation in the document does indicate that most of the adverse fetal effects occur at doses near to or causing maternal toxicity.

Comment 16. And, finally, historical control data, which were not considered, should always be considered when interpreting the significance of skeletal variants and malformations. This will ensure the findings truly exceed the range of control values for a larger population.

Response. Historical control data bear on the replicability of the concurrent control data. In general, as to control or experimental group data, where results have been replicated they warrant a greater degree of confidence.

The absence of historical control data is not a serious limitation in general. Where test animals are randomly assigned to control and experimental groups at the start of an experiment, it is the concurrent controls that are more likely to closely match the experimental groups for all appreciated and unappreciated variables at the start of the experiment. It is the comparison between the concurrent controls and experimental groups which is most probative.

Furthermore, individual studies often incorporate more than one control group. For instance, in Hudak and Ungvary (1978), the study design incorporated three different control groups (untreated controls, 24-hour air exposures in test chambers on days 9-14 of pregnancy, and 8-hour air exposures in test chambers on days 1-21 of pregnancy). These three control groups gave closely similar results that increased the confidence in each.

In other studies, the dose response information itself supports the results achieved in the null group. For instance, in Marks et al. (1982), the dose response relationship for average fetal weight itself afforded strong support to the accuracy of the control value (0 ml/kg-d - 0.982 g; 0.06 ml/kg-d – 0.982 g; 1.2 ml/kg-d – 0.975 g; 2.4 ml/kg-d – 0.861 g; 3.0 ml/kg-d – 0.785 g; 3.6 ml/kg-d – 0.708 g).

Comment 17. The above points demonstrate there are substantial weaknesses in the cited studies that diminish reliable interpretations of the data and conclusions on developmental toxicity. There is available a more definitive and well-conducted developmental toxicity study for xylene (Biodynamics, 1983) (copy attached). This study does not indicate that xylene is a developmental toxicant. We urge California to include this study in their assessment and to take account of the issues discussed above in their discussion of the other developmental studies.

Response. The most consistent adverse effect seen in the different developmental toxicity studies is decreased fetal weights. Different studies, including the Biodynamics (1983) study, have reported different NOAELS/LOAELs for this adverse effect on fetal development:

Study	Strain/Species	Exposure Duration	NOAEL	LOAEL
Mirakova et al. (1983)	"white" rat	6 h/day	2.3 ppm	12 ppm
Hass (1993)	Wistar rat	6 h/day	200 ppm	
Bio/dynamics (1983)	CrL-CD (SD) BR rat	6 h/day	250 pm	500 ppm
Shigeta et al. (1983)	ICR mice	6 h/day	230 ppm	460 ppm
Hudak et al. (1978)	CFY rat	24 h/day	230 ppm	
Ungvary et. (1985)	CFY rat	24 h/day		60 ppm
Ungvary et. (1985a)	CFY rat	24 h/day		140 ppm
Ungvary et al. (1985)	CFLP mice	24 h/day	120 ppm	230 ppm

With respect to NOAEL and LOAEL values, the Mirakova et al. (1983) is clearly an outlier. The ATSDR has suggested that this study may have been influenced by poor animal husbandry. Partially, for these reasons, OEHHA chose not to base its chronic REL upon the Mirakova et al. (1983) study.

Overall, the available data suggest that the 24 hour exposure regimens result in lower NOAELs than the 6 h/day exposure regimens. Regardless, these other observed NOAELs are sufficiently high so as to indicate the proposed chronic REL should provide an adequate margin of exposure. Thus OEHHA is proposing 700 $\mu g/m^3$ as the chronic REL for xylenes.

Geysers Geothermal

Comments on the chronic REL for **hydrogen sulfide** were made by the Geysers Geothermal Association (GGA), a non-profit, mutual benefit corporation with a membership of almost 300 companies and individuals participating in the production and utilization of geothermal energy at The Geysers geothermal field. In the draft document OEHHA proposed use of the U.S. EPA RfC of 0.7 ppb (0.9 $\mu g/m^3$) as the chronic REL.

Comment 1. The Office of Environmental Health Hazard Assessment (OEHHA) has made a great effort to involve input from risk managers and stakeholders throughout the Reference Exposure Level (REL) promulgation process. We support your approach and believe that it is important to seek input from various sources.

Response. OEHHA staff appreciate the comment. The legislation enabling the Hot Spots program included the requirement to obtain and consider input from risk managers and stakeholders.

Comment 2. However, it appears that OEHHA has taken an extremely conservative approach in determining the proposed H_2S REL of 0.7 ppb.

Response. The chronic REL proposed in the draft is a USEPA RfC, which has been available since 1995. The approach to developing RfCs is very similar to the development of chronic RELs. All USEPA Reference Concentrations (RfCs), available when the Technical Support Document (TSD) on chronic Reference Exposure Levels was drafted in October 1997, are being proposed as chronic RELs. RfCs are already used by the USEPA and by California's Department of Toxic Substances Control and were earlier incorporated by reference in Appendix F of the Emissions Inventory Criteria and Guidelines for the Air Toxics "Hot Spots" Program for use in screening risk assessments in the Hot Spots Program. These Guidelines were effective July 1, 1997. The Risk Assessment Advisory Committee (RAAC) recommended that CalEPA harmonize where possible with USEPA on risk assessment. Executive Order W-137-96 concerned the enhancement of consistency and uniformity in risk assessment between Cal EPA and USEPA. Use of RfCs as chronic RELs was one action that OEHHA took to address the RAAC recommendation and to implement the Executive Order. RfCs released after October 1997, including ones that are revisions of those in the October 1997 draft, will be evaluated for use in the Hot Spots program by reviewing the scientific basis of each RfC when it becomes available and by determining whether the scientific literature cited in the RfC is current. Appropriate RfCs will be submitted to the SRP for review and possible endorsement.

However, based on other comments and on OEHHA's assessment of the developmental toxicity data available, OEHHA staff have reviewed the value in the draft document and have calculated a revised chronic REL for hydrogen sulfide of 9 $\mu g/m^3$ (7 ppb).

Comment 3. We are aware that final reports should be available from the Chemical Industry Institute of Toxicology (CIIT) on the reproductive effects and developmental neurotoxicity of H_2S by mid-1998. We request that a final decision on the REL not be made until these studies are completed. A decision of this magnitude should be made in a collaborative setting with input from academia, industry, and regulators. This approach is consistent with OEHHA's development of the proposed REL.

Response. OEHHA staff will be happy to review the studies when they become available and hope that USEPA will do the same. As of January 1999, OEHHA had been provided with only an abstract of a CIIT study on the neurobehavioral and neurochemical effects of hydrogen sulfide. The study involved 5 consecutive days of exposure, which would not be a study length suitable for developing a chronic REL.

Comment 4. We strongly believe that OEHHA's decision to lower the REL to 0.7 ppb should be revisited. Based on the available data, the REL should be set no lower than 7 ppb. We recommend this revisitation based on the following: (1) The California ambient air quality standard for H_2S is 0.03 ppm. (2) The proposed REL of 0.7 ppb is one thousandth of the upper concentration for H_2S naturally occurring in human breath. (3) Low levels of H_2S are rapidly metabolized and detoxified by the human body and, therefore, are unlikely to be a chronic hazard at concentrations at or below the odor threshold. (4) The excessive conservative safety factors used in deriving the USEPA Reference Concentration (RfC), on which the new H_2S REL is based, should be decreased by at least one order of magnitude. (5) New studies on the toxicity of H_2S have been published or initiated since the 1994 USEPA RfC was finalized. We urge OEHHA to delay your decision on the REL until all of the information is updated.

Response. As stated above, OEHHA is now proposing 9 $\mu g/m^3$ (7 ppb) as a chronic REL for hydrogen sulfide. The commentator should also request USEPA to revisit the RfC. To decrease the UFs by an order of magnitude, changing the existing UFs would need to be addressed. If the available reproductive and developmental toxicity data are adequate for U.S. EPA, the modifying factor of 3 can be eliminated. Also if a chronic study were produced, the subchronic uncertainty factor could be eliminated. Thus the REL might increase 3, 10 or 30 fold depending on what studies are available.

Comment 5. The California H_2S ambient air quality standard of 0.03 ppm is based upon the low threshold for odor detection by humans. The Lake County Air Basin, located downwind of The Geysers, has been in attainment with all State and Federal ambient air quality standards, including H_2S, since 1990. This means that the H_2S ambient air quality level is significantly lower than the enforced level of 0.025 ppm. This attainment was accomplished by a cooperative effort of the public, regulatory agencies, and the geothermal industry. A tremendous amount of time, energy, and money was spent achieving this significant accomplishment. The proposed REL will not provide a greater level of public safety.

Response. The California H_2S ambient air quality standard of 0.03 ppm is for a 1 hour averaging time and is being retained as the acute REL in the Hot Spots program. Thus local residents should not experience acute adverse health effects from H_2S. The chronic REL is for much longer exposures and should be less than the acute REL. Although odor is one consideration with H_2S, it is not the only effect and odor is not necessarily a sentinel for other toxicity, since some chemicals have no odor and while for other with an odor adverse effects may occur above or below the odor threshold depending upon the chemical.

Comment 6. The economic impacts of the proposed REL will be enormous throughout California. It certainly could have a significant impact for the Geysers due to the deregulation of the electrical generating industry. Using the proposed REL for Air Toxics scoring purposes could subject some Geysers facilities to perform risk assessments with no corresponding benefit to public health and safety. We are attempting to control costs and remain competitive in a deregulated market. The proposed additional regulatory requirements imperil this goal.

Response. The determination of RELs is a risk assessment process and uses the best science available at the time. The economic impacts are part of risk management considerations. The risk manager can take into account the uncertainty in the REL and the delisting of H_2S as a federal Hazardous Air Pollutant as well as the known toxicity of H_2S, a hazardous gas reported to be the most common cause of sudden death in the workplace.

Lake County Air Pollution Control District

Comments on the **hydrogen sulfide** chronic REL were received from Robert Reynolds, Air Pollution Control Officer for Lake County. In the draft document OEHHA proposed use of the US EPA RfC of 0.7 ppb (0.9 $\mu g/m^3$) as the chronic REL.

Comment 1. Hydrogen sulfide is one of the air pollutants for which an Ambient Air Quality Standard (AAQS) exists, and for which the Recommended Exposure Level (REL) proposed would raise the issue as to whether the AAQS is as comparatively protective of health. The proposed action seems to be inconsistent with Cal-EPA's goal of coordinating programs, avoiding redundancies and lessening paper work. We suggest that either the AAQS should be reviewed and updated or OEHHA and the ARB should at least reconcile and comment on the Hydrogen Sulfide REL and the requirement to be protective of health as part of our state AAQS.

Response. The Ambient Air Quality Standard is for a 1 hour averaging time and is being retained in the Hot Spots program as the acute REL. The chronic REL is a USEPA RfC for long-term exposure. In order to coordinate with USEPA as recommended by the RAAC Committee and to comply with Governor's Executive Order W-137-96, all USEPA Reference Concentrations (RfCs), available when the Technical Support Document (TSD) on chronic Reference Exposure Levels was drafted in October 1997, are being proposed as chronic RELs. RfCs are already used by the USEPA and by California's Department of Toxic Substances Control and were earlier incorporated by reference in Appendix F of the Emissions Inventory Criteria and Guidelines for the Air Toxics "Hot Spots" Program for use in screening risk assessments in the Hot Spots Program.

Comment 2. The unintended consequences of some of the poorly substantiated RELs, especially those based on little or no directly applicable data, may be an erosion of public faith in the protectiveness of historic and ongoing air quality management programs. Potentially, this could result not from "poor science," but the absence of available science and effort in reaching the recommendations proposed by OEHHA.

Response. OEHHA is limited to the available data to develop a REL. Uncertainty factors which account both for known variability between humans and animals and within the human species as well as uncertainty due to extrapolating from LOAELS to NOAEL and from subchronic to chronic are used because there are seldom chronic exposures to sensitive humans available for use. The RfC for H_2S includes uncertainty due to lack of data on reproductive harm and a factor for subchronic to chronic extrapolation. Hopefully interested parties will be motivated to obtain better data.

Comment 3. The uncertainty factors, resulting from the lack of directly applicable information, may be appropriate to accept in some instances, but in those cases where the decision has much consequence in concern for public health protection, or extensive resource and cost demand, an additional effort should be made to increase certainty and the confidence in the recommendations of OEHHA. It would be better to fund necessary

work based in good science and carry it out prior to OEHHA advocacy or required recommendations being published.

Response. Risk assessment always involves uncertainty. The risk manager is expected to include that aspect in his decisions. OEHHA does not have a research budget and thus can only point out the need for more research.

Comment 4. Present state air toxic programs, while providing benefit to the public and industry, fail drastically in that they do not consider the cumulative effect of many sources within an airshed which is typical of the real world. Additionally, they are sometimes based upon a minimal effort that has tremendous downstream costs to others. I believe the subject effort potentially falls into this category and should receive more careful consideration, especially for the RELs proposed that are poorly supported but which are likely to have substantial importance and consequence.

Response. The consideration of cumulative effects within an airshed is of interest and of concern. Such considerations are theoretically possible anywhere and have been recently approached by the USEPA on a national basis (Woodruff TJ, Axelrad DA, Caldwell J, Morello-Frosch R, Rosenbaum A. Public health implications of 1990 air toxics concentrations across the United States. Environmental Health Perspectives 1998 May;106(5):245-51.) OEHHA staff does not have the resources to do such work and doubts that many air districts do either. OEHHA also recognizes that the actual costs of compliance are often less, and even considerably less, than the predictions made by affected stakeholders when a new regulation is proposed. The South Coast Air Basin has continued to thrive in spite of some of the most stringent air quality rules.

Comment 5. OEHHA needs to better identify sources and parties likely to be interested in and affected by the proposed recommendations, and then hold meaningful meetings and considerations which affords easy input. While it is obvious OEHHA has tried to include "stakeholders", "incorporate peer review," etc., I believe the effort should be redoubled and your final action delayed as necessary. Consider having workshops on specific component RELs of concern in those geographical areas of the state where the components are an air management and public exposure concern. In the long run it may save all of us time and effort, and better serve the public.

Response. The TAC program has been in place in California since 1983. The Hot Spots program has been in place since 1987. We have 1500 individuals on our mailing list for Hot Spots and contacted them regarding our Hot Spots documents. The information has been posted on the Internet and we have held public meetings in both the northern and southern parts of the state to present and discuss the issues with stakeholders. In addition we have received public comments. Based on the comments we have revised our document and we are responding to those comments. We believe that we have made every effort to involve stakeholders that have an interest in this process.

Comment 6. The recommendations seem to establish a need to protect against an exposure level that historically has been allowed as part of public policy (AAQS) and at a level that is extremely costly or virtually impossible to measure. This aspect of your recommendations should be identified for each of the RELs. The chosen approach and lack of factual information is likely to result in a great deal of confusion when applied differently than intended, and unnecessary resources going towards paper studies that provide no real benefit to air quality or public health. The worst consequences may be unfounded: fear on the part of the exposed public, wasteful efforts and costs to the regulated, and misused resources by those whom must implement programs based on the OEHHA recommendations.

Response. The CAAQS is for a 1 hour exposure which we had proposed adopting. The chronic REL is for continuous chronic exposures. The two values are not comparable and their uses are not comparable. In a risk assessment the chronic REL is compared to an annualized average, while the CAAQS (acute REL) is compared to the maximum one-hour concentration.

Based on other comments and on OEHHA's assessment of the developmental toxicity data available, OEHHA staff have reviewed the value in the draft document and have calculated a revised chronic REL for hydrogen sulfide of 9 $\mu g/m^3$ (7 ppb).

Metal Finishing Association of Southern California

Comments on the Draft Technical Support Document for the Determination of Noncancer Chronic Reference Exposure Levels were made by the Metal Finishing Association of Southern California (MFASC). The Association commented on 13 chemicals of relevance to their work. The comments included as an attachment a table titled Comparison of Limits for Selected Substances. Most of that information is in the Table included in the response to Comments 1-3.

Comments 1 – 3. For some of the substances, the proposed RELs are considerably different from those used before. … New data (i.e. more recent than 1992) were used to determine RELs for only 3 of the 13 chemicals [of interest to the MFASC]. Thus, the main difference between the new proposed RELs and the previous ones must be the methodology with which the existing data are handled.

For most of the new substances, the new RELs represent a substantial tightening of the regulatory burden. The 1992 REL for cadmium was 350 times less stringent than the proposed 1997 REL. Thus, sources that emit cadmium for which chronic non-cancer health effects were not previously predicted could now be subject to severe new regulatory requirements as a result of the change in the REL.

Response. The previous values were provided and presented by CAPCOA in response to the original Hot Spots Act. Subsequent legislation (Health and Safety Code Sec. 44360) required OEHHA to develop risk assessment guidelines for the Hot Spots program. OEHHA has used methods similar to those of the USEPA. Many of the CAPCOA values were, by contrast, derived from preexisting health risk guidance values (e.g., route-to-route extrapolation of oral Reference Doses, occupational exposure limits). These preexisting values were not originally intended for such purposes. CAPCOA used several indirect and ad hoc methodologies to derive its guidelines from these preexisting values. The CAPCOA effort was not as rigorous or time- and effort-intensive as the OEHHA effort. The comment is therefore correct: Most of the new proposed values represent intentional differences in methodology between OEHHA and CAPCOA. Cases where there would be substantial differences between the CAPCOA values and the proposed OEHHA were to be expected from the outset.

In particular, all the new values are based upon a much more thorough search of the existing scientific literature. The CAPCOA values were derived from preexisting health risk guidance values of quite varying vintage. Therefore, in many cases, the newly derived OEHHA proposed values incorporate additional data which, even if available prior to 1992, were not incorporated in the health risk guidance values upon which the CAPCOA values were based.

For instance, with respect to the case of the cited example of cadmium, in the CAPCOA document the then USEPA IRIS oral reference dose (RfD) was adjusted to an equivalent air concentration on the assumption that the oral and inhalation routes were of similar potency. However, in order to develop the OEHHA REL, OEHHA conducted an

extensive search of the inhalation toxicology literature. Through that effort, OEHHA identified the Lauwerys et al. (1974) key study of renal toxicity in workers exposed to cadmium. Unlike the original USEPA IRIS RfD, the proposed chronic REL value is based upon that 1974 epidemiological study. In 1996, the USEPA revised and greatly lowered its oral RfD for cadmium in light of health hazard information obtained from additional epidemiological studies. This recent change in the RfD supports the original presumption that oral and inhalation toxicities for cadmium would be similar. The new value for the cadmium RfD is therefore more in line with the proposed OEHHA chronic REL value.

The proposed OEHHA REL for cadmium of 0.01 $\mu g/m^3$ is 350-fold lower than the earlier CAPCOA value of 3.5 $\mu g/m^3$. The CAPCOA values were interim guidance values and were superseded when the appropriate governmental health risk assessments were completed. As a TAC, cadmium is regulated as a carcinogen with an OEHHA cancer unit risk value for cadmium is 4.2 E-3 $(\mu g/m3)^{-1}$. (At the proposed chronic REL the estimated lifetime cancer risk would be forty in a million.)

Chemical of Interest to MFASC	OEHHA Proposed REL $\mu g/m^3$	1992 CAPCOA Guidance Value $\mu g/m^3$	Basis of 1992 CAPCOA Value	Ratio of CAPCOA to OEHHA
Beryllium	0.001	0.0048	ACGIH TLV	4.8
Cadmium	0.01	3.5	USEPA IRIS	350
Chromium VI	0.0008	0.002	USEPA HEAST	2.5
Copper	0.02	2.4	USEPA IRIS	120
Hydrogen Chloride	7	7	USEPA IRIS	1.0
Hydrogen Cyanide	3	70	USEPA IRIS	23
Hydrogen Fluoride	30	5.9	ACGIH TLV	0.2
Methylene Chloride	300	3000	USEPA HEAST	0.1
Nickel	0.05	0.24	ACGIH TLV	4.8
Nitric Acid	40	none	(Not listed)	N/A
Perchloroethylene	40	35	USEPA IRIS	0.9
Sodium Hydroxide	2	4.8	ACGIH TLV	2.4
Zinc	0.9	35	Superfund PHEM	39

HEAST: Health Effects Evaluation Summary Table
IRIS: Integrated Risk Information System
TLV: Threshold Limit Value established by the American Conference of Governmental Industrial Hygienists
PHEM: Public Health Evaluation Manual

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

Comment 4. Many of the proposed RELs may be below detection levels. Thus, it would be impossible to prove that these RELs are not being exceeded through the use of ambient monitoring. Moreover, no future epidemiological studies with such low concentrations would be possible. These values thus represent purely theoretical concentrations with no verifiable basis in reality.

Response. The inability of epidemiological studies to "verify" a chronic REL is a general one. With respect to epidemiological studies, the chronic REL value assumes that there is a threshold concentration below which adverse effects do not occur. The OEHHA values estimate this threshold with a margin for uncertainty. Thus, if the OEHHA REL is satisfactory, epidemiological studies conducted upon populations exposed at, or somewhat above, the chronic REL (or RfC for that matter) should find no adverse effect.

The comment is correct that ambient monitoring could not be used at locations where the ambient levels fell below the analytical detection limits. However, in most circumstances, emission rate information and air dispersion modeling are used to estimate ambient exposures. In the abstract, where exposures substantially exceed the REL and so are more likely to yield evidence of an adverse effect in an epidemiological study, they are also more likely to exceed the limit of detection.

While not optimal, often epidemiological investigations are necessarily conducted in the absence of actual air concentration data. These studies use distance from a source, duration of exposure, or air dispersion modeling as surrogate exposure information that permits persons to be classified by their relative degree of exposure.

The ability of an epidemiological study to detect any difference in a particular effect is much reduced at low levels of exposure. As the magnitude of exposure declines, the magnitude and frequency of any particular effect also declines to a point where any effect becomes hard to discern. Null results from such studies are reassuring but can not meaningfully "verify" a chronic REL, absent an extraordinarily large number of exposed persons in the study. For these practical reasons, epidemiological studies usually target high exposure (e.g., occupational) populations for study. Where epidemiological studies have detected adverse effects of air pollution on sensitive subjects (PM_{10}, ozone), these studies encompassed an extraordinarily large number of exposed persons.

Comment 5. The OSHA PELs cannot be used to assess risk to the public health. Yet, they are another measure of health risk published by an agency other than OEHHA. The new RELs do not reflect the general relationship of health risks for the different compounds. For example, the PELs would indicate that copper is no more hazardous than nickel although neither of these substances are as toxic as other metals. Yet, the new REL for copper is less than half that for nickel.

Response. When OSHA was created in 1973, OSHA adopted the existing ACGIH TLVs for copper and nickel as the OSHA PELs. Those OSHA values have not been revised. Since that time, a great deal of toxicity information on nickel compounds has been generated. The OEHHA nickel REL is based upon new animal data provided by the National Toxicology Program in 1994. This information was unavailable in 1973.

The proposed REL for copper is based upon comparatively limited information. The OEHHA value is based upon the Gleason study of just 3 workers exposed to copper. The study measured copper levels on only one day for three exposure conditions. This study provided a LOAEL of 30 $\mu g/m^3$ and a NOAEL of 8 $\mu g/m^3$ for copper fumes. The only other available inhalation toxicity study was a subchronic mouse study that established a LOAEL of 130 $\mu g/m^3$. Both these studies have substantial limitations. The human data were preferred as they required a much smaller overall uncertainty factor and exposure duration adjustment. If the animal data had been used, an even smaller proposed REL would have been developed. As a result of this limited animal and human information, uncertainty factors and exposure duration adjustments particularly contributed to the very low proposed chronic REL for copper. However, in light of the extent, quality, and coherence of the available toxicity information, OEHHA has reconsidered its derivation of the chronic REL for copper.

Comment 6. Because new health data are not being used, it is important to consider the assumptions especially in light of the uncertainty factors being used by OEHHA in proposing these new RELs. In lieu of corresponding RfCs from the USEPA, OEHHA appears to have applied the most conservative assumptions with regard to uncertainty where that were possible.

Response. For most of the substances under consideration, OEHHA pioneered the development of chronic RELs for environmental exposures. Whether or not the health data for a given substance were 'new', OEHHA's use of the data for this purpose was new for most of the covered substances.

OEHHA followed a methodology closely similar to that of the USEPA. A comparative analysis of the uncertainty factors applied by OEHHA in the development of its RELs and by the USEPA in the development of the similar RfCs does not support the contention that OEHHA excessively applied uncertainty factors in lieu of an available RfC. OEHHA's average cumulative uncertain factor of 134 is in fact approximately one-half the USEPA's average cumulative uncertainty factor of 238.

	Geometric Mean of Uncertainty Factors	
Uncertainty Factor	**OEHHA REL**	**USEPA RfC**
LOAEL	2.6	1.9
Subchronic	2.2	2.1
Interspecies	2.4	2.7
Intraspecies	9.3	8.9
Modifying factor	1	2.4

Average Cumulative UF	**134**	**238**

Comment 7. It is recommended that an independent peer review committee that includes toxicological experts independent of OEHHA review all assumptions used in proposing these RELs before they are adopted for use in regulatory programs.

Response. Pursuant to Health and Safety Code Section 39670, California has established an independent scientific peer review committee to perform just this function. Under this regime, OEHHA's work is submitted to the state's independent Scientific Review Panel on Toxic Air Contaminants.

Comment 8. It is recommended that OEHHA continue to use the 1992 RELs until the USEPA adopts new RfCs or until the proposed RELs are reviewed by an independent peer review committee as suggested above.

Response. We will be submitting this work to the Scientific Review Panel along with the Public Comments and staff responses to the Public Comments. The RELs will not be used until and only if the Scientific Review Panel endorses them.

Pacific Gas and Electric (PG&E)

Comments on the chronic REL document were made by PG&E in a letter dated January 29, 1998. PG&E made comments on the general methodology, the role of California Ambient Air Quality Standards (CAAQS), nitrogen dioxide, formaldehyde, and H_2S.

Comment 1. PG&E requests that the draft chronic Reference Exposure Levels (RELs) be revised to separately identify "known effect levels" and "uncertainty elimination levels", with the idea that risk assessments could be required to calculate hazard indices with respect to both the "known effect levels" and the "uncertainty elimination levels".

Response. OEHHA has based its proposed chronic reference exposure levels (RELs) on methods developed by USEPA in its reference concentration (RfC) program. RELs and RfCs are intended as estimates of levels unlikely to result in observable adverse effects among the general public. They are definitely not "uncertainty elimination levels," and methods to determine absolutely risk-free exposure levels are unknown. The REL document presents observed effects data for most chemicals reviewed that represent examples of "known effect levels." These data give a partial picture of potential adverse effects associated with chemical exposure and are presented to inform risk managers and other readers about these observed effects. Direct comparison of various observed effect levels is difficult because of the great variability in the bases for these data. Some are observations among occupationally exposed workers while others are from experimental animal studies. Exposures may be brief, intermittent, or over an entire lifetime. Effects noted may be mild or severe. They may affect a few susceptible subjects or nearly all exposed individuals. The change in severity and incidence in effects observed may be rapid or gradual with increasing exposures. Studies vary in quality and comprehensiveness and some significant adverse effects may go undetected.

Comment 2. In the toxic air contaminant identification process, H&S 39660(c) requires the Office of Environmental Health Hazard Assessment (OEHHA) to estimate both "the exposure level below which no adverse health effects are anticipated" and "an ample margin of safety." But H&S 39660(a) requires OEHHA merely to 'Prepare recommendations." H&S 39661(a)(1) states that "the state board in consultation with, and with the participation of the office, shall prepare a report", and H&S 39661(c) stipulates that the final regulation adopted by the state board will account "for the factors described in subdivision (c) of Section 39660". State law relies upon OEHHA's technical experts to recommend levels, but also upon the Air Resources Board's (ARB's) elected and appointed "risk managers" to review those levels. But these chronic RELs are not identification documents subject to ARB risk manager control. Rather OEHHA is responding to a separate guidelines mandate in H&S 44360(b)(2) which does not even, cross reference H&S 39660(c). Instead, H&S 44362(b) clearly states that it will be up to the judgment of the districts what level of risk or hazard will be deemed significant.

Response. The Toxic Air Contaminant (TAC) mandate (H&SC Sec. 39660 et seq.) is a separate mandate from the Air Toxics Hot Spots Information and Assessment program

(H&SC Sec. 44300 et seq.). However, there is overlap. All TACs, including the 189 Hazardous Air Pollutants (HAPs) in the Clean Air Act Amendments of 1990 which became TACs in April 1993 as a result of AB2728, are subject to the Hot Spots program (H&SC Sec. 39655(d)). In addition chemicals appearing on other lists are also subject to Hot Spots (H&SC Sec. 44321). OEHHA is the state's expert on health risk assessment (e.g., see Governor's Executive Order W-137-96) and develops health guidance values. The air districts decide how to manage the risks estimated using the values.

Comment 3. The draft chronic Reference Exposure Levels (RELs) include factors of uncertainty that push the draft chronic RELs below current ambient air quality standards (for hydrogen sulfide), and below levels which the Scientific Review Panel concluded caused no adverse effects other than a cancer risk (for formaldehyde). The formaldehyde and hydrogen sulfide RELs are just two examples where high uncertainty factors have been proposed for relatively mild effects even though substantial human exposure data is available.

Response. The hydrogen sulfide ambient air quality standard addresses short-term exposures. OEHHA based its chronic REL for hydrogen sulfide on the USEPA reference concentration (RfC). The USEPA also did not adopt an ambient air quality standard for hydrogen sulfide since it has none, but rather used long-term exposure data.

All USEPA Reference Concentrations (RfCs), available when the Technical Support Document (TSD) on chronic Reference Exposure Levels was drafted in October 1997, are being proposed as chronic RELs. RfCs are already used by the USEPA and by California's Department of Toxic Substances Control and were earlier incorporated by reference in Appendix F of the Emissions Inventory Criteria and Guidelines for the Air Toxics "Hot Spots" Program for use in screening risk assessments in the Hot Spots Program. These Guidelines were effective July 1, 1997. The Risk Assessment Advisory Committee (RAAC) recommended that CalEPA harmonize where possible with USEPA on risk assessment. Governor Wilson's Executive Order W-137-96 concerned the enhancement of consistency and uniformity in risk assessment between Cal EPA and USEPA. Use of RfCs as chronic RELs was one action that OEHHA took to address the RAAC recommendation and to implement the Executive Order. RfCs released after October 1997, including ones that are revisions of those in the October 1997 draft, will be evaluated for use in the Hot Spots program. OEHHA staff will review the scientific basis of each RfC when it becomes available and determine whether the scientific literature cited in the RfC is appropriate. Appropriate RfCs will be submitted to the SRP for their review and possible endorsement.

The RfC for hydrogen sulfide was adopted by USEPA in 1995 and incoporates a 1,000-fold cumulative uncertainty factor. The RfC is derived from a 90-day inhalation study with mice conducted by CIIT (Chemical Industry Institute of Toxicology). The study was well-conducted with many appropriate endpoints examined, but the number of animals tested was small. The critical endpoint for the RfC is nasal histological changes. The RfC was reviewed by OEHHA for general adequacy and accepted, although there is

some concern that the cumulative UF may be too large. OEHHA is reevaluating the hydrogen sulfide RfC and will be discussing this issue with the Scientific Review Panel.

The cumulative uncertainty factor for the formaldehyde REL was only 10-fold. This factor was necessary because sensitive human groups such as children or the elderly may be considerably more susceptible to effects from long-term formaldehyde exposure than were the relatively healthy group of workers described in the Wilhelmsson and Holmstrom reports. Cancer is a separate issue.

Comment 4. The public and their risk managers may have differing perspectives about how feasible or necessary it is to provide so ample a margin of safety. Perspectives may also differ between districts, or over time. OEHHA does not need to obtain risk manager consensus on these uncertainty factors. But OEHHA should design its factors and its hazard identification guidelines to enhance, not reduce, risk manager flexibility.

Response. OEHHA fully acknowledged in the draft chronic REL document the many and varied uncertainties involved in the task of estimating exposure values protective against noncancer health effects. The nomenclature used by OEHHA and USEPA for its values, REL and RfC, respectively, incorporate the term "reference" because of the recognition that no single exposure value can be derived that demarcates "safe" from "hazardous." It is rather intended to be a useful risk management tool in assessing relative and cumulative risks associated with chemical exposures. Thus an important goal of the OEHHA chronic REL effort was to maintain a consistent basis for deriving the various RELs.

Comment 5. We recommend that OEHHA establish chronic "Known Effect Levels" (KELs) at the projected No Observed Adverse Effects Level (NOAEL), and separate "Uncertainty Elimination Levels" (UELs) that consider what added safety or uncertainty factors are finally adopted. We further recommend that OEHHA's chronic hazard evaluation guidelines require that the hazard index be calculated both with respect to the KELs and with respect to the UELs. This would provide the state and public with a uniform database on relative hazards posed by different sources in different districts, as well as a good indication of how much uncertainty there is about those hazards. It would also enable district risk managers to chose whether to relate their significant hazard level to either the KELs or the UELs. While most Districts may be content to relate acceptable levels to OEHHA's UELs for most compounds, some may prefer to relate significance levels for some compounds to the KELs - at least until it becomes feasible to provide the additional margins of safety that uniform adherence to the UELs would likely require.

Response. OEHHA developed its risk assessment methods for noncancer health effects from chronic exposures to be consistent with methods used by USEPA in the development of its reference concentrations. Levels associated with observed adverse effects are reviewed in the document. RELs and RfCs are intended as estimates of levels unlikely to result in observable adverse effects among the general public, but are not

"uncertainty elimination levels." RELs are presented with observed effect data (that could be termed "known effect levels") to inform risk managers and other readers. Direct comparison of various observed effect levels is difficult because of the great variability in the bases for these data. Some are observations among occupationally exposed workers while others are from experimental animal studies. Exposures may be brief, intermittent, or over an entire lifetime. Effects noted may be mild or severe. They may affect a few susceptible subjects or nearly all exposed individuals. The change in severity and incidence in effects observed may be rapid or gradual with increasing exposures. Studies vary in quality and comprehensiveness and some significant adverse effects may go undetected.

Comment 6. Exclude substances regulated by state or federal ambient air quality standards, like NO_2, from the toxic air contaminant hazard evaluations, or if hazard evaluation is deemed necessary, evaluate them only with respect to a chronic REL set at the most applicable adopted ambient standard.

Response. Chronic RELs are for use in the Hot Spots program. Many chronic RELs are for toxic air contaminants (TACs) because TACs are subject to the Hot Spots program. Other Hot Spots chemicals are not currently classified as toxic air contaminants. The ambient air quality standards are generally designed to protect against adverse effects resulting from exposures to concentrations for varying time periods which varies with the standard. The USEPA has an annual standard for nitrogen dioxide of 0.05 ppm (100 $\mu g/m^3$) to "prevent health risk and improve visibility." California has a 1-hour standard for nitrogen dioxide of 0.25 ppm (470 $\mu g/m^3$). OEHHA separately evaluated health effects of short-term exposures (1-hour time-weighted average exposure) and long-term exposures ("annual time"-weighted average exposure) for acute and chronic RELs, respectively. The focus of evaluation and the averaging time for an ambient air quality standards and a REL can differ. OEHHA used the 1-hour California nitrogen dioxide standard as its acute REL. The proposed chronic REL of 20 $\mu g/m^3$ (10 ppb) is based purely on health effects, in this case a 1993 report by Infante-Rivard in which effects in asthmatic children were observed at 15 ppb. This is tabulated in Section VI of the chronic REL summary. It would not be a responsible action for OEHHA to let the chronic REL be set at the annual Federal standard of 0.05 ppm (50 ppb) when adverse effects in children at 15 ppb nitrogen dioxide have been reported in the peer-reviewed literature.

Comment 7. In 1995, there was no place in California where either the federal annual NO_2 standard of 100 $\mu g/m^3$ or the state daily NO_2 standard of 470 $\mu g/m^3$ was exceeded. But ambient concentrations exceeded the proposed NO_2 REL of 20 $\mu g/m^3$ (0.01 ppm) at 90 of 123 monitoring sites during that year. Currently, 80% of 1995 California NO_x emissions were attributed to mobile sources not regulated under the "hot spots" program (see pp. 100-110 of the ARB's annual "Summary of 1995 Air Quality Data", and pp. 34 of the 10/10/97 statewide inventory tables available at http://arbis.arb.ca.gov/emisinv/95inven195inv.htm). Those fuel combustion sources

regulated under the "hot spots" program typically emit much more NO than NO_2, and it would be difficult for NO_x dominated "hot spot" sources to accurately estimate what percentage of their NO emissions might convert to NO_2 before their points of maximum ground level impact.

Response. Issues such as (1) whether ambient concentrations in any particular areas may exceed the health-based risk assessment values, (2) the relative sources of ambient concentrations, or (3) the technical difficulties in estimating emissions or reducing emissions to avoid exceeding such values are not relevant to the development of these values, though these certainly are additional risk management issues. Unlike other exposure values that incorporate such risk management concerns, OEHHA RELs and USEPA RfCs and RfDs are purely health data-based guidance values that ultimately will be one of a number of issues considered by risk managers.

Comment 8. Although NO destroys ozone while converting to NO_2, conversion in the center of an NO dominated plume can be incomplete 60 km downwind (page 8, Air & Waste Management Association paper 95-RAI13A.01, "The Significance of NO_x Emissions from Coal-Fired Power Plants in the Middle Tennessee Area on Tropospheric Ozone, by Prof. Wayne T. Davis, Univ. of Tenn., et al, June 18-23, 1995). Also precise calculation of NO to NO_2 requires data and models that won't be available at most locations, and very costly to acquire and use at those few locations where they might be available.

Furthermore, since the effects of ozone exposures appear more serious than those from NO_2, overestimating conversions might harm rather than protect - if the result was less NO in an area where NO helps to destroy ozone. Meanwhile, much of California is non-attainment of state ambient air quality standards for ozone or fine particulate, and as a result will already require most "hot spots" sized NO_x sources to impose either Best Available Retrofit Technology or All Feasible Control Technology. All of these factors suggest that NO_2 concerns remain more appropriately addressed under the ambient air quality programs, rather than within the chronic hazards portion of the "hot spots" program.

Response. The concerns raised by this comment should be more appropriately addressed in other settings, such as at the risk management level. It was beyond the scope of the OEHHA chronic REL document to address issues such as difficulties in estimating emissions and exposures, relative risks of chemicals, and the fate of chemicals in the ambient air. This document is focused on the development of strictly health-based exposure guidance.

Comment 9. Ambient air quality standard reviews focus immense attention upon one substance. For example, the joint ARB/OEHHA Technical Support Document "Review of the One-Hour Ambient Air Quality Standard for Nitrogen Dioxide" published in December 1992 required 232 pages to address NO_2 data. While OEHHA has prepared an excellent 8 page summary on its proposed NO_2 REL, a summary of that size is unable to

provide the detail on the key study needed to attract critical review, especially when it competes for agency/commentator attention with 750+ other pages on 119 other substances. Where a comprehensive review has already been undertaken, a briefer review should not be allowed to displace it. If desired, OEHHA could ensure NO_2 inclusion in calculated total hazard indices by simply referencing the existing federal annual standard. If a subsequent review were to result in revision of the standard, the REL could also change.

Response. The 1-hour ambient air quality standard for nitrogen dioxide is designed to protect against adverse effects resulting from short-term exposures to peak concentrations and has been endorsed by the Scientific Review Panel for use as an acute REL in the Hot Spots program. The USEPA's annual standard for nitrogen dioxide of 0.05 ppm (100 $\mu g/m^3$) is to "prevent health risk and improve visibility." The proposed chronic REL of 20 $\mu g/m^3$ (10 ppb) is based purely on health effects, in this case a 1993 report by Infante-Rivard in which effects in asthmatic children were observed at 15 ppb. This is tabulated in Section VI of the chronic REL summary. It would not be appropriate for OEHHA to let the chronic REL be set at the annual Federal standard of 0.05 ppm (50 ppb) when adverse effects have been reported in the peer-reviewed literature in children at 15 ppb.

Comment 10. If a chronic REL is proposed for hydrogen sulfide even though an ambient standard exists for that compound, then the existence of the hourly standard should at least reduce the need for a subchronic exposure uncertainty factor.

Response. OEHHA separately evaluated health effects of short-term exposures (1-hour time-weighted average exposure) and long-term exposures (1-year time-weighted average exposure). The proposed chronic REL for hydrogen sulfide is based on the USEPA RfC which was derived from subchronic exposure data. USEPA followed its RfC methodology in determining an appropriate subchronic uncertainty factor. The subchronic uncertainty factor is intended to account for potential differences in the magnitude of adverse effects between those observed in subjects exposed over less than a full lifetime and those that might be experienced by the general public over their entire lifetime. Thus short-term exposure data, even if extensive, do not eliminate uncertainties resulting from a lack of long-term exposure data.

Comment 11. For Hydrogen Sulfide, data showing no adverse effects at 5400 ppb is claimed to justify limiting exposures to 0.7 ppb. In other words, the proposed REL is 7,714 times as stringent as the No Observed Adverse Effects Level (NOAEL). This reflects the use of a factor of eight in extrapolating from mice to humans, and the multiplication of additional "uncertainty" factors amounting to 900, but tabulated as 1,000. Given that the effect that is not observed to occur at the 5400 ppb level was "inflammatory changes in the nasal mucosa", is such a high uncertainty factor necessary?

Response. The magnitude of the difference between concentrations known to cause adverse effects and those without appreciable risk can never be determined with absolute

certainty. Thus USEPA has developed and OEHHA has adopted, with some changes to ensure consistency, default and data-based methods to derive the RfC and REL "reference" levels. In some cases where overall uncertainty is low, a small or even no uncertainty factor has been used. In other cases, several areas of significant uncertainty exist. This results in a large cumulative uncertainty factor that is unsatisfying for all concerned but will require the development of better data to improve the situation. When better data become available, the RELs will be reevaluated and hopefully the use of uncertainty factors can be lessened or in some cases eliminated. Also some humans experience adverse effects of nausea and headache at the 30 ppb one-hour standard and some people may experience adverse effects at a somewhat lower concentration when exposed chronically. The point of using uncertainty factors is to get below these adverse effect levels. Comparing 5400 ppb and 30 ppb, it is no surprise that the extrapolation to the chronic REL must be at least 180-fold and probably more since 30 ppb is a LOAEL for people.

OEHHA is attempting to determine if USEPA inadvertently applied an incorrect uncertainty factor of 10 in the RfC calculation when the text indicated that 3 was appropriate. It is also not clear that a database deficiency factor is warranted. We will be discussing this issue with the Scientific Review Panel.

Comment 12. California previously adopted an ambient air quality standard for hydrogen sulfide at 30 ppb or 42 $\mu g/m^3$, averaged over one hour to protect against annoying odors. It is generally recognized that annual average concentrations are typically ten or more time lower than peak hourly concentrations. The "Toxic Air Pollutant Source Assessment Model for California Air Pollution Control Districts and Applicants for APCD permits" adopted October 1, 1987 uses a multiplying factor of 0.1 for conversion of hourly model results to annual in flat terrain downwash, and presents a similar hourly to annual ratio (4.0/0.4 = 0. 1) when 24 hour complex terrain model results are extrapolated. On page 111-5 of the 1993 California Air Pollution Control Officer's Association Risk Assessment Guidelines, the 0. 1 factor continues to be used for the conversion of hourly screening model results to annual average, and the only examples cited on page 111-13 all had peak hourly concentrations 10 to 15 times the corresponding annual average concentrations. On that basis, the state standard of 30 ppb should be sufficient to protect against chronic exposures of 3 ppb. 3 ppb would be a factor of 1800 below the reported NOAEL, and a factor of 220 below the OEHHA calculated equivalent human NOAEL.

Response. The 10-fold convention used in exposure estimation is based on only commonly observed differences in maximum 1 hour and maximum 1 year average exposure concentrations. This factor does not address differences in health effects that might be observed between a short-term exposure and those over a lifetime. OEHHA separately evaluated health effects of short-term exposures (1-hour time-weighted average exposure) and long-term exposures (1-year time-weighted average exposure). The proposed chronic REL for hydrogen sulfide is based on the USEPA RfC, which was derived from long-term exposure data. The ambient air quality standard for hydrogen sulfide is designed to protect against adverse effects resulting from short-term exposures

to peak concentrations. Therefore the focus of evaluation for the AAQS is different from the chronic REL.

Comment 13. It would be better for everyone if all available compliance resources were devoted towards ensuring continuous compliance with the existing state hourly standard, rather than dividing resources to separately evaluate compliance with separate standards. Therefore PG&E recommends that the Office of Environmental Health Hazard Assessment (OEHHA) not adopt any chronic REL for hydrogen sulfide, but instead rely upon the hourly standard to protect the public from chronic exposures as well.

Response. This concern should be more appropriately addressed in other settings, such as at the risk management level. This document is focused on the development of strictly health-based exposure guidance, and includes chemicals selected from substances of concern identified by the California Air Resources Board. Acute exposure standards are not necessarily protective of the general public exposed over a lifetime.

Comment 14. If OEHHA believes that it must adopt a chronic REL for a substance for which an hourly state standard exists, then we urge OEHHA to reconsider the proposed factors of uncertainty. For example, eliminating the subchronic uncertainty factor (because there is a separate subchronic standard), would be sufficient to raise the REL to 660 ppb / 90 - 7 ppb. If the chronic REL were set at 7 ppb, the hourly 30 ppb standard would remain the governing factor in almost all situations.

Response. OEHHA reviewed the USEPA RfC and concluded that it was adequate for use as an OEHHA chronic REL. There is no basis for eliminating a subchronic uncertainty factor because of the availability of short-term data and exposure guidelines. This factor is eliminated where adequate data on toxicity following long-term exposure are available, which was not the case for hydrogen sulfide.

Comment 15. Our chief concern with such a 7 ppb REL is whether geothermal power plants would be expected to evaluate compliance with such an REL within the secured geothermal steam supplier leasehold. If OEHHA adopts a 7 ppb REL, then we would hope that OEHHA would make provisions within its risk assessment guidelines for adjacent industrial sources to agree among themselves that risks/hazards need only be evaluated outside their common perimeters.

Response. This concern should be more appropriately addressed in other settings, such as at the risk management level. This document is focused on the development of strictly health-based exposure guidance.

Comment 16. OEHHA should use lesser uncertainty factors for natural compounds like formaldehyde for which abundant exposure data exist.

Response. From a risk assessment perspective, the natural occurrence of a chemical is not a factor in estimating risks from exposure. The large health effects database for formaldehyde was considered and is reflected in the relatively small 10-fold cumulative uncertainty factor for formaldehyde.

Comment 17. [OEHHA] should not adopt RELs in conflict with prior Scientific Review Panel identification report conclusions.

The proposed formaldehyde REL is equated to 1 ppb. This is 4.4 times below the mean annual outdoor population weighted exposure that 20 million Californians were deemed subject to in finding #6 on page 17 of the Executive Summary of the "Final Report on the Identification of Formaldehyde as a Toxic Air Contaminant" in July 1992 . On page 18 of that report, Scientific Review Panel finding #10 concludes that "Adverse health effects other than cancer are not expected to occur at mean statewide outdoor ambient concentrations". OEHHA should not adopt a REL that suggests hazards could exist at levels that more exhaustive prior identification report review concluded did not pose a hazard. There are often issues which cannot be adequately evaluated in these more generic REL reviews. OEHHA also appears to be changing an identification report finding outside the established process (see PG&E's comment #1).

The proposed formaldehyde REL is also equated to 2 $\mu g/m^3$, which is 130 times below the identified Lowest Observed Adverse Effects Level (LOAEL), and 45 times below the No Observed Adverse Effects Level (NOAEL). Given the lack of data suggesting that widespread ambient air exposures are causing problems, a lesser combined factor of uncertainty would appear appropriate. Replacing the current factor of uncertainty of 130 relative to the LOAEL with a factor of uncertainty of ten with respect to the NOAEL would raise the REL to 9 $\mu g/m^3$ (6 ppb). This level would be above recent average exposures, and protecting against above average exposures would be more consistent with the identification report findings.

Response. The health effects assessment document that is part of the "Final Report on the Identification of Formaldehyde as a Toxic Air Contaminant" focused on cancer risks associated with formaldehyde exposure, and did not extensively evaluate noncancer health effects. The proposed OEHHA REL for formaldehyde is based on a review of noncancer health effects data. The Scientific Review Panel will review the proposed formaldehyde REL. The magnitude of the REL relative to ambient exposure levels is not an appropriate factor to incorporate into the derivation of the REL, but is an issue of concern to the risk management of formaldehyde exposures. The Panel approved an acute REL for formaldehyde of 94 $\mu g/m^3$.

Comment 18. One key finding in the identification report was that the risk of cancer was the greatest concern. But adoption of a formaldehyde REL of 2 $\mu g/m^3$ would flip flop that conclusion at least in non-residential areas. Both cancer risks and chronic hazards

can be adjusted for hours worked per year of exposure. But chronic hazards are based upon the single worst year, whereas as cancer risks are based upon average exposure over 46 year working lifetime (versus a 70 year nominal lifetime). A single significant figure REL would have to be at least 3 $\mu g/m^3$ before worker risk would be more significant than chronic hazards for workers subject to non-variable exposures.

10 in a million [significant risk]		70 years [nominal]		chronic REL at
----------	x	----------	= 2.54 $\mu g/m^3$	which cancer and
6 in a million/($\mu g/m^3$) [unit risk]		46 years [working]		hazards equate

But most exposures vary from year to year. In our opinion 9 $\mu g/m^3$ offers a reasonable balance - a factor of 10 below the NOAEL, a factor of 2 above the historic exposures found not to cause adverse effects, and a factor of 3 above the level at which steady state sources would calculate more significant chronic hazard indices than cancer risks. Chronic hazards could still govern at sources with more variable emissions.

Response. The availability of relevant data was an important consideration in the development of the chronic RELs. While USEPA frequently uses its limited database factor, OEHHA did not use such a factor.

Comment 19. RELs (or KELs & UELs) should be presented with both all significant figures and with an appropriately rounded number of significant figures. It would be inconsistent to propose a cumulative factor of uncertainty of 1000 or more, while insisting upon the use of multiple significant figures. But even when numbers are highly uncertain, rounding does not render the rounded numbers more accurate, so neither would it be appropriate to insist upon rounding. If one calculates a hazard index of 0.999 relative to a significance level of 1.0 no one should ever round such "insignificant" results up to the significance level.

An OEHHA REL (or as we suggest, an OEHHA UEL) should be specified both as "originally calculated" with all available significant figures, and as rounded where the degree of rounding should reflect the assumed level of uncertainty. For example, compounds employing a factor of uncertainty of 1,000 or more could be rounded to one significant figure, while compounds employing a factor of uncertainty between 1,000 and 10 could be rounded to two significant figures, and compounds employing a factor of uncertainty of 10 or less could be rounded to three significant figures. But the risk assessment guidelines should allow hazard assessors to use either rounded or originally calculated RELs, as long as only "rounded" or only "originally calculated" numbers are used for all of the RELs employed in the same hazard index evaluation.

For NO_2, the calculated median of a 10- 15 range was 12.5, which was rounded to 10. If OEHHA were to adopt that proposed REL (KEL?) for NO_2 with no added

uncertainty factor, then all three significant figures (that is the 12.5 number) should be retained.

Response. The use of one significant figure is consistent with the practice of USEPA in its RfC program. Since OEHHA adopted many USEPA RfCs as RELs, OEHHA adopted USEPA practice of using one significant figure for chronic RELs. Furthermore, additional figures would not be meaningful given the degree of uncertainty associated with the proposed chronic REL values. The values used in the derivation of the RELs are fully presented, and risk managers using the chronic REL guidance may consider this issue as part of their evaluation of health impacts associated with chemical exposures.

Comment 20. The public and risk managers would benefit if risk assessments differentiated between levels actually associated with adverse effects (Known Effect Levels) and levels deemed necessary to provide added protection (Uncertainty Elimination Levels), and if ambient standard pollutants were evaluated as clearly separated chronic background adders rather than as part of a single initially calculated chronic hazard index.

Response. OEHHA has based its proposed chronic reference exposure levels (RELs) on methods developed by USEPA in its reference concentration (RfC) program. RELs and RfCs are intended as estimates of levels unlikely to result in observable adverse effects among the general public. The REL document presents observed effects data for most chemicals reviewed that represent examples of "known effect levels." These data give a partial picture of potential adverse effects associated with chemical exposure and are presented to inform risk managers and other readers about these observed effects. Direct comparison of various observed effect levels is difficult because of the great variability in the bases for these data. Some are observations among occupationally exposed workers while others are from experimental animal studies. Exposures may be brief, intermittent, or over an entire lifetime. Effects noted may be mild or severe. They may affect a few susceptible subjects or nearly all exposed individuals. The change in severity and incidence in effects observed may be rapid or gradual with increasing exposures. Studies vary in quality and comprehensiveness and some significant adverse effects may go undetected.

Comment 21. OEHHA should reconsider its use of the same factors of ten for each level of uncertainty for compounds with both abundant and sparse exposure data. We believe that lower factors of uncertainty should be used, particularly for naturally occurring substances like formaldehyde for which abundant exposure data exist.

Response. Uncertainty factors of between 1 and 10 were used in the chronic REL document, depending on data quality. From a risk assessment perspective, the natural occurrence of a chemical is not a factor in estimating risks from exposure. An "abundance of exposure data" does not provide information for developing a health-based Reference Exposure Level, unless accompanied by a corresponding study of the

health effects of exposure. The large health effects database for formaldehyde was considered and is reflected in the relatively small 10-fold cumulative uncertainty factor for formaldehyde.

Styrene Information and Research Center

Comments on the chronic REL for **styrene** were made by Jeffrey C. Terry, Manager for State Government Relations of the Styrene Information and Research Center (SIRC). OEHHA recommended use of the US EPA Reference Concentration of 1,000 $\mu g/m^3$ based on neurotoxicity in humans as the chronic REL for styrene.

Comment 1. Effective Exposure Level. SIRC supports the evaluation of the effective exposure level the USEPA included in determining the RfC for styrene in its IRIS review. Mutti et al. concluded that the workers with metabolites of up to 150 mmoles/mole appeared to have no significant effects. SIRC recommends, as OEHHA is adopting the USEPA RfC, that OEHHA not include any discrepancy between its analysis of the effective exposure level and that of the USEPA.

Response. While OEHHA has recommended that the USEPA RfC be adopted as the California chronic inhalation REL, OEHHA is also charged under Health and Safety Code Section 39660(c)1 with providing information on the completeness and quality of the available data. This "discrepancy" relates to determination of a LOAEL or NOAEL for use in the dose response assessment. The "discrepancy" has been disclosed as it reflects an important issue associated with California's adoption of the RfC as a chronic REL.

In the Mutti et al (1984b) study, tests for some individuals in the lowest exposure group did provide abnormal results; and, conversely, tests on some of the individuals in the highest exposed groups did not provide abnormal results. The statement that "workers with metabolites of up to 150 mmoles/mole appeared to have no *significant* effects" has meaning in so far as it pertains to statistical comparisons that bear on the experience of groups, not individuals. The mean exposure for the lowest exposure group was 75 mmoles/mole. The value of 150 mmoles/mole represents the designated upper limit of the exposures for this group. It is the mean value of 75 mmoles/mole, and not the designated upper exposure level of the lowest exposure group, which most accurately represents the exposure history of that group. Therefore, 75 mmoles/mole is the appropriate starting point for dose response assessment.

Comment 2. Uncertainty Factors. SIRC understands the difficulty in assessing the Mutti study. However, USEPA's interpretation of the study by imposing a cumulative uncertainty factor of 30 is appropriate. SIRC disagrees with an UF of 10 for intraspecies variability that OEHHA mentions. SIRC quoted the USEPA's IRIS:

" A partial UF of 3 was used for database inadequacy, including the lack of concentration-response information on respiratory tract effects. A partial UF of 3 instead of 10 was used for intraspecies variability since the lower confidence limit of the exposure extrapolation was used and because Perbellini et al. (1988) demonstrated that this biological exposure index (i.e. urinary metabolites) accounts for differences in pharmacokinetic/physiologic parameters such as alveolar ventilation rate. A partial

UF of 3 instead of 10 was also evoked for lack of information on chronic studies as the average exposure duration of the principal study of Mutti et al. (1984) was not long enough (8.6 years) to be considered chronic. The total uncertainty is therefore 30."

SIRC also disagreed with the OEHHA speculation that potential nutritional differences also supported use of the full intraspecies uncertainty factor of 10.

SIRC requested that the inconsistency with the USEPA RfC analysis be taken out of the OEHHA document.

Response. The USEPA based its rationale for a partial intraspecies uncertainty of 3 on its use of the lower 95 percent confidence limit of its estimate of the central tendency value for the air styrene concentrations predicted from the 150 mmole/mole urinary styrene metabolite concentrations observed in the Mutti et al. (1984) study. The USEPA opined that use of this partial uncertainty factor was justified since the urinary metabolites' biological index took into account differences in pharmacokinetic/physiologic parameters and also because use of the lower 95 per cent confidence limit takes into account some of the intraindividual variation in the toxicokinetics of styrene.

OEHHA does not dispute that the urinary metabolites' biological index takes into account differences in pharmacokinetic/physiologic parameters. If a chronic REL were to be expressed in terms of urinary metabolite levels, a partial uncertainty factor of 3 would be appropriate to the extent that the toxicokinetic contribution to intraindividual variance was substantially eliminated by use of a standard based upon urine metabolite levels. However, here, the chronic REL is expressed in terms of a styrene air concentration, not the concentration of styrene metabolites in the urine. The contribution of toxicokinetics to the overall variance is no longer taken into account when the standard is expressed in units of air styrene concentrations, and not urinary styrene metabolite levels.

The USEPA did, however, use the lower 95 per cent level confidence limit of the airborne styrene concentration associated with 150 mmoles/mole (mmoles styrene metabolite per mole of urinary creatinine) in its dose response assessment. The USEPA stated that the choice of this value took into account some of the population variance due to toxicokinetic differences. This value, which was 88% of the central value, is based upon the *standard error* of a mean value. Therefore, this 95% lower confidence limit is an inadequate measure of the range of individual response characteristics, which relate more reliably to the *standard deviation* of the study population. When sample sizes are large, standard errors especially convey very little information about the standard deviation of the population. The Guillemin et al. (1982) study employed a large study population (N = 90). The USEPA methodology could not capture the variability that it sought to take into account when it selected the 95% lower confidence limit of the air styrene concentration associated with the 150 mmoles/mole styrene metabolite level. Therefore, this approach may not have warranted use of a partial uncertainty factor.

While nutritional factors are known to alter the human response to other chemical species, OEHHA's opinion that an intraspecies uncertainty factor of 10 was preferable did not turn on the issue of malnutrition as a potential contributor to the variability of the human response to styrene. The study on which the RfC was based addressed the effects of styrene on an occupational cohort. Clearly, since the USEPA study is based upon a worker population, the issue of malnutrition was a secondary consideration.

Worker studies, as discussed in the OEHHA draft document, do not capture the variability of the general population, which is to be protected by the chronic REL. Working populations are typically healthier than the general population and also do not share its age distribution. Furthermore, the eligibility criteria of the Mutti et al. (1984) study excluded workers with a variety of diseases. Thus, even if the USEPA methodology had captured the magnitude of the intraindividual toxicokinetic variability of the worker population in Mutti et al. (1984), it could not have adequately captured the toxicokinetic variability of a general population comprised of the elderly and children as well as those with medical conditions.

OEHHA disagrees that mention of the Khanna et al. (1994) study indirectly imposes an interspecies uncertainty factor. No such factor was applied. The Khanna et al. (1994) study raises the potential for a greater than usual intraspecies variability due to the effects of malnutrition. Similar human data are not available. The Khanna et al. (1994) study was discussed in the context of what was the most appropriate *intraspecies* uncertainty factor to use in the risk assessment.

UNOCAL Geothermal

Comments on the **hydrogen sulfide** chronic REL were submitted by UNOCAL Geothermal, which has an operation at the Geysers. The comments are those of their consultant, Dr. Charles Lambert. OEHHA proposed use of the US EPA RfC of 0.7 ppb (0.9 $\mu g/m^3$) as the chronic REL.

Comment 1. After thorough review of the H_2S literature and the OEHHA supporting documentation for the proposed dramatic change in REL, I believe strongly that OEHHA's decision to lower the REL to 0.7 ppb should be revisited. The REL for H_2S should be set no lower than 7.0 ppb. This recommendation is based on the following conclusions: (1) The California ambient air quality standard for H_2S is 30 ppb. (2) The proposed REL of 0.7 ppb is one thousand times lower than the upper concentration for naturally occurring H2S in human breath. (3) Low levels of H_2S are rapidly metabolized and detoxified by the human body and therefore unlikely to be a chronic hazard at concentrations at or below the odor threshold. (4) The extremely conservative safety factors used in deriving the USEPA RfC, on which the new H_2S REL is based, should be decreased by at least an order of magnitude. (5) New studies on the toxicity of H_2S have been published or initiated since the 1994 USEPA reference concentration (RfC) was finalized. OEHHA should wait until all of this updated information is in before finalizing the REL.

Response. The dramatic change referred to in the comment is the change from the 1 hr CAAQS for H_2S of 30 ppb used in the CAPCOA risk assessment guidance (last updated in October 1993) to the proposed use of the USEPA RfC of 0.7 ppb in the Technical Support Document. All USEPA Reference Concentrations (RfCs), available when the Technical Support Document (TSD) on chronic Reference Exposure Levels was drafted in October 1997, are being proposed as chronic RELs. RfCs are already used by the USEPA and by California's Department of Toxic Substances Control and were earlier incorporated by reference in Appendix F of the Emissions Inventory Criteria and Guidelines for the Air Toxics "Hot Spots" Program for use in screening risk assessments in the Hot Spots Program. These Guidelines were effective July 1, 1997. The Risk Assessment Advisory Committee (RAAC) recommended that CalEPA should harmonize where possible with USEPA on risk assessment. Governor's Executive Order W-137-96 concerned the enhancement of consistency and uniformity in risk assessment between Cal EPA and USEPA. Use of RfCs as chronic RELs was one action, which OEHHA took to address the RAAC recommendation and to implement the Executive Order. RfCs released after October 1997, including ones that are revisions of those in the October 1997 draft, will be evaluated for use in the Hot Spots program by reviewing the scientific basis of each RfC when it becomes available and by determining whether the scientific literature cited in the RfC is current. Appropriate RfCs will be submitted yearly to the SRP for review and possible endorsement.

Comment 2. The odor threshold for H_2S is around 10-20 ppb, while the characteristic "rotten egg" odor associated with H_2S can be clearly noted at ambient concentrations of

30-100 ppb (odor recognition threshold). However, it is not until levels in excess of 50 ppm where irritation of the mucous membranes of the eyes and lungs may start to occur. This is an approximate 1,000 fold margin of safety between the odor threshold and signs of toxicity. The concentrations at which health effects begin to occur are well documented and are the basis for current, national, safe exposure limit concentrations. It is not until levels in excess of 50 ppm where irritation of the mucous membranes of the eyes and lungs may start to occur

Response. The national limits are for workplace exposure, not chronic ambient exposure of the general population including sensitive individuals, the target of chronic RELs. OEHHA staff notes that the ACGIH intends to lower the H_2S TLV from 10 to 5 ppm. The assertion that "it is not until levels in excess of 50 ppm where irritation of the mucous membranes of the eyes and lungs may start to occur" is not held by all observers. Concentrations of hydrogen sulfide that substantially exceed the odor threshold result in the annoying and discomforting physiological symptoms of headache or nausea (Amoore, 1985; Reynolds and Kauper 1985). The perceived intensity of the odor of hydrogen sulfide depends on the longevity of the concentration, and the intensity increases 20% for each doubling of the concentration (Amoore, 1985). Several studies have been conducted to establish the ratio of discomforting annoyance threshold to detection threshold for unpleasant odors (Winneke, 1975; Winneke and Kastka, 1977; Hellman and Small, 1974; Adams *et al.,* 1968; and NCASI, 1971). The geometric mean for these studies is 5, indicating that when an unpleasant odor reaches an average concentration of 5 times its detection threshold, the odor will result in annoying discomfort. Applying the 5-fold multiplier to the mean detectable level, 0.008 ppm, results in a mean annoyance threshold of 0.04 ppm. At the current California Ambient Air Quality Standard (CAAQS) of 0.03 ppm, the level would be detectable by 83% of the population and would be discomforting to 40% of the population. These estimates have been substantiated by odor complaints and reports of nausea and headache (Reynolds and Kauper, 1985) at 0.03 ppm H_2S exposures from geyser emissions. The World Health Organization (WHO) reports that in order to avoid substantial complaints about odor annoyance among the exposed population, hydrogen sulfide concentrations should not be allowed to exceed 0.005 ppm (5 ppb or 7 $\mu g/m^3$), with a 30-minute averaging time (WHO, 1987; National Research Council, 1979; Lindvall, 1970). The RfC of 0.9 $\mu g/m^3$ (0.7 ppb) is for a year's averaging time and is within a factor of 8 of WHO's recommendation for 30 minutes. The RfC seems rather low but was the result of following USEPA's documented procedure for developing RfCs which has evolved during the last 10 years and is compatible with WHO's recommendation for a 30 minute acute exposure. The RfC is based on a study in mice in which animals in the LOAEL group had histopathological inflammatory changes in the nasal mucosa, an endpoint compatible with respiratory irritation.

Comment 3. The major human health concern from hydrogen sulfide is from acute exposures in excess of 50 ppm. There are OEHHA acute RELs in place to deal with such exposure scenarios. There is a significant amount of literature documenting chronic human exposure to hydrogen sulfide. There is no convincing evidence that chronic low-level exposure to H_2S at levels around the odor threshold causes adverse health effects. One study of a community in Rotonia, New Zealand (an area of significant geothermal

activity) showed that no chronic health effects could be identified after long-term exposure to 5 to 1,900 ppb H_2S.

Response. If chronic low-level exposure to H_2S at levels around the odor threshold cause no adverse health effects, we should be able to develop a chronic REL based on that data. The referenced study (Siegel, S.M., Penny, P., Siegel, B.Z. et al. (1986) Atmospheric hydrogen sulfide at the Sulfur Bay wildlife area, Lake Rotonia, New Zealand. *Water Air Soil Pollut.* 28:385-391) should be submitted to the USEPA for review. However, as stated above, WHO reports that in order to avoid substantial complaints about odor annoyance among the exposed population, hydrogen sulfide concentrations should not be allowed to exceed 0.005 ppm (5 ppb) for a 30-minute averaging time.

Comment 4. H_2S has been measured in the human breath at levels of 65-698 ppb, and is the result of normal bacterial activity in the digestive tract. H_2S is also produced in various tissues, including the brain where it is thought to function as a neuromodulator, and also acts as a smooth muscle relaxant. Given the rapid metabolism of H_2S and the low levels naturally produced by the body, the lack of observations of toxicity after chronic exposure to low levels is not surprising. Even the work of Bhambhani and Singh cited in the OEHHA supporting documentation found that healthy subjects could safely exercise at their maximum at hydrogen sulfide concentrations of 5 ppm (5000 ppb) H_2S. In later studies, Bhambhani found small but statistically significant changes in oxygen uptake and increase in blood lactate after exposure to 10 ppm (10,000 ppb) H_2S, a physiologic effect, but not an adverse health effect. No subjective symptoms were reported in this study as subjects breathed either 5 or 10 ppm H_2S through a mouthpiece.

Response. Many toxic chemicals are produced by metabolism: CO, acetaldehyde, formate, NO, and H_2S. The chronic RELs are to protect against low-level, involuntary exposures. OEHHA staff are aware of the Bhambhani studies which are generally acute/subacute studies with normal individuals and thus not useful for developing a chronic REL.

Comment 5. The proposed OEHHA REL of 0.7 ppb for H_2S is based on the USEPA reference concentration (RfC) promulgated in 1994. A number of studies on the toxicity of H_2S have since been published or are near completion. This new information should be incorporated into the final REL.

Response. Comment acknowledged. OEHHA's use of RfCs was explained above. OEHHA and hopefully also USEPA will examine the new information for possible incorporation when it becomes available. We have revised our proposed REL as explained in responses to comments from Geyser's Geothermal using the same study as U.S. EPA, but different uncertainty factors. The new proposed REL is 9 $\mu g/m^3$ (7 ppb).

Comment 6. In both the derivations of the RfC and REL a large uncertainty factor of 1000 is used. A large uncertainty factor is only appropriate when there is a paucity of data. This is not the case for H_2S. Based on the significant amount of human and animal data available, this factor should be decreased by at least an order of magnitude.

The derivation of the REL uses a subchronic-to-chronic uncertainty factor of 10. This should be reduced to 3, based on available data suggesting that the types of lesions found in rodents at high sub-chronic exposures are unlikely to progress with longer duration of exposure. Moreover, given the rapid metabolism and detoxification of H_2S, these subchronic rodent studies performed at high H_2S concentrations (much higher than the OEHHA acute level II REL for H_2S) are not relevant to chronic low level human exposures.

Response. OEHHA agree that the uncertainty factor (UF) is large and close to the maximum uncertainty factor used by USEPA of 3,000. We revised our proposed REL as noted above.

Comment 7. The other significant part of the large uncertainty factor is the modifying factor of 3 used for the "lack of reproductive and developmental toxicity data". I believe this modifying factor is unwarranted. The developmental study cited in the OEHHA documentation demonstrates no developmental effects in rats, even at concentrations (150 ppm) high enough to cause slight maternal toxicity. This is clear evidence that H_2S is a compound the body is capable of metabolizing and detoxifying quite rapidly. Additionally, by mid-1998, final reports should be available from the Chemical Industry Institute of Toxicology (CIIT) on the reproductive effects and developmental neurotoxicity of H_2S. No final decision on the REL should be made until these studies are completed.

Response. This suggestion has merit and should be made to USEPA. There are other developmental studies with H_2S by S. Roth and coworkers in which adverse effects on the developing nervous system were seen at 20-25 ppm, the lowest concentration tested. As noted above, we revised our proposed REL.

Comment 8. OEHHA cites the "lack of adequate long-term human exposure data" as a major area of uncertainty and the reason for the conservativeness of the REL. Humans are constantly exposed to low levels of hydrogen sulfide, and life could not continue without the production of hydrogen sulfide. To set the REL one thousand times lower than the upper concentration for naturally occurring H_2S in human breath seems very conservative. OEHHA did not take this type of human data into consideration in its derivation of the REL. OEHHA uses a high uncertainty factor for a chemical for which there is a large amount of good animal and some human data.

If the subchronic-to-chronic uncertainty factor of 10 is reduced to 3, and a very conservative modifying factor removed, the REL uncertainty factor could be lowered by

an order of magnitude to 100. This would put the REL in the 7.0 ppb range, a concentration at the very limits of odor recognition and found naturally in the human body.

Response. This suggestion also has merit and should also be made to USEPA. However, OEHHA is not willing to unilaterally change USEPA uncertainty factors. OEHHA is harmonizing with USEPA where possible.

Comment 9. I hope the foregoing discussion and data, along with the soon-to-be-completed CIIT studies, will be taken into consideration by OEHHA before setting the final REL. The economic impacts of the proposed REL could be enormous throughout California. The final decision on the REL should therefore be made in a collaborative setting with industry. OEHHA has made a great effort to involve input from risk managers and stakeholders throughout the process

Response. Many of the comments above need to be made to the USEPA. OEHHA will certainly review the CIIT studies when they become available. However, based on this comment and other comments about the hydrogen sulfide chronic REL and on OEHHA's own assessment of the developmental toxicity data available including a study on spontaneous abortion published in 1998, OEHHA staff have reviewed the value in the draft document and have calculated a revised chronic REL for hydrogen sulfide of 9 $\mu g/m^3$.

Western States Petroleum Association (WSPA)

Comments on the Determination of Chronic Toxicity Reference Exposure Levels were received from WSPA in a letter dated January 29, 1998. WSPA made comments on the general methodology and on the chronic RELs for **benzene** and **hydrogen sulfide**. WSPA is a trade association representing members engaged in all aspects of the exploration for, and production, refining, transportation and marketing of, petroleum and petroleum products in the western United States.

Comment 1. WSPA is pleased to note the extent to which OEHHA has attempted to harmonize their approach for calculating RELs with that of USEPA. WSPA agrees that uncertainties exist in the characterization and quantification of potential health effects in humans, especially when extrapolating from animal studies. However, the potential to significantly overestimate the likelihood of these effects by compounding uncertainty factors must also be recognized. OEHHA has recognized the utility of pharmacokinetics in tempering the use of uncertainty factors in REL calculations. Indeed, information about the biochemical mechanism of the chosen toxic endpoint in key studies can be extremely important in reducing uncertainties regarding intraspecies and interspecies variability, and the likelihood of enhanced susceptibility based upon age, gender, etc. OEHHA should give greater consideration to the role of mechanistic data in the parent document and in calculating selected RELs.

Although WSPA generally agrees with OEHHA on the basic methodology for calculating inhalation RELs, we find that the choice of key study and the application of the REL methodology give rise to a number of concerns with certain chemical-specific RELs. The attached comments address WSPA's concerns with the proposed REL calculations for benzene and hydrogen sulfide. We understand that the Olefins panel of the Chemical Manufacturers Association (CMA) will submit comments on certain other RELs, some of which are also of interest to WSPA. Specifically, WSPA shares CMA's interest in the proposed RELs for ethylene, 1,3-butadiene and propylene. Rather than duplicate CMA's comments on these chemicals in this submittal, we will instead incorporate their comments herein by reference.

Response. Comment noted. OEHHA used the best study it could find in the medical and toxicological literature prior to the release of the document in October 1997. In the case of isopropanol a superior study appeared in 1997 and has been used to revise the REL. In other cases OEHHA used scientific judgment with which others might not agree. In the case of hydrogen sulfide OEHHA used the USEPA's chronic REL as part of its effort to harmonize with USEPA. OEHHA has contacted the USEPA to determine if USEPA made an error in calculating the RfC. OEHHA addressed the comments of the Chemical Manufacturers Association - Olefins Panel in a response above.

Comments on General Methodology

Comment 2. OEHHA should not include abstracts of presentations or posters as references in this document (e.g., Alexeeff et al., 1997; Foureman, et al ., 1995; Gillis, et al., 1997; Kadry, et al., 1995; Khodair et al., 1995; Mitchell, et al., 1993; Schmidt et al., 1997 and Swartout, 1997). A number of other citations are to secondary references such as book chapters. The value of such citations is extremely limited since the methodology and conclusions cannot be evaluated. In addition, these studies and their conclusions have not been subject to peer review. OEHHA should not include such citations as supporting documentation for these guidelines.

Similarly, journals from the former Soviet Union are of little use as citations (e.g., Chizikov, 1973). These documents are not available in English and cannot be translated in time to provide the opportunity for comment. In addition the frequent use of nonstandard terminology and the generally poor quality of English used in the abstract translations when present have not been subject to peer review outside of the former Soviet Union as evidenced the studies cited in these journals.

Response. OEHHA has attempted to use the best studies it could find. We would prefer peer-reviewed journal articles for all cases. However this is not always possible. We have used well-conducted, unpublished industry studies for the development of RELs if these had the best data available. USEPA used an unpublished study (at the time of promulgation of the RfC) to develop the RfC for MTBE. OEHHA also used as the basis for different RELs a case report (one individual) published in the peer-reviewed literature, a NIOSH Health Hazard Evaluation, and research institute and government (e.g., NTP) reports. In one case we based a REL on studies published in Russian that had been summarized by NIOSH. But we did not base any REL on just an abstract.

Comment 3. P. 11, Section 1.4, Para. 3: RELs may appropriately be based upon the most sensitive endpoint unless there is data demonstrating that the endpoint in question is not relevant. This will usually not be an issue for RELs based upon human studies. In the case of RELs based upon animal studies, there may be scientifically sound reasons why the most sensitive endpoint in an animal study is not relevant to human populations. These reasons may be based upon biochemical mechanism, metabolic pathways or pharmacokinetics. This possibility should be acknowledged by OEHHA here as it is in Section 2.1.2.

Response. The introduction is only an overview. The elaboration of this specific point has been done in the Hazard Identification section as noted by the comment.

Comment 4. P. 11, Section 1.4, Para 4. Under AB-2588, the Hazard Index is based on estimated exposure levels derived from air dispersion models, not from measurements as stated in the document.

Response. Comment noted. The exposure levels could be derived from measurements, but they rarely are.

Comment 5. P. 12, Section 1.5, Para 1. In the discussion of susceptible sub-populations, the reference to increased exposures should be deleted. Differences in susceptibility are the result of variations in physiological or biochemical processes characteristic of a specific sub-population. Variations in exposure are relevant to risk calculations but should be accounted for as such. Accounting for variations in exposure within a subject population is the subject of a companion technical support document, *Exposure Assessment and Stochastic Analysis.*

Response. OEHHA staff can not totally agree with this suggestion and will not delete reference to exposure differences. At the same external exposure there may be different susceptibilities due to physiological processes such as the increased absorption of ingested lead by children compared to adults and of inhaled pollutants due to the increased breathing rates of children relative to adults.

Comment 6. P. 13, Section 1.6. The last sentence would benefit from some additional clarification.

Response. The last sentence states: "Thus, human exposures of greater than 8 years are not adjusted either in their calculation or application." OEHHA has added text clarifying the concept.

Comment 7. P. 17, Section 2.1.2, Para 2. In the discussion of relevance of animal data to human response, OEHHA should include mechanism of action with pharmacokinetics and metabolism as information useful in selecting the relevant animal model.

Response. OEHHA will include mechanism of action as information useful in selecting the relevant animal model.

Comment 8. P. 17, Section 2.1.2, Para 3. Although useful information may be obtained from studies that may not conform to every detail of sound design or comply with a rigorous application of Good Laboratory Practices, clearly regulatory standards should not be based on poorly designed or executed studies. WSPA hopes that OEHHA would agree that data from studies of questionable scientific validity should only be considered in the calculation of RELs if supported by data from separate valid studies.

Response. OEHHA would prefer to only use studies that conform to every detail of sound design or comply with a rigorous application of Good Laboratory Practices. If such a study is not available for a chemical, we must act to protect public health by using the best data we can find. Hopefully affected parties will be motivated to get better data.

Comment 9. P. 19, Section 3.1.1, Para 2. The first sentence needs to have a reference and more discussion to support the allegation of such a high potential for undetected adverse effects. Clearly the statistical power of a study to detect an incidence of an adverse effect will vary with the size of the study populations. The concern that a relevant endpoint may not have been detected is reasonable if a chronic REL is being calculated from a short term study. WSPA believes that concern is addressed adequately by the inclusion of an uncertainty factor for a less-than-chronic study, especially in the light of numerous other uncertainty factors which are applied because of concerns that *may be true*, but are not known to be true.

Response. The commentator apparently does not agree that the NOAEL may be associated with an incidence of adverse effects of 1 to 20%. One relevant reference is the paper by Leisenring and Ryan (1992) which is given at the end of the paragraph 2. They report that "average risk levels associated with the NOAEL may be substantial." Another reference is Crump (1984) which is cited elsewhere in the introduction. It is true that the sample size in part determines statistical power. That is the basis for the statements in the 2 papers cited.

OEHHA prefers to address the subchronic to chronic differences separately from the LOAEL/NOAEL consideration.

Comment 10. Studies should be evaluated for thoroughness in considering appropriate endpoints before they are used for REL calculation. This is another area in which consideration of pharmacokinetic and mechanistic information can be useful. Increasing the degree of uncertainty adjustment because one can never answer all possible "what if" scenarios is not a sound basis for calculation of useful health based standards.

Response. OEHHA has evaluated all relevant studies for use in the REL calculations. The database for most chemicals is limited. Uncertainty factors are used when insufficient data are available to support the use of chemical-specific and species-specific extrapolation factors. The human intraspecies factor is in many ways a variability factor since humans are known to be variable in response to chemicals. While the default factor of 10 may be too large for some chemicals it is probably not adequate for others (Hattis D. 1996. Variability in susceptibility – how big, how often, for what responses to what agents? Environmental Toxicology and Pharmacology. 2:133-145). As one example, in a study of DNA adducts due to PAHs the interindividual variability was about 24-fold (Dickey C et al. Variability in PAH-DNA adduct measurements in peripheral mononuclear cells: implications for quantitative cancer risk assessment. Risk Anal 1997;17(5):649-656).

Comment 11. P. 20, Para 2. Although WSPA agrees with the general approach in addressing the uncertainty in NOAEL to LOAEL relationships, the comparison of

NOAELs and LOAELs is not as straightforward as implied in the discussion. The ratio of LOAEL to NOAEL will usually be an overestimate. This is unavoidable unless a study has many dose levels. Discussions of population statistics notwithstanding, the study NOAEL will usually underestimate the true value. This is especially true when there is large variation among dose levels. Again, when there are large differences among dose levels it is also likely that the LOAEL determined will be higher than the true value. The portion of the Alexeeff et al., 1997 study that compared LOAELs for serious effects to NOAELs for all effects should not be used to justify large uncertainty corrections, since comparably based parameters were not being considered. The comparison based on mild effects has a firmer theoretical foundation and showed ratios within the 10-fold range. Unfortunately the methodology of this study could not be evaluated for these comments since the reference is to a meeting abstract.

Response. OEHHA agrees that in practice the comparison of NOAELs and LOAELs is not straightforward. Based on a review of the literature by ATES staff the SRP recommended in December 1998 that staff use a LOAEL to NOAEL default adjustment factor of 6 instead of 10 for acute RELs. The Alexeeff et al. (1997) report is available as Appendix F of the final Acute Reference Exposure Level Technical Support Document. ATES has considered whether a LOAEL to NOAEL factor other than 10 is justified for chronic RELs also and has described its approach in Section 3.1.2 of the Introduction. As examples in which a factor other than 10 was used, in the propylene chronic REL developed by OEHHA, after doing the RGDR adjustment, a LOAEL to NOAEL factor of 3 was used due to low severity of the adverse effect. For the sulfuric acid REL OEHHA used 3 due to slight, low incidence adverse effects. Finally, for silver the LOAEL to NOAEL factor was 1 because there were the effects were cosmetic without associated adverse health effects.

OEHHA disagrees with the comment that the LOAEL and NOAEL are generally underestimates. There is no basis for this statement. A NOAEL is sometimes incorrectly viewed as an estimate of a threshold level for adverse effects. However, a NOAEL could be associated with a substantial (1-20%) but undetected incidence of adverse effects among the exposed population, or alternatively it could be lower than a true population threshold (Gaylor DW. Incidence of developmental defects at the no observed adverse effect level (NOAEL). Regul Toxicol Pharmacol 1992 Apr;15(2 Pt 1):151-160; Leisenring W, Ryan L. Statistical properties of the NOAEL. Regul Toxicol Pharmacol 1992 Apr;15(2 Pt 1):161-171).

Comment 12. Page 20, Para 3. WSPA agrees with the OEHHA scheme for use of an intermediate uncertainty factor, but suggests that EPA grade 6 be the cutoff for a low severity effect since by definition the changes have no functional effect on the organism.

Response. OEHHA staff have weighed the cutoff level thoroughly and decided that level 5 was appropriate. Degenerative or necrotic tissue changes are considered serious, even though they are not accompanied by an apparent decrement in organ function.

Comment 13. Page 23, Para 1. It is not clear why 3 + 3 equals 10. OEHHA should provide some justification for adding intermediate uncertainty factors in this manner.

Response. Uncertainty factors are multiplied, not added. The factor of 3 is really 3.16, the square root of 10, which has been rounded to 3. When 2 of these are multiplied together, each is actually the square root of 10 and the product is therefore 10.

Comment 14. P. 27, Section 3.4.1.2, Para 2. OEHHA should justify the use of a 10-fold factor rather than the HEC in the absence of chemical- and species- specific information. There is no thermodynamic reason to expect that the blood:air partition coefficients between species will vary to any great extent. Therefore, unless OEHHA has data to indicate that this is not the case, the calculation of an HEC seems to be warranted.

Response. OEHHA is unable to calculate an HEC in the absence of a blood:air partition coefficient for the specific chemical. Rather than using the HEC adjustment and the lower interspecies UF of 3, the interspecies default value of 10 is used.

Comment 15. P. 28, Section 3.4.2. The use of the Schmidt et al., 1997 reference to justify the default use of a 10-fold uncertainty factor for animal to human extrapolation is inappropriate. This reference is to an abstract and neither the methodology nor the interpretation of the results can be adequately evaluated.

Response. The report of Schmidt et al. is consistent with known data on interspecies uncertainty factors. The report was presented at the 1997 Annual Meeting of the Society of Toxicology. It is unfortunate that there are limited analyses of this type in the peer-reviewed literature.

Comment 16. P. 29, Section 3.5, Para 1. The phenomenon is not indicative of hyper-susceptibility and should not be part of this discussion. Idiosyncratic response refers to a response, which is qualitatively different than that seen in study populations. The true idiosyncratic response does not necessarily occur at doses or exposures below those at which the "normal" response is seen.

Response. OEHHA staff believe that the inclusion of idiosyncratic response is appropriate. According to Casarett and Doull's Toxicology (4th edition, p. 16), the chemical idiosyncratic response "is usually qualitatively similar to that observed in all individuals but may take the form of extreme sensitivity to low doses or extreme insensitivity to high doses of the chemical." In addition, allergic hypersensitivity is also considered by OEHHA to be an idiosyncratic response.

Comment 17. P. 30, Para 1. While the default use of a 10-fold uncertainty factor is consistent with USEPA default methodology, OEHHA should recognize that this is an area in which the consideration of basic mechanisms of toxicity can reduce uncertainty. OEHHA should consider an intermediate uncertainty factor for those chemicals for which the chronic REL is based upon direct irritation as the endpoint. Since direct irritation responses do not involve sources of population variation such as metabolism, pharmacokinetic considerations or enzyme mediated responses, the opportunity for inter-individual variation within a population is much smaller than for systemic effects. An intermediate UF of 3 would be consistent with OEHHA's approach for developing intermediate UFs for LOAEL to NOAEL conversions.

Response. There are a number of studies indicating wide variability in the population in response to irritant chemicals (e.g., formaldehyde). There are no data indicating less variability for irritants than for other toxicants that we are aware of. The commentator presents an attractive hypothesis but without supporting data.

Comments on Specific Chemical RELs: Benzene

For benzene OEHHA developed a chronic REL of 60 $\mu g/m^3$ based on hematologic effect seen in the Tsai et al. (1983) study of 303 male refinery workers.

Comment 18. WSPA takes issue with a number of points in the calculation of the REL for benzene and believes that the REL should be at least 2-fold higher than the OEHHA estimate. While we agree on the choice of toxicological endpoint we disagree with the exposure estimate chosen as the NOAEL in the Tsai et al. study and with some of the supporting documentation for the resultant REL. In addition, we believe that there is biochemical information supporting the use of an UF for intraspecies variation less than the default value of 10.

The Tsai et al. (1983) retrospective epidemiology study of refinery workers exposed to benzene was chosen by OEHHA as the key study and the endpoint of depressed red and white blood cell counts as the critical effect for this REL. An examination of the WBC and RBC counts of a subset of 303 workers, approximately 75% of the total cohort, indicate that all counts, including multiple counts on many workers over the course of their employment in a benzene-exposed job, were within normal limits. The study authors stated that the overall median benzene exposure of this group as determined by personal monitors was 0.53 ppm. OEHHA chose this value as the NOAEL for the group. If the value of the median exposure is 0.53 ppm, then that means that 50% of all exposures were greater than that value. Since Tsai et al. reported that all blood counts were within normal limits, 0.50 ppm is clearly an underestimate of the NOAEL for this group. Tsai et al also determined, as reported by OEHHA, that 85% of all exposures to benzene in their study were less than or equal to 1.0 ppm. It is this latter figure that WSPA believes should be used as the NOAEL for the hematologic effects of benzene in this cohort. Other considerations notwithstanding, making this adjustment would increase the REL by an effective value of 2.

Response The comment is correct in pointing out that Tsai et al. (1983) determined that 84% of all exposures to benzene in their study were less than or equal to 1.0 ppm. This statistic applies to the entire study population. Tsai et al. (1983) reported the central tendency for each of the three reported subgroups as median exposure values: "benzene-related" subgroup - 0.53 ppm; "other benzene" subgroup - 0.24 ppm; and "all others" - 0.07 ppm. The central tendency of a value, and not its upper exposure range, most accurately represents the population exposure history. The benzene chronic REL is based upon the median (half higher/half lower) exposure value (0.53 ppm) reported for the highest exposed subgroup ("benzene-related") without a reported adverse health effect in the Tsai et al. (1983) study.

The chronic REL value is based upon the medical surveillance program results obtained for the subset of workers who worked in the benzene areas. These workers mostly included those assigned to the "benzene related" category (benzene, aromatic distillate hydrogenation (ADH), ethylene, and cumene) with a median exposure of 0.53 ppm. However, workers assigned to the "other benzene" category (pumps, docks) with a median exposure of 0.24 ppm were also included. Therefore, it appears that the choice of 0.53 ppm to represent the median exposure history of the medical surveillance population is likely to be somewhat above the actual median for this group. However, since the "benzene-related" subgroup included in that surveillance population could reasonably be considered to have shown no ill effects since the whole group showed no ill effects, the use of the 0.53 ppm value is justified.

Comment 19. Citing the existence of a healthy worker effect, OEHHA applies the default 10-fold UF for intraspecies variation to the NOAEL adjusted for continuous exposure to calculate the final REL. While acknowledging that a healthy worker effect for mortality or all causes and cardiovascular diseases existed, with regard to those factors known to be important for the hematotoxicity of benzene there is no reason to believe that the variation within the population of the Tsai et al., study was less than in the general population, including the very young and the elderly. To produce a toxic effect, benzene must first be metabolized to active metabolites by cytochrome P-450 system, specifically Cyp2EI (Medinsky et al., 1997). In addition it has also been reported by Martyn Smith (but not yet peer-reviewed) that the enzyme DT-diaphorase, or reductase-NQO 1, is important in the detoxification of quinones such as those generated as metabolites of benzene. In neither case can WSPA imagine a medical condition caused by a variant form (or degree of activity) of either of those enzymes that would disqualify an individual from employment in a refinery and through its omission contribute to a "healthy worker" effect. In other words, there is no reason to believe that the worker population studied by Tsai et al., differed from the general population in these two critical aspects. In fact, if the very young or very old differ from the general population in the activity of Cyp-IIE I, it is most likely in the direction of having lower than average levels of this enzyme, since P-450 mediated metabolism is generally agreed to be decreased in infants and the elderly. In the absence of other plausible bases for the

full 10 fold default intraspecies UF, WSPA believes that an intermediate factor of 3 or 5 could be used and remain health protective of sensitive individuals.

Response. The application of the 10-fold intraspecies uncertainty factor was not predicated upon the existence of a healthy worker effect in the study populations. The parenthetical statement following the listing of the intraspecies uncertainty factor in the derivation section was misleading and will be deleted. The intraspecies uncertainty factor reflects the fact that the study populations typically do not and can not (given study size limitations and the non-random selection of workers pursuant to occupational qualifications and requirements) capture the variability of the general population's susceptibility to toxic injury. The healthy worker effect observed in the Tsai et al. study suggests the presence of prior selection. However, the absence of a healthy worker effect would not demonstrate that the workers were, in fact, representative of the broader population. Here, for instance, the Tsai et al. (1983) study reported the noncancer chronic endpoints only for males.

The Tsai et al. (1983) study also lacked a comparison of the exposed group to matched controls. Thus, although none of the observed hematology parameters were considered clinically abnormal, there was limited ability to detect changes in mean values attributable to exposure. By way of illustration, in the Rothman study[1] which compared a control group to exposed groups, even where the ranges of the reported hematology parameters were similar for control and exposed groups, the mean values for several health effects (e.g., reduced white blood cell counts, reduced absolute lymphocyte counts) were statistically different. Rothman et al. (1996) reported a LOAEL of 7.6 ppm which is just slightly more than 10-times the NOAEL from Tsai et al. (1983). However, even considering the lack of a comparison group, the Tsai et al. (1983) study remains suitable for use in risk assessment. It followed a large number of workers over a long period of time and included up to four hematological tests per year for each worker. However, since the Tsai et al. (1983) study did not compare an exposed to an unexposed population, and especially since it did not provide dose response information, the Tsai et al. (1983) study provides limited information as to population variability. These limitations militate against use of a smaller intraspecies uncertainty factor.

As indicated by the comment, recent research by Rothman et al.[2] (published after the comments were submitted) indicates that known genetic variants in the enzyme pathways which activate benzene (CYP2E1) and then detoxify (NQ01) its metabolites affect the potential to develop benzene poisoning. In this Rothman et al. (1997) case-control study, individuals with benzene poisoning (abnormal blood counts) were 7.8-fold more likely than other workers to have enzyme genotypes which would result in fast activation and slow detoxification. Since the majority of the workers in the case control study were not fast activators and slow detoxifiers, other factors are likely important to the development of benzene poisoning. It is improbable that these enzymes are the only substantial source of variation in the human poisoning response to benzene exposure.

[1] Rothman et al. American Journal of Industrial Medicine 29:236-246 (1996).
[2] Rothman et al. Cancer Research 37, 2839-2842, 1977

Given uncertainties as to the range of human susceptibility, an uncertainty factor of ten for intraspecies variation is appropriate.

Comment 20. A number of studies have been cited by OEHHA as support for the accuracy of the proposed REL of 0.02 ppm. The Cody et al. (1993) study was mentioned as correlating decreased WC and RBC counts in a subset of the Pliofilm cohort with median, job-specific exposures to benzene in the range of 30 to 54 ppm. For the comparison, the lower value of 30 ppm was selected by OEHHA and a hypothetical REL of 0.01 ppm calculated as if this study had been selected as the critical study. The Cody et al, (1993) study used the Crump and Allen exposure estimates for the Pliofilm cohort as a basis for the 30-54 ppm median exposure estimates. Again, by definition, 50% of the exposure estimates for the subject workers were above 30 ppm, using the Crump and Allen estimates. In addition, the exposure estimates for the Pliofilm cohort calculated by Paustenbach et al. (1992) are significantly higher than those of Crump and Allen for most job categories and years and have been acknowledged as superior by the senior author of the Crump and Allen reference, Crump (1994). Typically, Paustenbach et al. (1992) exposure estimates were 50% to 100% higher than those of Crump & Allen on a job-specific basis. This strongly suggests that the 30 ppm exposure estimate used by OEHHA for Cody et al. (1993) should be considered a significant underestimate of the majority of exposures in that study, and the calculated REL should be revised upward accordingly.

Response. The comment is correct that OEHHA used the 30 ppm value which is the low end of the range of median values (30 – 54 ppm) used in the Cody et al. (1993) study. OEHHA notes this fact in our document. The purpose of the discussion and related dose response calculation from Cody et al. (1993) was to assess our use of the Tsai et al. (1983) free standing NOAEL as the basis for the proposed chronic REL. The dose response analysis of the Cody et al. (1993) data resulted in a derived comparative REL of 0.01 ppm. This value was close enough to the proposed chronic REL of 0.02 ppm to indicate that reliance upon the free standing NOAEL reported for Tsai et al. (1983) study, a study which lacked a control group for comparison, would not yield results which were inconsistent with those which might be derived from the Cody et al. (1993) study. For these purposes, 30 ppm was selected as the most health conservative median value. However, whether the dose response analysis of the Cody et al. (1993) data was based upon the lowest or highest end of the range, or something in between, would not affect our conclusion that the results achieved with either the Cody et al. (1993) or the Tsai et al. (1983) data would be consistent. This conclusion satisfied prudential concerns regarding the selection of a study with a free-standing NOAEL as the key study.

Utterback and Rinsky[3] (1995) have critically evaluated in detail the Paustenbach et al. (1992) reanalyses of the Pliofilm cohort exposures. They reported that the Paustenbach et al. (1992) exposure estimates are greatly skewed by the use of unrealistically large dermal absorption factors and unrealistically large estimates of the exposed body surface area. They also provided substantial evidence also that the

[3] Utterback, David F. and Rinsky, Robert A. American Journal of Industrial Medicine 27:661-676 (1995).

Paustenbach et al. (1992) reanalyses inadequately incorporated the available historical airborne exposure information. Furthermore, Utterback and Rinsky (1995) noted that the Paustenbach et al. (1992) reconstructions entailed exposures which were on the order of 100 to 200 ppm and lasted as long as a decade. Yet, there was no epidemic of hematopoietic disorders which would be expected from chronic exposures to these high doses. Furthermore, given the repeated visits by industrial hygiene inspectors from the State of Ohio to evaluate the benzene exposures, it seems unreasonable to conclude that there were persistent exposures to benzene grossly over the recommended level.

Nevertheless, ultimately the exposure history uncertainties for the Pliofilm cohort favor our use of the Tsai et al. (1983) study for purposes of dose-response assessment. To adjust the proposed chronic REL upward, as suggested by the comment, on the basis of analyses of the Pliofilm cohort would in fact negate the selection of the Tsai et al. (1983) cohort as the basis of the dose response assessment and import the uncertainties associated with analyses of the Pliofilm cohort into the proposed chronic REL.

Comment 21. OEHHA briefly mentions the study of Kipen et al. (1988), continues on to a discussion of the Cody et al. (1993) study and never returns to Kipen. The reason for this is unclear. The Cody study clearly identifies itself as a sequel to the earlier Kipen et al. study which was designed to respond to criticisms of the earlier study (See Hornung et al., 1989). The results of the Kipen et al study were never invalidated and should be more thoroughly considered by OEHHA. That study identified a median exposure for benzene exposed workers subject to WBC & RBC counts as 75 ppm during the early 1940s. The Cody et al. study was limited to workers for whom pre-employment physicals were available as a baseline. The results of the Kipen et al. study indicate that the effect on WBC and RBC counts disappeared after the 1940's when regulatory levels and additional engineering controls decreased benzene exposures below 50 ppm. The longer term of follow-up for workers in this study versus those in the Cody study support the use of a smaller UF for subchronic to chronic extrapolation and support a higher REL than the current proposal.

Response. The Kipen et al. (1988) study reported that as benzene exposure levels fell during the 1940's worker blood counts went up. However, Hornung et al. (1988) challenged the Kipen analysis on the basis that similar temporal trends showed up in preemployment blood samples. Thus, the analyses in Kipen et al. (1988) with respect to the time period in question were subject to confounding. Kipen et al. (1988) did not closely analyze the reported effect of benzene exposure for later periods when exposures were lower and the preemployment blood count trends were stable. However, the Ward et al. (1996) study did apply a more sensitive nested case control methodology to the same study population and reported a relationship between benzene exposure and reduced white blood cell counts whether or not the pre-1947 data was included. Thus, the Ward et al. (1996) study reported an association for exposures occurring after 1947, a time when the pre-employment blood values had stabilized and when the benzene exposures were much reduced and less uncertain. Given, the Ward et al. (1996) study

findings and the primary focus of the Kipen et al. (1993) study on the earlier exposure period, there was no reason to use the Kipen et al. (1993) study as the basis for the REL.

The proposed chronic REL for benzene of 0.02 ppm was derived using a subchronic to chronic uncertainty factor of one. The derivation of the comparative chronic REL from the Cody et al. (1993) study used a subchronic to chronic uncertainty factor of ten. This factor of ten was based upon the fact that the Cody et al. (1993) study focused upon the blood dyscrasias developing over the first year of exposure.

Comment 22. The Ward et al. (1996) study is cited in support of the 0.53 ppm NOAEL chosen by OEHHA. This study analyzed the same data set as that of Kipen et al. (1988) and Cody et al. (1993) with the important exception that the exposure estimates for the individuals from whom the blood count data were obtained were based upon the work of Rinsky et al. (1987). This was the earliest set of exposure estimates for the Pliofilm rubber-worker cohort and used the most simplistic set of exposure assumptions, i.e., that the exposures of the workers in the early 1940s were essentially the same as those in the 1970s. A later exposure estimate was made by Crump and Allen in 1984 for the OSHA benzene risk assessment and is the one used by Cody et al., 1993 cited by OEHHA. The most recent assessment is that of Paustenbach et al. (1992) which has been accepted by Crump as the most thorough and best assessment to date (Crump, 1994). Both the Crump and Allen and the Paustenbach exposure assessments conclude that the workers in this cohort had much higher exposures during the 1940s than estimated by Rinsky et al. (Paustenbach, et al., 1992). Accordingly, the Ward et al. (1996) study cannot be used for accurate quantitative assessment of exposures or any calculations based on those exposures.

Response. The proposed chronic REL is not based upon the Ward et al. (1996) study. Our document briefly describes the Ward et al. (1996) study and concludes that the results are not inconsistent with each other. While the comparisons at issue are directed toward the proposed chronic REL value, the principal value of these comparisons was in assessing the reasonableness of OEHHA's choice of the Tsai et al. (1983) study as the source of the NOAEL value to be used in deriving the chronic REL. This confirmation was of particular importance as the Tsai et al. (1983) study provided a free-standing NOAEL with respect to frank toxicity. Given that the key study lacked a control group for internal comparison, the power to detect an adverse effect based upon a comparison of means was reduced. These factors reduced confidence in null results reported for the Tsai et al. (1983) study. Therefore, OEHHA sought to compare the proposed chronic REL obtained using the Tsai et al. (1983) study to those obtained from other studies which reported LOAELs but not NOAELs.

As stated above, Utterback and Rinsky[4] (1995) have critically evaluated in detail the Paustenbach et al. (1992) reanalyses of the Piofilm cohort exposures. They reported that the Paustenbach et al. (1992) exposure estimates are greatly skewed by the use of unrealistically large dermal absorption factors and unrealistically large estimates of the

[4] Utterback, David F. and Rinsky, Robert A. American Journal of Industrial Medicine 27:661-676 (1995).

exposed body surface area. They also provided substantial evidence that the Paustenbach et al. (1992) reanalyses inadequately incorporated the available historical airborne exposure information. Furthermore, Utterback and Rinsky (1995) noted that the Paustenbach et al. (1992) reconstructions entailed exposures which were on the order of 100 to 200 ppm and lasted as long as a decade. Yet, there was no epidemic of hematopoietic disorders which would be expected from chronic exposures at these high levels. Furthermore, given the repeated visits by industrial hygiene inspectors from the State of Ohio to evaluate the benzene exposures, it seems unreasonable to conclude there were persistent exposures to benzene grossly over the recommended level.

Comment 23. In the general discussion of animal data and in the last paragraph of Page A-63, the work of Farris et al., (1997) is not discussed. Specifically, with respect to the report of Baarson et al., (1984) the Farris study demonstrated that 10 ppm was a NOAEL for any hematologic effects after 8 weeks of inhalation exposure in mice. The response of the study animals was assessed at 1, 2, 4, and 8 weeks at 4 exposure concentrations with recovery groups. Although not 13 weeks in length, the pattern of the data in this study strongly supports 10 ppm as a true NOAEL for benzene in this species.

Response. OEHHA thanks the commentator for pointing out the more recent Farris et al. (1997) reference. The document will be updated to include a summary of the information provided by Farris et al. (1997). The Baarson et al. (1984) study utilized C57Bl mice. The Farris et al. (1997) study utilized $B6C3F_1$ mice. Any differences in the results of these two studies may reflect the difference in the strains used. Baarson et al. reported marked depression in erythropoietic colony formation after 178 days of exposure to benzene. The Baarson et al. (1984) study also reported decreases in circulating red blood cells and lymphocytes at 60 and 178 days of exposure. The NOAEL for a species is determined by the most sensitive strain. Here, C57B1 is the most sensitive strain. Although the pattern of the data in the Farris et al. (1997) study may support 10 ppm as a true NOAEL for benzene in mice (or at least this strain), 8 weeks is not a chronic exposure.

Comment 24. In summary, WSPA believes that evaluation of the full data set, including the most recent animal data, available mechanism-based information and a full assessment of the Pliofilm worker hematologic data supports the assertion that the chronic REL for benzene should be 2- to 6-fold higher than the current proposal.

Response. OEHHA staff appreciate the thoroughness of the comments and hope that we have adequately addressed them. In accordance with the above responses and information, OEHHA continues to prefer the proposed chronic REL.

References cited by commentator for benzene

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Comments on Specific Chemical RELs: Hydrogen Sulfide

[In the draft TSD OEHHA proposed use of the US EPA RfC of 0.7 ppb (0.9 $\mu g/m^3$) as the chronic REL for hydrogen sulfide.]

Comment 25. OEHHA used the 1994 USEPA IRIS database as the basis for their calculation and documentation. On July 1, 1995, USEPA updated the IRIS database record for H_2S. Additional studies on H_2S have been published or initiated since that date. OEHHA should review this new information and revise their recommendation accordingly.

OEHHA recommended that the inhalation reference exposure level for H_2S should be 0.7 parts-per-billion (0.9 $\mu g/m^3$). The calculation and documentation of this value have numerous flaws. WSPA recommends that OEHHA consider a value between 9 and 30 ppb H_2S as the reference exposure level in California. The California ambient air standard for H_2S is 30 ppb to prevent nuisance odor situations. There is no evidence or expectation of toxicity at this concentration. The odor detection level for H_2S is approximately 9 ppb (AIHA, 1989), although this is highly variable. A reference level between 9 and 30 ppb is adequate to prevent adverse health effects as well as community annoyance due to the odor of H_2S (Amoore, 1985). OEHHA should acknowledge that the basis for a reference exposure level in this range is based on aesthetic (odor) rather than toxicity concerns.

Response. All USEPA Reference Concentrations (RfCs), available when the Technical Support Document (TSD) on chronic Reference Exposure Levels was drafted in October 1997, are being proposed as chronic RELs. RfCs are already used by the USEPA and by California's Department of Toxic Substances Control and were earlier incorporated by reference in Appendix F of the Emissions Inventory Criteria and Guidelines for the Air Toxics "Hot Spots" Program for use in screening risk assessments in the Hot Spots Program. These Guidelines were effective July 1, 1997. The Risk Assessment Advisory Committee (RAAC) recommended that CalEPA harmonize where possible with USEPA on risk assessment. Governor's Executive Order W-137-96 concerned the enhancement of consistency and uniformity in risk assessment between Cal EPA and USEPA. Use of RfCs as chronic RELs was one action that OEHHA took to address the RAAC recommendation and to implement the Executive Order. RfCs released after October 1997, including ones that are revisions of those in the October 1997 draft, will be

evaluated for use in the Hot Spots program by reviewing the scientific basis of each RfC when it becomes available and by determining whether the scientific literature cited in the RfC is current. Appropriate RfCs will be submitted to the SRP for review and possible endorsement. OEHHA also noted that IRIS currently lists the RfC as 1 $\mu g/m^3$.

Comment 26. The 1995 USEPA documentation of their inhalation reference concentration (RfC) contains a numerical error. The summary (Section I.B. 1) reports a total uncertainty factor of 1000 and a modifying factor of 1. In Section I.B.3, USEPA explains, "The uncertainty factor of 1000 reflects a factor of 10 to protect sensitive individuals, a factor of 10 to adjust from subchronic studies to a chronic study, and a factor of 10 for both interspecies conversion and database deficiencies." However, this is contradicted in Section I.B.4 when, after a long discussion about the progression of respiratory irritation from repeated exposure, USEPA reports, "On this basis, the standard uncertainty factor of 10 for subchronic-to-chronic extrapolation is reduced by half to a threefold factor." USEPA obviously forgot to use the 3X uncertainty factor in their final calculation. OEHHA also used this subchronic-to-chronic uncertainty factor of 10. This should be reduced to 3.

Response. OEHHA confirms the finding that the text of the IRIS document contains the reference to reducing the subchronic to chronic UF to 3. This comment should also be directed to the USEPA.

Comment 27. A single uncertainty factor of 10 for both interspecies conversion and database deficiencies is unusual. USEPA typically uses separate values for each item. OEHHA followed suit using 3 for interspecies and 3 for a modifying factor because of the lack of reproductive and developmental toxicity data.

We believe that a modification factor of 3 is unwarranted for several reasons. H_2S is a product of bacterial action in the human body. H_2S concentrations exceeding the proposed RfC have been measured in human mouth air, saliva, and periodontal pockets (Blanchette and Cooper, 1976, Rosenberg et al. 1991, Person, S., 1992, Coil and Tonzetich, 1992). Intestinal gas can contain H_2S far in excess of the proposed RfC (Kirk, E. 1949, EPA 1990, Beauchamp et al. 1984). H_2S is emitted from saltwater marshes, animal waste, landfills, rice fields, and by geothermal activity (EPA 1993). Ambient air concentrations of H_2S from natural sources have been estimated to be 0.11 to 0.33 ppb (EPA 1993). Because of our endogenous production of H_2S and its ubiquitous presence in the environment, there is no reason to use a modifying factor to prevent unforeseen effects at low part-per-billion concentrations.

Response. OEHHA staff agree that a single uncertainty factor of 10 for both interspecies conversion and database deficiencies is unusual. In regard to the modifying factor OEHHA staff generally have not used them in the development of RELs. However, there are many substances produced normally in the body that can be hazardous to other parts of the human organism. The hydrochloric acid in the stomach (present in the stomach as

a normal constituent made by the body rather than bacteria) can etch the enamel from teeth when regurgitated and cause serious respiratory problems when aspirated. The body produces carbon monoxide as a result of heme metabolism. Formate is also produced endogenously. Route of exposure must also be considered; for example, hexavalent chromium and beryllium are much less toxic by the oral route compared to the inhalation route. Finally, the modifying factor of 3 was applied by USEPA because of a deficiency of information on the effects of hydrogen sulfide on development, a database deficiency not necessarily related to our endogenous production of H_2S and its ubiquitous presence in the environment. The estimated ambient air concentrations of H_2S from natural sources between 0.11 and 0.33 ppb are below the RfC of 0.7 ppb. (For comparison ozone is another ubiquitous chemical whose background levels of 0.01 to 0.04 ppm are fairly close to the air quality standards of 0.08 to 0.12 ppm.)

Comment 28. Also, by mid-1998, final reports should be available from ongoing studies on the reproductive effects and developmental neurotoxicity of H_2S. Those studies are sponsored by the American Petroleum Institute and can be forwarded to OEHHA if desired. These studies should directly address the reasons that EPA and OEHHA used a modification factor of 3 to calculate their chronic exposure level.

Response. As of January 1999, the only study that OEHHA has been furnished with is an abstract of a 5 consecutive day exposure study on neurobehavioral and neurochemical effects carried out at the CIIT. This study is unlikely to be the basis for a chronic REL.

Comment 29. We agree with the OEHHA interspecies uncertainty factor of 3. Irritant gases like H_2S have a steep dose-response curve for respiratory effects across species. However, data are available that should significantly change the documentation presented by OEHHA. The citation of Bhambhani and Singh (1991) should be deleted as the results reported were not due to H_2S. A larger and more carefully controlled study by Bhambhani et al. (1994) found no effects in human subjects exposed to 5 ppm H_2S**.** Other studies by Bhambhani et al. (1996 and 1997) in human subjects did observe small but statistically significant changes after exposure to 10 ppm H_2S. OEHHA also cites Bhambhani and Singh, 1985, to suggest, "... either that humans are more sensitive to H_2S, or that the measurements in laboratory animals are too crude to detect subtle measures of irritation." OEHHA should note that Bhambhani and Singh (1985) reported only subjective symptoms. No objective measures of respiratory irritation were done. In the subsequent work in Bhambhani's laboratory, no subjective symptoms are reported in their publications as subjects breathed either 5 or 10 ppm H_2S through a mouthpiece. No objective measurements of respiratory irritation were part of the experimental design.

Response. Bhambhani and Singh (1991) conclude that “healthy young male subjects could safely exercise at their maximum metabolic rates while breathing 5.0 ppm H_2S without experiencing a significant reduction in their maximum physical work capacity during short-term incremental exercise.” Bhambhani et al. (1996) found that exposure to H_2S at 5 ppm “might inhibit aerobic metabolism during exercise in healthy men, thereby

increasing their dependency on anaerobic metabolism." Unfortunately the commentator does not indicate what the results are due to, if not due to H_2S.

OEHHA considers that 3 is appropriate as a subchronic to chronic uncertainty factor for the hydrogen sulfide study used (CIIT, 1983). Also OEHHA does not agree with the U.S. EPA position that there is a lack of data on developmental effects of hydrogen sulfide. In addition to the Saillenfait et al. (1989) study in rats in the chronic REL summary, there are several other developmental studies available by S.H. Roth and colleagues on the effects of hydrogen sulfide on the developing nervous system. Also there is now available an epidemiological study by Xu et al. (1998) which is described in our revised summary. Using these changes OEHHA staff calculate a chronic REL of 9 $\mu g/m^3$ for hydrogen sulfide.

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Nickel Development Institute, NiPERA, and INCO United States, Inc.

Comments on the chronic REL proposed for nickel were made by the Nickel Development Institute, the Nickel Producers Environmental Research Association (NiPERA), and INCO United States, Inc. in a letter dated January 27, 1998. OEHHA proposed a chronic inhalation REL of 0.05 $\mu g/m^3$ for nickel for respiratory system and immune system toxicity.

Introductory comment. The Comments focus on OEHHA's derivation of a noncancer chronic Reference Exposure Level (REL) for nickel and nickel compounds based on the results of a two-year bioassay of nickel sulfate hexahydrate. As explained in the Comments, it is scientifically inappropriate to establish a single REL to be applied to metallic nickel and all nickel compounds. Such an approach ignores the well-documented differences in toxicity among the various forms (or species) of nickel. Accordingly, using OEHHA's methodology, we have calculated separate RELs for nickel sulfate hexahydrate (and other soluble nickel species), nickel oxide (and other insoluble nickel species), and nickel subsulfide. Because they are far and away the predominant nickel species in the ambient air of California, the RELs for nickel sulfate and nickel oxide are the most relevant of the RELs for purposes of the Air Toxics "Hot Spots" Program.

Nickel subsulfide constitutes a negligible fraction of total nickel in the ambient air. Consequently, the REL for nickel subsulfide has no practical relevance under the Air Toxics "Hot Spots" Program. Metallic/elemental nickel also constitutes a negligible percentage of the total nickel to which California residents may be exposed via inhalation, so there is no need to calculate a REL for metallic nickel. Furthermore, there are no inhalation data from which such a REL could be calculated directly. It is clear, however, that metallic nickel is less toxic than the nickel compounds for which RELs can be calculated. Hence, if a REL is set for metallic nickel, it would have to be at least as high or higher than the highest REL for any of these nickel compounds.

Response. OEHHA responds to the substantive points on each issue below.

Comment 1. Establishing a single REL for elemental nickel and all inorganic nickel compounds ignores the importance of speciation in evaluating the toxicity of the different forms of nickel. Each compound or species of a metal has its own physico-chemical properties that dictate how it behaves under a given set of conditions, including interactions with biological organisms. This point holds even if the free metal ion is assumed to be the toxic species, because the different physico-chemical properties of various forms of the metal will largely determine the extent to which the free metal ion can be made bioavailable and delivered to a relevant biological site within an organism.[a]

[a] See Conard, B., "Is Nickel Safe? A Toxicology Primer," in Pyrometallurgical Operations Environment Vessel Integrity in High-intensity Smelting and Converting

As U.S. EPA has emphasized: "Speciation and associated solubility of metal species ... are key factors that influence the bioavailability of metals" and their "fate, transport, and uptake in various media (e.g., plant tissue, animal tissue) and receptors."[b]

It is not surprising, then, that different forms of nickel exhibit different toxicities. For example, the oral LD50 value for nickel carbonyl is 50 mg/kg body weight; for nickel sulfate hexahydrate, it is 300 mg/kg - while for green nickel oxide and nickel subsulfide, it is >5000 mg/kg.[c] While the LD50 values relate to acute toxicity, speciation also is important in evaluating chronic toxicity and potential carcinogenicity of the various forms of nickel. U.S. EPA, for example, has distinguished among different nickel species for purposes of cancer classifications.[d] So has the American Conference of Governmental Industrial Hygienists ("ACGIH"), which recently adopted three different carcinogen classifications for different nickel species as part of its Threshold Limit Value (TLV) program.[e] Similarly, in the two-year bioassay studies referenced by OEHHA in the TSD, the U.S. National Toxicology Program (NTP) found markedly different results with regard to the potential carcinogenicity of nickel subsulfide, nickel oxide, and nickel sulfate hexahydrate in rats and mice.[f]

Processes. C. Diaz, et al., Editors. Proceedings of the Nickel-Cobalt 97 International Symposium-Vol. 111, August 1997, Sudbury, Ontario.

[b] Hazardous Waste Identification Rule, 60 Fed. Reg. 66344, 66363/1-2 (December 21, 1995).

[c] See Reagan, E.L. Acute oral toxicity study in rats with green high temperature nickel oxide. Journal of the American College of Toxicology 11(6):689, 1992; Reagan, E.L. Acute oral LD(50) study in rats with nickel sulfate hexahydrate. Journal of the American College of Toxicology11(6):685, 1992; Reagan, E.L. Acute oral toxicity study in rats with nickel subsulfide. Journal of the American College of Toxicology 11 (6):691, 1992.

[d] See 51 Fed. Reg. 34135 (September 25, 1986); see also 59 Fed. Reg. 15504 (April 1, 1994) (EPA divides nickel species into four subsets for purposes of setting proposed de minimis emissions levels and establishing toxicity rankings) under a Clean Air Act hazardous air pollutant program.

[e] Insoluble nickel compound and nickel subsulfide were designated Category Al - Confirmed Human Carcinogens. Soluble nickel compounds were placed in Category A4 – Not Classifiable as a Human Carcinogen. Elemental/metallic nickel was placed in Category A5 – Not Suspected as a human Carcinogen. See ACGIH, 1997 TLVs ® and BEIs® at 42-43 (Notice of Intended Changes). These proposed TLV recommendations and carcinogen classifications were ratified as "adopted" values by the ACGIH Board of Directors on November 1, 1997.

[f] Nickel subsulfide showed clear evidence of carcinogenic activity in male and female rats, and no evidence of carcinogenicity in mice of either sex. Nickel oxide showed some evidence of carcinogenic activity in male and female rats but no dose-response between the mid- and high-dose groups, no evidence of carcinogenic activity in male mice, and only equivocal evidence in female mice. Nickel sulfate hexahydrate showed no evidence

Speciation has long been recognized as a critical factor in evaluating the noncancer chronic toxicity of nickel as well. Thus, in setting time-weighted average TLVs for long-term occupational exposure, ACGIH historically differentiated between metallic nickel and insoluble nickel compounds on the one hand (TLV = 1.0 mg Ni/m^3) and soluble nickel compounds on the other (TLV = 0. 1 mg Ni/m^3).[g] The most recent update of the TLVs draws additional distinctions among the different forms of nickel.[h]

A large body of research has been conducted to elucidate the relative respiratory toxicities of the primary nickel compounds in animals. Much of the most relevant recent work in this area has been performed by the same researchers who conducted the NTP bioassays of nickel compounds referenced by OEHHA in the TSD. (Benson et al. 1985; 1986a; 1986b; 1987; 1988; 1989; 1990; and Dunnick, 1989; 1995). These studies have related the toxicity of nickel compounds to their water solubility and subsequent clearance from the respiratory tract, which is most rapid for water soluble nickel (and nickel chloride) followed by nickel subsulfide and nickel oxide.[i]

The observed toxicity for soluble nickel compounds is due to a direct cytotoxic action of the nickel ion, released in the fluid of the alveolus, on the stromal cells in the lung.[j] Insoluble nickel compounds, by contrast, do not readily release nickel ions in the alveolar fluid. Instead, they elicit a large macrophage "hyperplasia," and their toxicity is related to the phagocytosis of the insoluble particles and the subsequent release of nickel

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of carcinogenic activity in male or female rats and no evidence in male or female mice. See 61 Fed. Reg. 66054-66057 (December 16, 1996).

[g] See ACGIH, 1997 TLVs® and BEIs® at 30. The U.S. Department of Labor's Occupational Safety and Health Administration (OSHA) adopted this same distinction for its permissible exposure limits (PELs) in 1989. See 54 Fed. Reg. 2332, 2946 (January 19, 1989). However, the PELs for nickel and nickel compounds, along with hundreds of other updated PELs, were set aside by the U.S. Court of Appeals for the Eleventh Circuit in 1992 for reasons unrelated to the specific values that OSHA had adopted for the different forms of nickel. See AFL-CIO v. OSHA 965 F.2d 962 (11th Cir. 1992).

[h] See ACGIH, 1997 TLVs® and BEIs® at 42 (setting different numerical TLV values for elemental/metallic nickel, insoluble nickel compounds, and soluble nickel compounds/nickel subsulfide). As noted above, these proposed TLVs were ratified as adopted values on November 1, 1997. See note 6, supra.

[i] See Dunnick, J. K., *et al.* Lung toxicity after 13-week inhalation exposure to nickel oxide, nickel subsulfide, or nickel sulfate hexahydrate in F344/N rats and B6C3F1 mice. Fundamental and Applied Toxicol 12: 584-594, (1989)

[j] See Benson, J.M., *et al.* Biochemical responses of rat and mouse lung to inhaled nickel compounds. Toxicology 57(3):255-266 (1989).

ions inside the cell.[k] Nickel subsulfide has been shown to be appreciably more cytotoxic in vivo than nickel oxide.[l] In fact, the toxicity of nickel oxide approximates the particle overload effects seen with compounds such as carbon black rather than the direct stromal or phagocytic cell cytotoxicities seen with soluble nickel compounds and nickel subsulfide, respectively.[m]

Against this background, it is difficult to understand how OEHHA can justify establishing a single REL for elemental nickel and all nickel compounds based on toxicological results for nickel sulfate hexahydrate. OEHHA's apparent rationale for doing so is that in the NTP studies, nickel sulfate hexahydrate, nickel subsulfide, and nickel oxide "all showed similar non-carcinogenic effects in rats and mice.[n] That may well be, but that does not mean they cause the effects by the same mechanism or at the same dose level. In fact, as indicated above, soluble and insoluble nickel compounds exert their toxicity by different mechanisms, and the dose levels for the various compounds in the NTP studies were not the same.[o] Moreover, elemental/metallic nickel was not administered in the NTP studies at all, so there is no basis for concluding that it would produce the same toxic effects and at the same dose as nickel sulfate hexahydrate.

In sum, it is not appropriate to apply a REL derived from rodent studies of nickel sulfate hexahydrate to all other forms of nickel - including insoluble nickel species and metallic nickel. To do so would be like calculating a REL for methanol and applying it to ethanol, ethylene glycol, and all other "alcohols." Just as the various forms of nickel have different acute toxicities and carcinogenic potentials, they have different noncancer chronic toxicity profiles. By assigning a single nickel sulfate-derived REL to elemental nickel and all inorganic nickel compounds, OEHHA has ignored the fundamental importance of speciation in evaluating the potential toxicity of the different forms of nickel. We urge OEHHA to reconsider this overly simplistic approach and to establish species-specific RELs instead.

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[k] See Dunnick, J. K., *et al.* Comparative carcinogenic effects of nickel subsulfide, nickel oxide, or nickel sulfate hexahydrate chronic exposures in the lung. Cancer Res. 55:5251-5256 (1995).

[l] See Benson J.M., *et al.* Comparative acute toxicity of four nickel compounds to F-344 rat lung. Fundamental and Applied Toxicology 7(2):340-347 (1986).

[m] See Dunnick, J. K. *et al.* Comparative carcinogenic effects of nickel subsulfide, nickel oxide, or nickel sulfate hexahydrate chronic exposures in the lung. Cancer Res.55:5251-5256 (1995); Oller A.R., M. Costa, and G. Oberdorster. Carcinogenicity assessment of selected nickel compounds. Toxicol. Appl. Pharmacol. 143(l):152-66 (1997).

[n] See TSD Appendix A at A-538.

[o] In the two-year NTP studies, the LOAEL for nickel sulfate hexahydrate (0.06 mg Ni/m^3) was roughly one-half of the LOAEL for nickel subsulfide (0. 11 mg Ni/m^3) and an order of magnitude lower than the LOAEL for nickel oxide (0. 5 mg Ni/m^3).

Response. The risk assessment for nickel compounds proceeded under a presumption that compounds comprised of the same inorganic element will have somewhat similar health effects and potencies. The presumption does not require that the toxicities be identical and, in fact, acknowledges the existence of differences by selecting the most sensitive effect of the most potent chemical species in order to assure protection over a broad chemical class. All results, including null results, should be evaluated to determine whether they do establish a substantial difference amongst the species in the class. The evidence sufficient to sustain speciation of a substance would correspondingly also sustain the development of any needed, alternative, health-risk guidance values.

In addition, the question of speciation needs to be addressed, not in general, but with respect to the particular health endpoints of concern and the agents to be speciated. Chemical species differences which are material with respect to one mechanism of action or health effect may not be similarly material for another. For example, with respect to inhalation exposures, speciation of a particular form of nickel may be warranted for one effect of concern (e.g., lung irritation) or route of exposure (oral, inhalation) but not another (e.g., lung cancer).

The comment offers several lines of evidence which support the speciation of nickel compounds with respect to the derivation of a noncancer, chronic REL based upon respiratory toxicity. The comment cites several kinds of indirect and direct toxicological evidence (differences amongst nickel compounds with respect to physico-chemical properties, acute oral toxicities, inhalation carcinogenic potential, and respiratory system effects and mechanisms) to support the speciation of nickel compounds in general and with respect to the proposed REL.

With respect to differences in physico-chemical properties, OEHHA agrees that the different nickel species vary greatly (from soluble to insoluble) with respect to their physico-chemical properties. OEHHA also agrees, as discussed in our 1991 risk assessment document[5], that "the different physico-chemical properties of various forms of the metal will largely determine the extent to which the free metal can be made bioavailable and delivered to a relevant biological site within an organism." OEHHA also agrees with the comment that the different nickel species present different acute *oral* toxicities which may relate to their solubility. For instance, insoluble compounds are more likely to simply pass through the digestive tract without absorption.

With respect to inhalation exposures, it is less clear how solubility will affect the lung response. After inhalation, both insoluble and soluble compounds are directly deposited into the lung. It might be presumed that more soluble species will be more quickly removed from the lung and that such compounds would in general be less harmful than the insoluble forms of nickel thought to be retained by the lung. However,

[5] Office of Environmental Health Hazard Identification, Identification of Nickel and Nickel Compounds as Toxic Air Contaminants. 1991

the NTP non-cancer, chronic inhalation toxicity findings for (insoluble) nickel subsulfide, (insoluble) nickel oxide, and (soluble) nickel sulfate suggest otherwise and do not support such easy interpretations. In fact, much of the discussion of solubility/bioavailability related differences in mechanisms cited by the comment were offered by the original investigators as possible reasons to explain the apparently greater toxicity (carcinogenicity) of the insoluble nickel species in the rat. Here, the same data would be offered to argue for a lesser non-cancer, chronic respiratory toxicity. Clearly, such indirect evidence needs to be particularly interpreted with caution.

The comment cites, as indirect evidence of the merits of its position, that the American Conference of Governmental Industrial Hygienists (ACGIH), the Occupational Safety and Health Administration (OSHA), and the United States Environmental Protection Agency (USEPA) have speciated nickel compounds. With respect to the ACGIH, the ACGIH is a non-governmental body that develops exposure guidelines, which are not regulatory standards, to limit occupational exposures, not environmental exposures. The ACGIH holds that its limits are not to be used for any other purpose including the "evaluation and control of community air pollution nuisances." Not withstanding this distinction, OEHHA in responding below to the major substantive issues has indicated where and why OEHHA differed with the ACGIH approaches.

With respect to OSHA, the current OSHA position reflects the statutorily mandated blanket adoption, upon its creation over 25 years ago, of the ACGIH guidelines existing at that time. The OSHA position on nickel speciation is therefore not independent of the ACGIH.

OSHA in the cited (and overturned) 1989 rulemaking proposed to adopt as its own standards the updated ACGIH guideline values for the various nickel compounds. That effort was a small part of a much larger effort to adopt, with correspondingly minimal critical review, as governmental standards over 400 other occupational exposure guidelines developed by the ACGIH. While that ruling was overturned on general principles which were not "specifically" related to nickel, the findings of the court bar any reasonable inference that the OSHA rulemaking adequately reached the scientific merits as to whether or how nickel compounds might be speciated. The federal court stated in its conclusion "It is clear that the analytical approach used by OSHA in promulgating its revised Air Contaminants Standard is so flawed that it cannot stand. OSHA not only mislabeled this a "generic" rulemaking, but it inappropriately treated it as such. The result of this approach is a set of 428 inadequately supported standards. OSHA has lumped together substances and affected industries and provided such inadequate explanation that it is virtually impossible for a reviewing court to determine if sufficient evidence supports the agency's conclusions. The individual substances discussed in this opinion are merely examples of what is endemic in the Air Contaminants Standard as a whole." [AFL-CIO v. OSHA, 965 F.2d 962]. OSHA simply did not reach the merits of nickel speciation in the overturned effort. Nor, in that effort, did OSHA propose to adopt the recommendations of the National Institute for Occupational Safety and Health (NIOSH) for an occupational Reference Exposure Level of 15 $\mu g/m^3$ for nickel compounds.

The USEPA quotation [60 Fed. Reg. 66344, December 21, 1995] cited by the comment, "Speciation and associated solubility of metal species … are key factors that influence the bioavailability of metals" and their "fate and uptake in various media (e.g., plant tissue, animal tissue) and receptors," is uncontroversial as a general proposition (see above). Here, we are concerned with inhalation exposures to nickel compounds and their effects at the site of exposure, the lung. Issues related to environmental fate and transport that often are greatly affected by solubility considerations and that are important to the context of the proffered quotation (hazardous waste regulations) are clearly not involved.

By contrast, the Agency for Toxic Substances Disease Research (ATSDR), in its 1997 document Toxicological Profile for Nickel (updated), recommended a Minimal Risk Level of 0.2 $\mu g/m^3$ for nickel compounds. The ATSDR, in stating that the MRL value (derived from the same NTP nickel sulfate study used by OEHHA in this proposed rulemaking) was most appropriate for use in evaluating the health risks associated with soluble nickel compounds, did not limit its application to only soluble compounds.

Footnote d of the comment states that the USEPA speciated nickel compounds in a Clean Air Act rulemaking [51 Federal Registrar 34135]. However, in that rulemaking, the USEPA relied upon exposure information to exclude nickel carbonyl and nickel subsulfide from its regulatory efforts. It did not address nickel speciation according to relative solubilities.

The question of speciation needs to be addressed, not in general, but with respect to the particular health endpoints of concern, the agents to be speciated, and the route of exposure. With respect to the differential carcinogenicity of nickel compounds by inhalation, OEHHA believes that this evidence is not closely on point as to the non-cancer health effects of nickel compounds. OEHHA also believes that the comment overstates what is known about the relative carcinogenic potential of various nickel species either in animals:

NTP Cancer Bioassay Results in $B6C3F_1$ Mice.

Nickel subsulfide and nickel sulfate each gave null results in the mouse inhalation carcinogenicity bioassays. Nickel oxide provided equivocal results. These results make the mouse results moot with respect to the speciation of these compounds as to their carcinogenic potential.

NTP Lung Cancer Observations in F344/N Rats.

As noted in the comment, nickel sulfate hexahydrate did not cause lung cancers in the F344/N rat by inhalation. Nickel subsulfide did cause lung cancers in rats of both sexes and nickel oxide provided some evidence of lung cancers in rats of both sexes. In accord with the comments, OEHHA accepts these experimental results. However, in stating that the "(NTP) found markedly different results with regard to the potential carcinogenicity of nickel subsulfide, nickel oxide, and nickel sulfate hexahydrate in rats

and mice," the comment gives undue weight to the null results obtained for nickel sulfate given the assay conditions and results. The question as to whether or not the NTP bioassays do reliably distinguish the carcinogenic potency of soluble nickel compounds from the insoluble nickel compounds deserves further examination.

In order to either qualitatively or quantitatively distinguish the carcinogenic potential of nickel sulfate from that of nickel subsulfide and nickel oxide, not only the results, but the conditions, of the NTP bioassays for these compounds need to be compared. The issue turns on the relative meaning of the null result for nickel sulfate. This difference in outcomes for the three nickel species may reflect any of three general possibilities: 1. qualitative differences in effect among the three compounds, 2. a lower potency for nickel sulfate, or 3. the relative power of the different bioassays to detect a carcinogenic effect under their test conditions.

The conditions of the rat bioassay make it difficult to distinguish whether the difference for nickel sulfate represents a qualitative difference in carcinogenic potential, a small quantitative difference in potency, or no difference in potency. The highest exposure concentration for nickel sulfate was equivalent to the lowest exposure concentration for nickel subsulfide (0.11 mg nickel/m^3). The differences in incidence for lung adenomas and carcinomas combined among the various groups at these exposure levels were small: For nickel sulfate, the incidences were 1/54 female rats and 3/55 male rats. For nickel subsulfide the incidences were 6/53 and 6/53. The incidences of lung cancer in the rats exposed to nickel oxide at a level equivalent to 0.5 mg nickel/m^3 were even lower: 0/53 and 1/53 for females and males respectively. Such small differences do not well distinguish the carcinogenic potential of nickel sulfate from nickel subsulfide and, especially, nickel oxide. It is not possible to reliably distinguish between the possibility that the null result for nickel sulfate reflects no carcinogenic potential, a slightly lesser potency than that of nickel subsulfide, or the possibility that the nickel sulfate bioassays lacked the experimental power to detect an effect of nickel sulfate which is of equal magnitude to that of nickel subsulfide.

OEHHA does not fault the NTP bioassay procedures. Nickel sulfate possessed greater pulmonary toxicity than the other two nickel species in the 13-week range finding studies. This toxicity limited the range of exposure levels at which nickel sulfate could be tested and reduced the sensitivity of the bioassay to detect a carcinogenic effect at concentrations of interest. In addition, in the two year bioassay, the toxic responses in the lung of rats and mice exposed by inhalation to nickel sulfate were less severe than those in the lungs of rats and mice exposed to either nickel oxide or nickel subsulfide. Nickel sulfate may not have been tested as close to the maximally tolerated exposures as were the other two compounds.

Nor does analysis of the available lung burden information help with interpreting the differences in results among the three nickel species. Exposure to nickel sulfate (0.11 mg nickel/m^3) was associated with a lung burden of 1-2 μg Ni/g lung at 15 months. Exposure to the insoluble nickel subsulfide at (0.11 mg nickel/m^3) was associated with a lung burden of 4 μg nickel/g lung at 15 months. However, nickel oxide did substantially

accumulate in the rat lung over the course of the two-year bioassay. Therefore, nickel oxide exposure (0.5 mg nickel/m^3) gave a much higher lung burden of about 300 μg nickel/g lung at 15 months. This result, coupled with the equivocal effects found for nickel oxide, suggests that the toxicokinetics of the nickel species can not reliably guide interpretations of the observed differences in response amongst these three species of nickel compounds.

Based upon these uncertainties in the available information, the null result in the nickel sulfate bioassays, when contrasted to the results obtained for nickel subsulfide and nickel oxide, is not sufficient to reliably distinguish, even with respect to the rat lung, the carcinogenic potential of nickel sulfate from either nickel subsulfide or nickel oxide.

OEHHA also believes that the comment overstates what is known about the relative carcinogenic potential of the various nickel species in humans[6,7,8]. OEHHA[9] has similarly determined that the available epidemiological studies do not demonstrate material and substantial differences amongst the nickel species studied as to their potential carcinogenicity for the respiratory tract.

The proposed chronic REL is based upon the 1994 NTP rat inhalation study using nickel sulfate hexahydrate. It is with respect to the respiratory effects observed in that study that the speciation of nickel compounds needs to be addressed. To that end, the

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[6] Report of the International Committee on Nickel Carcinogenesis in Man. Scand. J. Work Environ. Health 16(1):1-82 (1990).

The ICNCM summary position with respect to soluble nickel compounds is found on p.70 of their report: Their conclusion begins "There was strong evidence, primarily based upon the large excesses observed for electrolysis workers of the Kristiansand, Norway refinery that exposure to soluble nickel was associated with increased respiratory cancer risk." In their overall conclusion to the document, the ICNCM report states (p.74, Concluding Remarks, first paragraph) "There was also evidence that soluble nickel exposure increased the risk of these cancers (lung and nasal cancers) and that it may enhance risks associated with exposure to less soluble forms of nickel.

[7] International Agency for Research on Cancer, Nickel and Nickel Compounds, IARC Monographs 49, p. 410.

IARC also evaluated the carcinogenicity of nickel and nickel compounds, and largely based upon the epidemiological evidence assembled by the ICNCM, concluded that there was "sufficient evidence in humans for the carcinogenicity of nickel sulfate, and of the combinations of nickel sulfides and oxides encountered in the nickel refining industry."

[8] This point also speaks to the conclusions drawn by the American Conference of Governmental Industrial Hygienists, and cited by the comment, with respect to speciation of nickel compounds and carcinogenicity. Based upon the NTP bioassay results, the ACGIH concluded, "It is clear that carcinogenicity varies with the form of nickel used."(TLV Recommendation, p.8). Therefore, as the ACGIH sought to address cancer and non-cancer hazards, this conclusion of the ACGIH implicitly influenced their decision to speciate.

[9]Office of Environmental Health Hazard Identification, Identification of Nickel and Nickel Compounds as Toxic Air Contaminants. 1991

comment marshaled the above indirect evidence. This indirect evidence is not determinative to the extent that it is not known how any differences in physico-chemical properties, acute toxicity, or carcinogenicity relate to the chronic respiratory system health effects upon which the REL is based and their particular mechanisms.

B. Direct Evidence Regarding Speciation

OEHHA concurs that the NTP chronic inhalation bioassays provide the most reliable information with respect to the speciation of nickel compounds as to their chronic inhalation health effects. The results to be compared were obtained under very similar laboratory conditions and protocols and also under the auspices of the NTP, which provides assurances that the results for the different species are readily comparable and highly reliable. This information bears directly on dose-response differences amongst nickel species with respect to chronic inhalation injury to the rat lung. Indeed, the experiments were designed with speciation in mind. However, the dose response analyses of the comment (discussed below) gave alternative chronic RELs for (insoluble) nickel oxide (0.33 $\mu g/m^3$) and (soluble) nickel sulfate (0.29 $\mu g/m^3$) that are within 10% of each other. Within the range of scientific uncertainty, the values are not distinguishable and, at the relevant level of one significant digit, in fact, they are the same (0.3 $\mu g/m^3$). Thus, by the comment's analyses, there would be no practical consequences to speciation. Any material differences would also be insubstantial.

However, OEHHA disagrees (see response to Comment 2 below) with the comment's approach to dose response assessment for soluble nickel and continues to believe that OEHHA's proposed value of 0.05 $\mu g/m^3$ is more appropriate. The difference between the value for nickel oxide of 0.33 $\mu g/m^3$ and the value for nickel sulfate of 0.05 $\mu g/m^3$ is over 6-fold and would be clearly substantial regardless of the extent to which the similar respiratory effects of nickel oxide and nickel sulfate are mediated by the same or different mechanisms.[10] Therefore, if the comment's dose response assessment satisfies the OEHHA chronic REL guidelines, it would be appropriate to provide a separate REL for nickel oxide which reflects this difference. OEHHA responds to the comment's derivation of proposed alternative RELs for nickel oxide, nickel subsulfide, and metallic nickel below (see response to comment 3).

Comment 2. In calculating the REL for nickel sulfate hexahydrate, OEHHA made an unwarranted dose adjustment. In calculating the REL for nickel sulfate hexahydrate, OEHHA made an adjustment to translate the 6 hours/day/week intermittent exposure regimen of the rats in the NTP study to a continuous exposure scenario. Such an adjustment is justified for substances whose toxic effects are mainly duration-dependent, rather than concentration-dependent, and that are slowly excreted from the body. A dose

[10] Regardless of expected differences in the efficacy of soluble and insoluble forms of nickel as vehicles for the Ni ion, the *Benson* and *Dunnick* references relied upon by the comment each found that both soluble and insoluble nickel species caused macrophage hyperplasia and chronic active inflammation of the lung in rats and mice.

adjustment of this sort is not appropriate, however, for a substance like nickel sulfate hexahydrate whose effects are mainly concentration-dependent and that is rapidly metabolized and excreted. Thus, as stated by the Agency for Toxic Substances and Disease Registry (ATSDR) in its Guidance for Derivation of Minimal Risk Levels (which correspond in terms of purpose and basic derivation technique to OEHHA's RELs): "When the critical effects are mainly dependent on the exposure concentrations and the substance being tested is rapidly metabolized and/or excreted, dose adjustment is inappropriate."

Response. Many studies have shown that the effects of nickel on the lung are concentration-dependent. Effects such as fibrosis, which are observed only upon long duration exposure, suggest the accumulation of harm over time. These studies do not examine how the duration of any assumed concentration-dependent mediating effects, such as active inflammation, relate to the chronic outcomes.

With respect to inflammation, the data also indicate duration-dependence:

Comparison of the 13-week inhalation study results for nickel sulfate hexahydrate to the 2 year study results with respect to chronic inflammation of the rat lung[11]:

Study duration:		13 weeks		2 years	
Nickel sulfate air concentration (mg/m^3):		0.25	0.5	0.25	0.5
Lung Chronic inflammation					
	Males	0/10	0/10	42/53	46/53
	Females	0/10	0/10	49/52	52/53

These results show an effect of duration of exposure.

Furthermore, given a lung half-life of from one to three days in the rat, the potential for nickel sulfate to concentrate in the rat lung over the course of several days of administration seems clear. Most of the time-adjustment factor relates to the 6-hour/day exposure regimen which entailed a four-fold adjustment factor to reflect that for only one-fourth of the time were the animals exposed each day. The remainder of the adjustment factor represents a $7/5^{ths}$ term to account for the lack of study exposures during weekends. Even if the effects of nickel sulfate on the lung were related solely to the concentration of nickel sulfate in the lung, a time adjustment factor of at least four-fold for partial exposures each day would be appropriate. In addition, in the instance of a lung half-life of one to three days, the smaller seven-fifths adjustment for two day gaps in exposure during the weekends would be appropriate.

This analysis is consistent, in fact, with the ATSDR's own treatment of the nickel sulfate data in the document, Toxicological Profile for Nickel,[12] cited by the comment. There,

[11] National Toxicology Program, Toxicology and Carcinogenesis Studies of Nickel Sulfate Hexahydrate in F333/N Rats and B6C3f1 Mice.

[12] ATSDR, Toxicological Profile for Nickel (September 1997 update), p. 32.

in developing a Minimal Risk Level for nickel compounds, the ATSDR adjusted these nickel exposures by factors of four and seven-fifths to account for the exposure gaps.

Comment 3. Setting RELs for Nickel Oxide, Nickel Subsulfide, and Metallic Nickel. The NTP two-year bioassay results for green nickel oxide and nickel subsulfide can be used to derive RELs for those substances as well. In contrast to nickel sulfate, excretion of these compounds is moderate to slow; hence, a dose adjustment to translate intermittent exposure concentrations into continuous exposure concentrations may be appropriate. In addition, because NOAELs were not identified in those studies, LOAELs must be used to derive the RELs. Consequently, a LOAEL uncertainty factor must be applied as part of the calculation. Under OEHHA's methodology, a LOAEL uncertainty factor of 10 is applied where the adverse effects are severe, and a LOAEL uncertainty factor of 3 is applied when the adverse effects are mild. In the NTP studies, lesions were scored on the following severity scale: 1 = minimal; 2 = mild; 3 = moderate; 4 = marked. Bearing these factors in mind, RELs for nickel oxide and nickel subsulfide may be derived as follows.

A. Nickel Oxide.

In the two-year NTP study, the LOAEL for green nickel oxide based on chronic inflammation in the lung was 0.5 mg Ni/m^3, and the lesions were graded as 1.6 in male rats and 1.7 in female rats, indicating that the inflammation was in the minimal to mild range.[p] Accordingly, under OEHHA's methodology, a LOAEL uncertainty factor of 3 should be applied in calculating the REL for nickel oxide. The resulting value is 0.33 mg Ni/m^3 calculated as follows:

LOAEL:	500 μg Ni/m^3
Exposure continuity:	6 hours/day, 5 days/week
Exposure duration:	104 weeks
Average experimental exposure:	89.5 μg Ni/m^3 (using dose adjustment factor of 0.179)
Human equivalent concentration:	30 μg Ni/m^3 (using RDDR = 0.29)
LOAEL uncertainty factor:	3
Interspecies uncertainty factor:	3
Intraspecies uncertainty factor:	10
Cumulative uncertainty factor:	90
Inhalation REL:	0.29 μg Ni/m^3

[p] See NTP, Toxicology and Carcinogenesis Studies of Nickel Oxide in F344/N Rats and B6C3F1 Mice, Technical Report Series No. 451 (NIH Publication No. 96-3367, July 1996) at 63-64, Table 14. The nickel oxide concentration of 0.62 mg/m^3 was equivalent to 0.5 mg Ni/m^3. See id. at 40.

$$REL = \frac{500\ \mu g\ Ni/m^3 \times 0.179 \times 0.29}{3 \times 3 \times 10} = \frac{30\ \mu g\ Ni/m^3}{90} = 0.33\ \mu g\ Ni/m^3$$

In the absence of additional compound-specific data, it would be reasonable to apply the REL for nickel oxide as a surrogate for other insoluble nickel compounds (e.g., nickel carbonate) and sparingly soluble nickel compounds (e.g., nickel hydroxide) as well.

B. Nickel Subsulfide.

In the two-year NTP study, the LOAEL for nickel subsulfide based on chronic inflammation in the lung was 0. 11 mg Ni/m', and the lesions were graded as 1.8 in male rats and 1. 7 in female rats, indicating that the inflammation was in the minimal to mild range.[q] Accordingly, under OEHHA`s methodology, a LOAEL uncertainty factor of 3 should be applied in calculating the REL for nickel subsulfide. The resulting value is 0.06 μg Ni/m3, calculated as follows:

LOAEL	110 μg Ni/m^3
Exposure continuity:	6 hours/day, 5 days/week
Exposure duration:	104 weeks
Average experimental exposure:	19.7 μg Ni/m^3 (using dose adjustment factor of 0.179)
Human equivalent concentration:	5.7 μg Ni/m^3 (using RDDR = 0.29)
LOAEL uncertainty factor:	3
Interspecies uncertainty factor:	3
Intraspecies uncertainty factor:	10
Cumulative uncertainty factor:	90
Inhalation REL:	0.06 μg Ni/m^3

$$REL = \frac{110\ \mu g\ Ni/m^3 \times 0.179 \times 0.29}{3 \times 3 \times 10} = \frac{5.7\ \mu g\ Ni/m^3}{90} = 0.06\ \mu g\ Ni/m^3$$

Response: OEHHA disagrees with the comment's use of a LOAEL uncertainty factor of three in deriving the nickel oxide REL. In order to use a LOAEL uncertainty factor of three rather than ten, OEHHA requires first that the effect of concern be of slight severity and second that less than half the animals exposed at the LOAEL be affected.[13] These criteria help to insure that the LOAEL is likely to be closer to the NOAEL than otherwise.

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[q] See NTP, Toxicology and Carcinogenesis Studies of Nickel Subsulfide in F344/N Rats and B6C3F, Mice, Technical Report Series No. 453 (NIH Publication No. 96-3369, July 1996) at 63-64, Table 14. The nickel subsulfide concentration of 0. 15 mg/m^3 was equivalent to 0.11 mgNi/m^3. See id. at 40.

[13] OEHHA, Cal/EPA. Determination of Chronic Noncancer Reference Exposure Levels, p. 20, October 1997 Draft for Public Comment.

OEHHA agrees with the comment that the pulmonary effects at issue were classified by the NTP as being in the minimal to mild range (1.6 - 1.7) at the LOAEL dose. However, the OEHHA guidance also requires that the effect be observed in less than half the subjects at the LOAEL dose. In the NTP study, for male and female rats combined, the frequencies of chronic lung inflammation were greatly increased for the LOAEL group (105/106) and as compared to the controls (46/105). It could be argued that about one-half the LOAEL incidence reflects a contribution from the background rate and that the background rate should be excluded. If this were done, it would still be found that nearly all the remaining animals (constituting more than half of the original groups) were affected. In addition, if the expected control/background were excluded, it would also be appropriate to correct for their influence on the overall severity score. If this correction were made, an adjusted effect severity score of slightly greater than 2.0 (a mild effect) would result.

Applying the LOAEL uncertainty factor of 10 would result in a proposed REL for nickel oxide of 0.1 μg Ni/m^3. This value is twice the value (0.05 μg Ni/m^3) developed by OEHHA.

The comment stated that its nickel oxide alternative REL of 0.33 μg Ni/m^3 should also be used to regulate other insoluble and partially soluble forms of nickel: "In the absence of additional compound specific data, it would be reasonable to apply the REL for nickel oxide as a surrogate for other insoluble nickel compounds (e.g., nickel carbonate) and sparingly soluble nickel compounds (e.g., nickel hydroxide) as well". OEHHA disagrees. In setting inhalation exposure RELs for groups of compounds, OEHHA uses the most sensitive strain, species, sex, chronic endpoint, and agent for each group of substances. The comment's proposed alternative REL of 0.33 μg/m^3 for nickel oxide is also substantially different from the comment's REL of 0.06 μg/m^3 for (insoluble) nickel subsulfide. Therefore, it would be inappropriate to apply the nickel oxide value to all other "insoluble and sparingly soluble" nickel compounds. The comment's alternative value for nickel subsulfide of 0.06 μg/m^3 would be preferred for all other forms of insoluble nickel compounds[14].

Furthermore, as the value proposed for (insoluble) nickel subsulfide is not substantially different from that proposed by OEHHA for (soluble) nickel sulfate, regardless of any extent to which there are any differences in the mechanisms of action or

[14] This result would not be changed even if the ARB were to exclude nickel subsulfide from regulation on the strength of the comment's assertion that no one was exposed to nickel subsulfide in California. Nickel subsulfide's membership in the set of "insoluble and poorly soluble" nickel compounds is simply a matter of physico-chemical fact, not regulatory fiat. The relevance of the health findings for nickel subsulfide to other members of the "insoluble and poorly soluble" set of nickel compounds stands regardless of where ever else nickel subsulfide might be consigned in a regulatory scheme. The comment also requests that if a REL is to be provided for metallic nickel that the REL be at least as high as that of nickel oxide (0.33 ug/m^3). However, for these reasons, OEHHA also believes that the proposed REL value of 0.05 ug/m^3 should be applied to metallic nickel as well.

effect, there would also be no reason to even further speciate nickel compounds with respect to the chronic REL.[15]

However, for similar reasons to the nickel oxide case, OEHHA also disagrees with the comment's use of a partial LOAEL factor of three in the dose response assessment for nickel subsulfide. OEHHA considers a value of ten to have been more appropriate. The combined incidence of adverse effects for male and female rats in the nickel subsulfide LOAEL group was much greater than that seen in controls with respect to lung fibrosis (98/106 vs. 2/106) and chronic inflammation (104/106 v. 16/106); the average severity of the chronic inflammation in the LOAEL group (2.5) indicated mild to moderate effects. If a LOAEL factor of ten were applied to the nickel subsulfide dose-response assessment, the resulting REL value would be 0.02 ug Ni/m^3.

In developing its response to these comments, OEHHA has identified the following possible REL values:

Form of Nickel	REL Value	Based Upon	Cumulative Safety Factor
Nickel oxide:	0.1 μg Ni/m^3	LOAEL	300
Nickel sulfate:	0.05 μg Ni/m^3	NOAEL	30
Nickel subsulfide	0.02 μg Ni/m^3	LOAEL	300

The above results, which span a four-fold range, are generally consistent with the presumption that compounds comprised of the same inorganic elements will have somewhat similar health effects and potencies. In providing a REL for "Nickel and Nickel Compounds," OEHHA prefers to use the REL value derived from the soluble nickel data, and not the value derived from the nickel subsulfide data. Nickel sulfate and nickel subsulfide produced similar chronic, noncancer pulmonary effects of similar severity. The NOAEL in the nickel sulfate study was below the LOAEL in the nickel subsulfide study. This preference for the REL value derived from the nickel sulfate study data eliminates the additional uncertainty inherent in the use of the nickel subsulfide study data with its higher LOAEL.

However, the results of the NTP studies and these dose response analyses do support the speciation of nickel oxide. The health effects data for nickel oxide indicate that its adverse pulmonary effects were less severe (absence of fibrosis, lower chronic lung inflammation severity scores) at higher doses than the pulmonary effects observed for nickel sulfate and nickel subsulfide. The higher chronic REL value for nickel oxide of 0.1 μg/m^3 reflects these dose response differences. Furthermore, while it is based upon a LOAEL, the lower severity of the adverse health effects at the LOAEL mitigates some of the uncertainty associated with use of a LOAEL rather than a NOAEL. OEHHA therefore concludes that 0.1 μg/m^3 is an appropriate REL for nickel oxide.

[15] This result speaks to the ACGIH's assertion that speciation of nickel is warranted as soluble nickel compounds pose a greater risk of pulmonary inflammation than insoluble compounds (TLV documentation, page 9).

Comment 4. Having calculated a REL for nickel subsulfide, we would like to add an important caveat. The vast preponderance of nickel emitted to the ambient air in California is in the form of nickel sulfate and oxidic nickel.[r] Nickel subsulfide constitutes a negligible fraction of total nickel in the ambient air; thus, the general population in California will have virtually no exposure to nickel subsulfide. Consequently, the REL for nickel subsulfide has no practical relevance under the Air Toxics "Hot Spots" program.

Response. To the extent that the predominant exposures to nickel in California are to oxidic nickel and nickel sulfate, the inclusion and provision of RELs for other nickel compounds in the regulatory scheme is without practical consequences. However, to the extent that the inclusion of other nickel compounds in the regulatory scheme dissuades the substitution of one regulated nickel species by another unregulated species (e.g. nickel sulfate by nickel chloride), the inclusion of these other nickel compounds protects the public health. In addition, to the extent to which there are or may develop exposures to these other forms of nickel, the inclusion of other nickel compounds serves to directly protect the public health.

Comment 5. Metallic nickel has not been the subject of an inhalation toxicology study, so there are no data from which a REL for metallic nickel can be calculated directly. And there really is no reason to establish a REL for metallic nickel because members of the general population (for whom RELs are established) are not exposed to metallic nickel via inhalation. Furthermore, because of its limited bioavailability[s] and the largely negative findings of epidemiological investigations, it is generally accepted that metallic nickel is less toxic than nickel compounds. Thus, ACGIH's recently adopted TLV for elemental/metallic nickel is 15 times higher than the TLVs for soluble nickel compounds and nickel subsulfide and 7 ½ times higher than the TLV for insoluble nickel compounds.[t] Similarly, while the International Committee on Nickel Carcinogenesis in Man (ICNCM) concluded that workplace exposures to certain nickel compounds have been associated with increased risks of lung and nasal cancers, it found no evidence that metallic nickel was associated with increased lung and nasal cancer risks."[u]

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[r] See CARB, Proposed Identification of Nickel As A Toxic Air Contaminant: Technical Support Document Part A (June 199 1) at A-6 through A- 12 and Table 11- 1.

[s] Since elemental/metallic nickel is not soluble in water, it cannot become bioavailable without first undergoing an oxidizing chemical reaction - referred to as corrosion - that produces a different nickel species.

[t] See ACGIH, 1997 TLVs© and BEIs© at 42. As noted above, these proposed TLVs were ratified as adopted values on November 1, 1997. See note 6, supra.

[u] See Report of the ICNCM, 16 Scandinavian J. Work, Environ. & Health, February 1990 at 74. The

In these circumstances, there is no need to set a REL for metallic nickel, and we suggest that none be set. If OEHHA is determined to identify a REL for metallic nickel, however, it seems clear that, even using the most conservative assumptions, the REL should be at least as high - indeed, higher - than the REL for nickel oxide, i.e., equal to or greater than 0.33 μg Ni/m^3. This REL clearly would be far lower than is necessary to protect against any chronic health hazards that might be associated with inhalation exposure to metallic nickel. But, in the absence of relevant studies from which a REL for metallic nickel can be calculated directly, applying the REL for insoluble nickel oxide to insoluble metallic nickel may be viewed as the most logical, if overly conservative, approach - particularly since metallic nickel, as noted above, must undergo an oxidizing reaction before it can become bioavailable.

Response. With respect to speciation of elemental nickel, the comment also states: "Moreover, elemental/metallic nickel was not administered in the NTP studies at all, so there is no basis for concluding that it would produce the same toxic effects and at the same dose as nickel sulfate hexahydrate." The comment is correct, but applies the wrong test. The risk assessment for nickel compounds proceeded under a presumption that compounds comprised of the same inorganic elements will have somewhat similar health effects and potencies. As elemental/metallic nickel was not administered in the NTP studies at all, those studies provide no basis for concluding that elemental/metallic nickel would not produce similar harmful effects.

The comment also correctly points out that the ICNCM study found "no evidence that metallic nickel was associated with increased lung and nasal cancer risks". However, OEHHA disagrees with the comment that this is a reason to not set a chronic REL for metallic nickel. The California chronic RELs are not set to protect against cancer. They are meant to protect against non-cancer, chronic health effects. The lack of carcinogenicity findings therefore is not determinative. Given the absence of comparable inhalation toxicity studies for metallic nickel, this presumption is not overcome as to respiratory effects from inhalation exposures.

With respect to whether to apply a nickel oxide REL value to metallic nickel, while there are physico-chemical differences between metallic nickel and soluble nickel, there are also physico-chemical differences between metallic nickel and insoluble forms of nickel. OEHHA selects the most sensitive effect of the most potent chemical species in order to assure protection over a broad chemical class. Nickel sulfate and nickel subsulfide, and not nickel oxide, are the most potent forms of nickel with respect to inhalation exposures. The nickel sulfate REL value therefore applies to metallic nickel.

International Agency for Research on Cancer (IARC) also has distinguished between metallic nickel and nickel compounds in assigning cancer classifications, with metallic nickel being classified as having a much lower carcinogenic potential than nickel compounds. See IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol. 49 (1990) at 411.

As indicated above, to the extent that the predominant exposures to nickel in California are to oxidic nickel and nickel sulfate, the inclusion and provision of RELs for other nickel compounds in the regulatory scheme is without practical consequences. However, to the extent that the inclusion of other nickel compounds in the regulatory scheme dissuades the substitution of one regulated nickel species by another unregulated species (e.g., nickel sulfate by nickel chloride), the inclusion of these other nickel compounds protects the public health. In addition, to the extent to which there are, or may develop, exposures to these other forms of nickel, the inclusion of other nickel compounds serves to directly protect the public health.

Finally, facilities subject to the Hot Spots program do not speciate their emissions of metals. Without such speciation, different RELs for different forms of nickel would be of toxicological interest but not of practical use in the Hot Spots Program.

PUBLIC HEALTH GOALS FOR CHEMICALS IN DRINKING WATER

BERYLLIUM AND BERYLLIUM COMPOUNDS

September 2003

Governor of the State of California
Gray Davis

Secretary for Environmental Protection
California Environmental Protection Agency
Winston H. Hickox

Director
Office of Environmental Health Hazard Assessment
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Public Health Goal for
Beryllium and Beryllium Compounds
in Drinking Water

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PREFACE

Drinking Water Public Health Goals
Pesticide and Environmental Toxicology Section
Office of Environmental Health Hazard Assessment
California Environmental Protection Agency

This Public Health Goal (PHG) technical support document provides information on health effects from contaminants in drinking water. PHGs are developed for chemical contaminants based on the best available toxicological data in the scientific literature. These documents and the analyses contained in them provide estimates of the levels of contaminants in drinking water that would pose no significant health risk to individuals consuming the water on a daily basis over a lifetime.

The California Safe Drinking Water Act of 1996 (amended Health and Safety Code, Section 116365), amended 1999, requires the Office of Environmental Health Hazard Assessment (OEHHA) to perform risk assessments and publish PHGs for contaminants in drinking water based exclusively on public health considerations. Section 116365 specifies that the PHG is to be based exclusively on public health considerations without regard to cost impacts. The Act requires that PHGs be set in accordance with the following criteria:

1. PHGs for acutely toxic substances shall be set at levels at which no known or anticipated adverse effects on health will occur, with an adequate margin of safety.
2. PHGs for carcinogens or other substances that can cause chronic disease shall be based upon currently available data and shall be set at levels that OEHHA has determined do not pose any significant risk to health.
3. To the extent the information is available, OEHHA shall consider possible synergistic effects resulting from exposure to two or more contaminants.
4. OEHHA shall consider the existence of groups in the population that are more susceptible to adverse effects of the contaminants than a normal healthy adult.
5. OEHHA shall consider the contaminant exposure and body burden levels that alter physiological function or structure in a manner that may significantly increase the risk of illness.
6. In cases of insufficient data to determine a level of no anticipated risk, OEHHA shall set the PHG at a level that is protective of public health with an adequate margin of safety.
7. In cases where scientific evidence demonstrates that a safe dose-response threshold for a contaminant exists, then the PHG should be set at that threshold.
8. The PHG may be set at zero if necessary to satisfy the requirements listed above.
9. OEHHA shall consider exposure to contaminants in media other than drinking water, including food and air and the resulting body burden.

10. PHGs published by OEHHA shall be reviewed every five years and revised as necessary based on the availability of new scientific data.

PHGs published by OEHHA are for use by the California Department of Health Services (DHS) in establishing primary drinking water standards (State Maximum Contaminant Levels, or MCLs). Whereas PHGs are to be based solely on scientific and public health considerations without regard to economic cost considerations, drinking water standards adopted by DHS are to consider economic factors and technical feasibility. Each standard adopted shall be set at a level that is as close as feasible to the corresponding PHG, placing emphasis on the protection of public health. PHGs established by OEHHA are not regulatory in nature and represent only non-mandatory goals. By federal law, MCLs established by DHS must be at least as stringent as the federal MCL if one exists.

PHG documents are used to provide technical assistance to DHS, and they are also informative reference materials for federal, state and local public health officials and the public. While the PHGs are calculated for single chemicals only, they may, if the information is available, address hazards associated with the interactions of contaminants in mixtures. Further, PHGs are derived for drinking water only and are not intended to be utilized as target levels for the contamination of other environmental media.

Additional information on PHGs can be obtained at the OEHHA Web site at www.oehha.ca.gov.

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PUBLIC HEALTH GOAL FOR BERYLLIUM AND BERYLLIUM COMPOUNDS IN DRINKING WATER

SUMMARY

The Office of Environmental Health Hazard Assessment (OEHHA) has developed a Public Health Goal (PHG) of 1 μg/L (1 ppb) for beryllium in drinking water. This is based on lesions in the gastrointestinal tract of beagle dogs given beryllium in the diet. Public-health protective concentrations were estimated based on a no-observed-adverse-effect level (NOAEL) of 0.15 mg/kg per day and a benchmark dose calculation of the same data, yielding a 95% lower confidence limit on the five percent incidence level for beryllium-associated lesions of 0.20 mg/kg-day. The lowest-observed-adverse-effect level (LOAEL) for this effect was 1.5 mg/kg-day. For both calculations an uncertainty factor of 1,000 was used, which accounts for differences between species (3)[1], intraspecies variability (10), data deficiencies (3), and carcinogenic potential of ingested beryllium (10), and the same health-protective value is derived by both methods, 1 ppb (rounded). In calculating the PHG, it was assumed that dermal uptake of beryllium from water is negligible. The PHG level is also protective against potential carcinogenic effects from inhalation exposures to beryllium aerosols in showering and in other household uses of water.

Exposure to beryllium by the oral route also produced mild anemia and bone marrow hypoplasia in dogs at a dose rate of 12 mg/kg-day, and produced osteoporosis in rats at a dose of 10 mg/kg-day or higher. Exposure to airborne particles containing beryllium has been shown to cause lung cancer in both humans and experimental animals. Beryllium and certain beryllium compounds have also been shown to produce bone cancer (osteosarcoma) following intravenous injection or injection directly into bone in rabbits. After review of scientific evidence, it was determined that there is not an adequate basis for estimating a carcinogenic potency for exposure to beryllium or beryllium compounds in drinking water.

INTRODUCTION

The purpose of this document is to describe the development of a PHG for beryllium and beryllium compounds in drinking water. The federal MCL for beryllium or beryllium compounds, established in 1992, is 4 μg beryllium per liter (4 ppb), and the federal MCLG is also set at this level. In 1994, the federal standard of 4 ppb was adopted as the California MCL for beryllium and beryllium compounds. The U.S. EPA (1998a,b) has established a reference dose (RfD) of 0.002 mg/kg-day, which was derived from the same feeding study in male and female beagle dogs used for developing the proposed PHG.

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[1] "3" means one-half log unit, or half of 10 on a logarithmic scale; in this notation, 3 x 3 = 10 (or literally, 3.1623 x 3.1623 = 10).

On October 1, 1987, beryllium and beryllium compounds were placed on the list of chemicals known to the State of California to cause cancer, as required under the Safe Drinking Water and Toxic Enforcement Act of 1986 (Proposition 65). The International Agency for Research on Cancer (IARC) has classified beryllium and beryllium compounds in IARC group 1 (carcinogenic to humans) based on sufficient evidence for carcinogenicity in humans and sufficient evidence for carcinogenicity in experimental animals. U.S. EPA's Office of Water has classified beryllium and beryllium compounds in group B1 (probable human carcinogen) (ASTDR, 2002). However, the U.S. EPA's more recent evaluation (U.S. EPA, 1998a,b) concluded that the human carcinogenic potential of ingested beryllium could not be determined.

CHEMICAL PROFILE

Chemical Identity

Beryllium is the fourth element in the periodic table. In its oxidized state, it forms a large number of compounds. The chemical formula, synonyms, and Chemical Abstracts Service (CAS) Registry numbers of beryllium compounds formed during the refining of beryllium or used in commerce are listed in Table 1 (U.S. EPA, 1998b).

Physical and Chemical Properties

Beryllium is the lightest chemically stable metal. It melts at a higher temperature and is harder than steel but is more brittle. Copper alloys containing two percent beryllium are six times harder than copper and are resistant to oxidation. Aluminum alloys containing 4.5-6.0 percent beryllium are lightweight and are stronger than aluminum. Beryllium oxide is used to make ceramics and ceramic coatings that can withstand high temperatures and are resistant to corrosion (IARC, 1993).

Naturally-occurring beryllium is oxidized and is found in more than 40 minerals. Examples of naturally occurring beryllium compounds are beryl ($3BeO.Al_2O_3.6SiO_2$), bertandite ($4BeO.2SiO_2.H_20$), emerald, and aquamarine (IARC, 1993). The chemical formula and physical properties of beryllium and beryllium compounds are listed in Table 2.

Production and Uses

Beryllium is produced from beryl ore by melting the ore, quenching the melted ore in water, reheating to 900 ^oC, and extracting beryllium (as beryllium hydroxide) in sulfuric acid. The next step in beryllium metal production is formation of beryllium fluoride by dissolving beryllium hydroxide in a solution of ammonium hydrogen fluoride. This produces ammonium tetrafluoroberyllate as a precipitate, which upon heating decomposes to yield beryllium fluoride and ammonium fluoride. Heating beryllium fluoride with magnesium produces metallic beryllium.

Table 1. Chemical Identity of Beryllium and Its Compounds (U.S. EPA, 1998b)

Chemical name	Chemical formula	CAS Registry number	Synonyms
Beryllium metal	Be	7440-41-7	Beryllium element; beryllium metallic; glucinium; glucinum
Beryllium-aluminum alloy	Al.Be	12770-50-2	Aluminum alloy, nonbase, Al, Be; aluminum-beryllium alloy
Beryllium-copper alloy	Be.Cu	11133-98-5	Copper alloy, base, Cu,Be; copper-beryllium alloy
Beryl	$Al_2Be_3(SiO_3)_6$	1302-52-9	Beryllium aluminosilicate; beryllium aluminum silicate
Beryllium chloride	$BeCl_2$	7787-47-5	Beryllium dichloride
Beryllium fluoride	BeF_2	7787-49-7	Beryllium difluoride
Beryllium hydroxide	$Be(OH)_2$	13327-32-7	Beryllium dihydroxide
Beryllium sulfate	$BeSO_4$	13510-49-1	Sulfuric acid, beryllium salt (1:1)
Beryllium sulfate tetrahydrate	$BeSO_4.4H_2O$	7787-56-6	Sulfuric acid, beryllium salt (1:1), tetrahydrate
Beryllium oxide	BeO	1304-56-9	Beryllia; beryllium monoxide Thermalox™
Beryllium carbonate basic	$BeCO_3.Be(OH)_2$	1319-43-3	Carbonic acid, beryllium salt, mixture with $Be(OH)_2$
Beryllium nitrate	$Be(NO_3)_2$	13597-99-4	Beryllium dinitrate; nitric acid, beryllium salt
Beryllium nitrate trihydrate	$Be(NO_3)_2.3H_2O$	7787-55-5	Nitric acid, beryllium salt, trihydrate
Beryllium nitrate tetrahydrate	$Be(NO_3)_2.4H_2O$	13510-48-0	Beryllium dinitrate tetrahydrate; nitric acid, beryllium salt, tetrahydrate
Beryllium phosphate	$BeHPO_4$	13598-15-7	Phosphoric acid, beryllium salt (1:1)
Beryllium silicate	$Be_2(SiO_4)$	13598-00-0	Phenazite; phenakite
Zinc beryllium silicate	Unspecified	39413-47-3	Silicic acid, beryllium zinc salt

Table 2. Physical and Chemical Properties of Beryllium and Its Compounds (from U.S. EPA, 1998b)

Chemical name	Molecular weight	Melting point (^{o}C)	Physical description	Density (g/cm^3)	Solubility
Beryllium metal	9.0122	1287	Grey, close-packed, hexagonal, brittle metal	1.85 (20 ^{o}C)	Sol in most dilute acids and alkali; decomposes in hot water; insol in mercury and cold water
Beryllium chloride	79.92	399.2	Colorless to slightly yellow, orthorhombic, deliquescent crystal	1.8899 (25 ^{o}C)	Sol in water, ethanol, diethyl ether and pyridine; sl sol in benzene, carbon disulfide and chloroform; insol in acetone, ammonia and toluene
Beryllium fluoride	47.01	555	Colorless or white, amorphous, hygroscopic solid	1.986	Sol in water, sulfuric acid, mixture of ethanol and diethyl ether; sl sol in ethanol; insol in hydrofluoric acid
Beryllium hydroxide	43.03	138	White, amorphous, amphoteric powder	1.92	Sol in hot concentrated acids and alkali; sl sol in dilute alkali; insol in water
Beryllium sulfate	105.07	550	Colorless, crystal	2.443	Forms sol tetrahydrate in hot water, insol in cold water
Beryllium sulfate tetrahydrate	177.14	NR	Colorless tetragonal crystal	1.713	Sol in water, sl sol in concentrated sulfuric acid; insol in ethanol
Beryllium oxide	25.01	2530	Colorless to white, hexagonal crystal or amorphous, amphoteric powder	3.01 (20 ^{o}C)	Sol in concentrated acids and alkali; insol in water
Beryllium carbonate	69.02	NR	NR	NR	Sol in acids and alkali; insol in cold water; decomp in hot water
Beryllium carbonate basic	112.05	NR	White powder	NR	Sol in acids and alkali; insol in cold water; decomp in hot water
Beryllium nitrate, trihydrate	187.97	60	White to faintly yellowish, deliquescent mass	1.56	V sol in water and ethanol
Beryllium phosphate	104.99	NR	NR	NR	Sl sol in water

sol = soluble; sl sol = slightly soluble; insol = insoluble; v sol = very soluble; decomp = decomposes

Beryllium sulfate tetrahydrate is produced by dissolving beryllium hydroxide in sulfuric acid. Beryllium sulfate is produced by heating beryllium sulfate tetrahydrate or by dissolving beryl ore in sulfuric acid. Beryllium nitrate is produced by dissolving beryllium hydroxide in nitric acid. Beryllium oxide is produced by heating beryllium sulfate tetrahydrate to 1150-1450 ^{o}C. Beryllium carbonate is produced by adding a beryllium salt to a solution of ammonium carbonate.

In 1989, U.S. mine shipments of beryllium ores were 184 metric tons of beryllium metal equivalent, and consumption of beryllium and beryllium compounds in the U.S. was estimated to be 230 metric tons of beryllium metal equivalent (ATSDR, 2002). Beryllium metal is used in nuclear reactors to reflect neutrons. It is used in windows for some X-ray tubes and is used in mirrors and other components of satellites. Beryllium-copper alloys are used to make moving parts of aircraft engines and to make electrical switches and relays. Beryllium-aluminum alloys are used in the manufacture of high-performance aircraft. Beryllium oxide is used for microelectronic substrates and transistor mountings. It is also used for the manufacture of crucibles and coatings that withstand high temperatures. Other uses are listed by Cunningham (1998).

ENVIRONMENTAL OCCURRENCE AND HUMAN EXPOSURE

Air

Beryllium and beryllium compounds occur in air as aerosols, which can be produced during the mining of beryllium ore and during refining and processing beryllium ore and beryllium compounds. Solid waste or soil contaminated with beryllium can also be sources of beryllium-containing aerosols. Beryllium is a component of smoke from combustion of coal, cigarettes, and certain other sources (HSDB, 2002). Beryllium was detected in 12 percent of air samples collected from 16 cities, with concentrations ranging from 0.001 to 0.002 $\mu g/m^3$ in urban areas, versus 0.00013 $\mu g/m^3$ in more rural areas (U.S. EPA, 1980).

Soil

Beryllium (as beryllium-containing minerals) comprises 6 mg/kg of the earth's crust (Reeves, 1986). The major anthropogenic source is coal ash where the concentration is approximately 100 mg/kg. Beryllium concentrations in sediments from Lake Pontchartrain, Louisiana were 0.5-5.0 mg/kg dry sediment (Byrne and DeLeon, 1986), and concentration from Detroit River and Western Lake Erie sediment were 0.1-3.8 mg/kg dry sediment (Lum and Gammon, 1985).

Water

The beryllium concentration in one survey of drinking water throughout the U.S. was below the limit of detection (10 ng/L) in 94.6 percent of 1,588 samples analyzed. The

mean concentration in samples where beryllium was detected was 190 ng/L, and the range was 10 ng/L - 1,220 ng/L (U.S. EPA, 1980). In a survey of beryllium in New Jersey wells (1977-79), a mean concentration of 1 μg/L was detected, with a maximum concentration of 84 μg/L (HSDB, 2002). In California, beryllium was detected in 59 out of 9669 samples analyzed from 1984-2001, where the detection limit for the purpose of reporting (DLR) was 1 μg/L (DHS, 2002).

Food

Beryllium is commonly found as a trace element in foods. It was reported as 0.08 ppm in polished rice, 0.12 ppm in bread, 0.17 ppm in potatoes, 0.24 ppm in tomatoes, and 0.33 ppm in lettuce, all expressed on a dry weight basis (U.S. EPA, 1980). Its concentration in fresh corn and carrots was reported to be less than 25 ppb, the limit of detection in this study (Wolnick *et al*., 1984). The beryllium content of English sole from Commencement Bay near Tacoma, Washington was 6 ppb (Nicola *et al*., 1987). The beryllium level in cow's milk has been reported as 0.02 ppm in ash (U.S. EPA, 1980). Beryllium may be accumulated in some plants, being found at concentrations as high as 3 ppm in birch, aspen, and willow (HSDB, 2002). The average daily beryllium intake has been estimated as about 20 μg/day, mostly from foods (HSDB, 2002).

METABOLISM AND PHARMACOKINETICS

Absorption

In the study of Furchner *et al*. (1973) discussed in the section on elimination, the fraction of an orally-administered dose of beryllium that was detected in the urine excreted during the following two days by rats, monkeys and dogs was, respectively, 0.11, 3.71 and 0.38 percent. These data are consistent with the study of Reeves (1965) showing that rats given an oral dose of beryllium sulfate excreted less than 0.5 percent of the administered dose in their urine. These results suggest that only a small fraction of ingested beryllium is absorbed in the gastrointestinal (GI) tract. However, beryllium absorption in the GI tract cannot be accurately estimated from quantification of beryllium in urine because some absorbed beryllium is excreted in feces and some remains in body tissues. Finch *et al.* (1990) provide support for biliary excretion with their measurements of radiolabeled beryllium in the feces following an inhalation exposure. The authors reported that the predominant mode of excretion at early times after exposure was through the feces, with urinary excretion assuming predominance at later times.

The study of Furchner *et al*. (1973) presents additional data that can be used to estimate GI absorption. Furchner *et al*. (1973) administered carrier-free ^{7}Be as $BeCl_2$ to groups of mice, rats, dogs and monkeys by the oral route and by intravenous injection. The same substance was administered to mice and rats by intraperitoneal injection. Following intravenous injection of beryllium in monkeys, the amount recovered in urine during the six days following administration was 18.13 percent, and nearly all of this was detected

in urine excreted during the first two days. Assuming that the distribution and elimination of intravenous beryllium is identical to distribution and elimination of beryllium absorbed from the GI tract, the observed 3.71 percent urinary elimination in monkeys corresponds to an absorption of 20 percent in the GI tract. Lower estimates can be calculated for mice, rats and dogs from the data presented by Furchner *et al*. (1973).

Distribution

Finch *et al*. (1990) exposed beagle dogs to aerosols of beryllium oxide for up to 42 minutes. In dogs exposed to beryllium oxide calcined at 500 ^{o}C, approximately 16 percent of the dose initially deposited in the respiratory tract remained at this site and 16 percent was present in bone 180 days after treatment. For beryllium oxide calcined at 1,000 ^{o}C, 88 percent of the initial amount deposited remained in the lungs and 1.5 percent was in bone after 180 days. Following a single dose of beryllium oxide administered by inhalation, beryllium was detected in tracheobronchial lymph nodes in rats (Sanders *et al*., 1975) and in dogs (Finch *et al*., 1990). Following a single dose of beryllium oxide (calcined at 1,000 ^{o}C) by intratracheal instillation, small amounts of beryllium were detected in bone, liver, heart, and kidney (Clary *et al*., 1975). The two calcined forms of beryllium do have different chemical properties, which may account for the differences in absorption noted by Finch *et al* (1990).

In rats killed 24 hours after intravenous injection of carrier-free ^{7}Be as beryllium chloride at pH 2, 43 percent of the injected dose was in bone and bone marrow, four percent was in the liver, 0.1 percent was in the spleen, and 47 percent had been excreted predominantly in urine. When ^{7}Be was injected at pH 6, the fraction in liver was 25 percent and that in the spleen was one percent. Addition of unlabeled beryllium chloride to the radioactive beryllium chloride further increased the amount of beryllium in the liver, but addition of citrate reduced the amount taken up by the liver (Klemperer *et al*., 1952). At neutral pH, beryllium rapidly forms insoluble complexes with phosphate, and it is these complexes that appear to be taken up by phagocytic cells in the liver and spleen (Skilleter, 1984).

While the levels of trace elements in mother sera and umbilical cord were evaluated, Krachler *et al.* (1999) provide evidence that beryllium is transferred across the placenta and excreted via breast milk. The levels of several trace elements and toxins, including beryllium, were determined in umbilical cord (n = 29) and corresponding maternal sera (n = 29) as well as in colostrum (n = 27). The levels of beryllium in the umbilical cord serum and in colostrum were higher than in maternal serum.

Metabolism

Beryllium and beryllium compounds are not known to participate in metabolic reactions, but soluble beryllium compounds may form insoluble complexes (*e.g*., beryllium phosphate) within tissues (Reeves and Vorvald, 1967).

Excretion

Furchner *et al*. (1973) administered carrier-free ^{7}Be as $BeCl_2$ to groups of mice, rats, dogs and monkeys by the oral route and by intravenous injection. The same substance was administered to mice and rats by intraperitoneal injection. Beryllium excreted in feces and urine was measured and the dose remaining in the body was calculated. Following oral administration of carrier-free ^{7}Be as $BeCl_2$, at least 97 percent of administered beryllium was eliminated rapidly (half time of 0.1-0.4 days). In mice, rats, monkeys and dogs, urinary excretion was, respectively, 0.24, 0.11, 3.71, and 0.38 percent of the administered dose.

Following intravenous administration, there was an initial rapid phase of elimination with a half time of 0.2-0.5 days followed by a slow phase with a half time of 50-53 days. During the first day following administration (when rapid elimination occurred), the ratio of urinary elimination to fecal elimination in mice, rats, monkeys, and dogs was 3.5, 21.3, 4.0, and 48.6, respectively. However, on the second day, these decreased to 0.5, 1.0, 0.5, and 4.6, respectively. The ratio of cumulative urinary excretion to cumulative fecal excretion over the first 6-7 days in mice, rats, monkeys and dogs was, respectively, 2.7, 9.7, 1.7, and 10.2.

Following intraperitoneal administration in mice and rats, approximately 50 percent of the dose was eliminated during the initial phase with a half time of 0.3 days. This was followed by a slow phase with half time of 51-52 days. The ratio of urinary elimination to fecal excretion in mice and dogs was 3.2 and 10.2, respectively, and this ratio during the first seven days was 2.7 and 5.1, respectively. Following intratracheal injection of beryllium sulfate in rats, approximately 50 percent of the amount excreted was found in feces and approximately 50 percent was found in urine (Van Cleave and Kaylor, 1955), indicating that biliary elimination may be significant.

TOXICOLOGY

Toxicological Effects in Animals

Acute Toxicity

Oral

In rats, the acute LD_{50} for orally administered beryllium sulfate, beryllium chloride, beryllium fluoride and beryllium oxyfluoride was 120 mg beryllium/kg (Reeves, 1986), 200 mg beryllium/kg (Kimmerle, 1966), 18.8 mg beryllium/kg, and 18.3 mg beryllium/kg (Venugopal and Luckey, 1977), respectively. In mice, the acute oral LD_{50} was 140 mg beryllium/kg for beryllium sulfate (Ashby *et al*., 1990) and 18-50 mg beryllium/kg for beryllium fluoride (Kimmerle, 1966; Venugopal and Luckey, 1977; Reeves, 1986). The greater toxicity of beryllium fluorides may be largely due to the fluoride ion (ATSDR, 1993b).

Inhalation

Rats and mice exposed for one hour to a beryllium sulfate aerosol (1.1 mg Be/m^3) were killed and examined on days 1 to 21 after exposure (Sendelbach *et al*., 1986). DNA synthesis increased to a maximum eight days after exposure in rats and five days after exposure in mice. Cell proliferation in rats involved type II alveolar cells, interstitial cells and capillary endothelial cells, and there was an increase in the number of macrophages and neutrophils. In mice, there was proliferation of interstitial and capillary endothelial cells and an increase in the number of macrophages.

Sendelbach *et al*. (1989) exposed male rats to an aerosol of beryllium sulfate (4.05 mg beryllium/m^3) for one hour and observed the course of lung injury by assaying bronchoalveolar lavage fluid. The concentration of alkaline phosphatase and lactate dehydrogenase peaked three months after exposure. Histopathologic examination revealed a progressive focal pneumonitis characterized by infiltration of macrophages and neutrophils.

Haley *et al*. (1989) administered a single inhalation dose of BeO to groups of dogs and examined the lungs of dogs killed 8, 32, 64, 180 and 365 days after exposure. Perivascular and peribronchiolar lymphocytes and macrophages were seen in lung tissue eight days after exposure. In animals killed 32 days or more after exposure, microscopic granulomas were seen in lung tissue. Following administration to dogs of a single dose of BeO by inhalation, Haley *et al*. (1997) incubated lymphocytes from blood or bronchoalveolar lavage fluid in the presence of irradiated monocytes and $BeSO_4$ and derived cell lines from lymphocytes that proliferated during this incubation. These lymphocyte cell lines proliferated in the presence of $BeSO_4$ but not in the presence of $ZnSO_4$ or $NiSO_4$.

Haley *et al*. (1990) exposed rats for 50 minutes to an aerosol of 0.8 mg/m^3 beryllium metal and examined animals 3, 7, 10, 14, 31, 59, 115 and 171 days after exposure. The initial reaction was a necrotizing hemorrhagic pneumonitis that peaked at 14 days. At 31 days, necrotizing inflammatory lesions were minimal. At 59 days, necrotizing inflammatory lesions were again noted, and these became progressively more severe.

Nikula *et al*. (1997) administered a single dose of beryllium metal by inhalation to strain A/J mice and to strain C3H/HeJ mice. Histopathological examination of the lungs of mice killed six months after exposure found granulomatous pneumonia in both strains. Microscopic granulomas were present in interstitial regions as were infiltrates of lymphocytes and plasma cells. Lymphocytes in granulomas displayed the T-helper phenotype. Neutrophils, macrophages, and giant cells were seen in alveoli.

Dermal

Marx and Burrell (1973) administered 0.5 µg beryllium sulfate to guinea pigs by intradermal injection on two days per week for 12 weeks and then applied beryllium fluoride, beryllium sulfate and beryllium oxide at doses of 0.48, 0.25 and 1.8 µg, respectively, to the surface of the skin. Each beryllium compound initiated an inflammatory reaction at the site of application characterized by the accumulation of giant cells, histiocytes, eosinophils, and lymphocytes. Similar results were reported by

Belman (1969) following sensitization of guinea pigs by dermal or intradermal administration of beryllium fluoride followed by topical application of beryllium chloride or beryllium fluoride.

Intravenous

Intravenous administration of 0.5 mg/kg beryllium (as beryllium sulfate) was lethal in rats, and administration of 0.75 mg/kg beryllium was lethal in rabbits (Aldridge *et al.*, 1950). The cause of death was liver failure.

Subchronic Toxicity

Administration of beryllium carbonate in feed to groups of rats at dose rates calculated to be 10, 20, 40, 80, 160 or 240 mg beryllium per kg per day for 24-28 days resulted in fragility of bones that increased in severity with increasing dose. The bone pathology appeared to be similar to human osteoporosis (Guyatt *et al*., 1933). Administration of beryllium carbonate in feed to rats at dose rates of 141 or 242 mg beryllium per kg per day for 42 days also produced osteoporosis (Jacobson, 1933). These authors noted that beryllium in the diet may form an insoluble complex with dietary phosphate and that this may result in inadequate phosphate for normal bone formation.

Immunotoxicology

As noted in the section on acute toxicity, intradermal administration of beryllium compounds to guinea pigs results in a delayed hypersensitivity reaction when beryllium compounds are applied to the skin of previously treated animals. Inhalation studies reviewed in the section on acute toxicity demonstrate granuloma formation in the lungs of dogs and mice given beryllium by the respiratory route. As reviewed by Finch *et al*. (1996), there are similarities between beryllium-induced lung disease in these species and chronic beryllium disease. The human lung effects are discussed in the section on toxicological effects in humans.

Developmental and Reproductive Toxicity

Mathur *et al*. (1987) administered 0.021 mg/kg beryllium nitrate by intravenous injection to groups of female Sprague-Dawley rats on day 1, 11, 12, 13, 15 and 17 of gestation. Beryllium injection on day 11 resulted in fetal death. Following injection on day 1, 12, 13, 15, and 17, fetuses survived but all pups died within three days of delivery. The dose in this experiment is equivalent to 0.045 mg beryllium per kilogram, which is approximately one-tenth the intravenous LD_{50} for rats. Other parenteral studies (as reviewed by U.S. EPA, 1991) have found developmental effects (increased fetal mortality, decreased fetal body weight, internal abnormalities, and delayed neurodevelopment) in the offspring of rodents following intratracheal or intraperitoneal administration of beryllium chloride, beryllium oxide, or beryllium sulfate during gestation.

Chronic Toxicity and Carcinogenicity

Oral

Schroeder and Mitchener (1975a) administered beryllium sulfate at a beryllium concentration of five ppm in drinking water to 52 male and 52 female Long-Evans rats, starting at the time of weaning and continuing until natural death occurred. Groups of 52 males and females were observed as controls. The dose rate for groups given 5 ppm beryllium was calculated to be 0.63 and 0.71 mg beryllium/kg per day for males and females, respectively. At death, animal weight was recorded, and gross necropsy was performed. Heart, lung, kidney, liver, spleen, and tumor tissues were examined histopathologically. No signs of systemic toxicity were reported in treated animals. Average body weight and life span were not reduced in treated animals as compared to control animals. The incidence of tumors at all sites in the control group and treated group of males was 4/26 and 9/33, respectively, and was 17/24 and 14/17 in control and treated females, respectively. The authors classified animals with multiple tumors as malignant-tumor-bearing animals. With this definition, the incidence of malignant tumors in males was 2/26 and 4/33 in control and treated rats, respectively, and in these groups of females was 8/24 and 8/17. None of the increased incidences is statistically significant. The NOAEL for this study would be 0.63 mg/kg-day for the males and 0.71 mg/kg-day for the females. No explanation is given for the large differences between the number of animals in treatment groups and the number of animals examined for tumors.

Morgareidge *et al*. (1975, 1977) administered beryllium sulfate in feed to groups of 50 male and 50 female Wistar rats for 104 weeks at beryllium concentrations of 0, 5, 50, or 500 ppm. The doses corresponded to 0.36, 3.6, and 37 mg/kg-day for males in the 5, 50, and 500 ppm groups, and 0.42, 4.2, and 43 mg/kg-day for females in the 5, 50, and 500 ppm groups, respectively. No statistically significant increases in tumors were found in groups of treated rats. There was a small decrease in body weight (within 10 percent of control body weights) of high-dose males compared to controls and decreases in mean weight of the liver and kidneys in this group. No other treatment-related effects were found. The NOAELs for this study were 37 and 42 mg/kg-day for the males and females, respectively.

Schroeder and Mitchener (1975b) administered beryllium sulfate in drinking water at beryllium concentrations of 0 or five ppm to groups of 54 male and 54 female Swiss mice, starting at weaning (18-20 days of age) and continuing until natural death occurred. The dose rate for groups given 5 ppm beryllium was calculated to be 1.2 mg beryllium/kg-day for both sexes. At death, animal weight was recorded, and gross necropsy was performed. Heart, lung, kidney, liver, and spleen were examined histopathologically. No statistically significant increases in tumor incidence were noted in males (11/38 in control and 17/48 in treated mice) or in females (14/47 in control and 20/52 in treated mice), and no signs of systemic toxicity were reported in treated animals. Average body weight and life span were not reduced in treated animals as compared to control animals. The NOAEL for this study was 1.2 mg/kg-day.

Morgareidge *et al*. (1976) administered beryllium sulfate in feed to groups of five male and five female beagle dogs (aged 8 to 12 mo) at concentrations of 0, 5, 50, or 500 ppm beryllium. Animals in the high-dose groups were killed and examined after 33 weeks because signs of severe toxicity were noted. At this time, a replacement group of 5 male and 5 female dogs was added. This group was fed a diet containing 1 ppm beryllium for a period of 143 weeks. In the other groups, the study was terminated at 172 weeks. From measured body weights and food consumption, the dose rate in dogs administered 1, 5, 50 or 500 ppm beryllium was calculated to be 0.023, 0.12, 1.1 or 12 mg/kg-day, respectively, in males and 0.029, 0.15, 1.3 or 17 mg/kg-day in females. Individual animal examinations included hematology, clinical chemistry and urine analysis, organ weight measurement, and histopathology. In animals receiving the high dose, lesions of the small intestine were found in four of five males and in all five females (Table 3). Pathological changes included edema and desquamation, necrosis and ulceration of the epithelium, acute and chronic inflammation, and fibrin thrombi. Bone marrow hypoplasia, accompanied by mild anemia, and vasculitis of the liver were also found. One female dog given 50 ppm beryllium died during week 71 and was found to have gastrointestinal lesions that were qualitatively similar to those seen in high-dose animals but were less severe. The study authors believed these lesions to be treatment-related. No treatment-related lesions were found in other animals given 50 ppm beryllium, and no treatment-related adverse effects were found in animals given 5 ppm beryllium. This concentration was established as the NOAEL (0.15 mg/kg-day) and will be used in the calculation of the proposed PHG.

Table 3. Incidence of Lesions of the Small Intestines in Dogs (N = 5/group/sex) Fed Beryllium (Morgareidge et al., 1976)

Treatment Group	Dose	Sex	Incidence
0 ppm	0	Male	0
	0	Female	0
1 ppm	0.023	Male	0
	0.029	Female	0
5 ppm	0.12	Male	0
	0.15	Female	0
50 ppm	1.1	Male	0
	1.3	Female	1
500 ppm	12.2	Male	4
	17.4	Female	5

Inhalation and intratracheal instillation

The International Agency for Research on Cancer (IARC) concluded that there is sufficient evidence for the carcinogenicity of beryllium in experimental animals (IARC,

1993). The summary of evidence stated "Beryl ore and bertandite ore were tested for carcinogenicity in rats, hamsters and monkeys by inhalation exposure in three experiments in one study. Beryl ore was shown to produce malignant and benign lung tumors in rats. The experiments in hamsters and monkeys were inadequate for evaluation, as were all experiments with bertandite ore."

"In one study in rats by single intratracheal instillation, beryllium metal, passivated beryllium metal (99% beryllium, 0.26% chromium as chromate) and beryllium-aluminum alloy (62% beryllium) produced dose-related increases in lung tumors, which were mostly adenocarcinomas and adenomas."

"Various beryllium compounds were tested by inhalation in five studies in rats, rabbits and monkeys. In two studies in rats, beryllium sulfate tetrahydrate produced lung tumors, which were mostly adenocarcinomas. In one study, both beryllium oxide and beryllium chloride produced dose-related increases in the incidence of malignant epithelial lung tumors in rats. The studies in rabbits and monkeys were considered to be inadequate for evaluation. Beryllium hydroxide and low- and high-temperature-fired beryllium oxide were tested in rats by intratracheal instillation; beryllium hydroxide produced lung adenocarcinomas and adenomas in one study, and low-temperature-fired (below 900^{o}C) beryllium oxide produced malignant lung tumors in two studies."

Intravenous injection

The IARC (1993) review of evidence for carcinogenicity stated "Rabbits given intravenous injections of beryllium metal and various compounds of beryllium (zinc beryllium silicate, beryllium silicate, beryllium oxide and beryllium phosphate) developed osteosarcomas." This refers to the study by Araki *et al*. (1954). Basically, the authors gave a single *i.v*. injection of one g beryllium phosphate and found that osteosarcomas developed in two of four rabbits within 18 months. No bone tumors occurred in three untreated rabbits. Similar findings were obtained in rabbits treated by implantation or injection into the bone of beryllium oxide, zinc beryllium silicate, and beryllium carbonate.

Genetic Toxicity

In the *Salmonella typhimurium* mutagenesis test, beryllium chloride produced conflicting results in strains TA1537 and TA2637 in the absence of metabolic activation. It did not produce mutations in strains TA98, TA100, TA102 and TA1535 in the absence of metabolic activation (Ogawa *et al.*, 1987). It did not produce mutations in TA98 in the presence of metabolic activation (Kuroda *et al*., 1991). In the *Bacillus subtilis rec* assay, it inhibited growth when spores were used but not when vegetative calls were used (Nishioka, 1975; Kuroda *et al*., 1991). In *Escherichia coli,* it did not induce prophage (Rossman *et al*., 1984), and it produced mutations in one strain but not in another (Zakour and Glickman, 1984; Rossman and Molina, 1986). It produced mutations and sister chromatid exchanges in Chinese hamster V79 cells *in vitro* (Miyaki *et al*., 1979; Kuroda *et al*., 1991), and it produced chromosomal aberrations in swine lymphocytes *in vitro* (Vegni-Talluri and Guigiani, 1967).

In the *Salmonella typhimurium* mutagenesis test, beryllium nitrate did not produce mutations in strain TA100 in the absence of metabolic activation (Tso and Fung, 1981), and it did not produce mutations in TA98 and TA100 in the presence or absence of metabolic activation (Kuroda *et al*., 1991). It produced growth inhibition in the *Bacillus subtilis* spores *rec* assay and caused sister chromatid exchanges in Chinese hamster V79 cells *in vitro* (Kuroda *et al*., 1991).

In the *Salmonella typhimurium* mutagenesis test, beryllium sulfate produced conflicting results in strain TA100 (Simmon, 1979; Dunkel *et al*., 1984; Arlauskas *et al*., 1985; Ashby *et al.,* 1990). It did not produce mutations in other *Salmonella* strains (Simmon, 1979; Rosenkranz and Poirier, 1979; Dunkel *et al*., 1984; Arlauskas *et al*., 1985; Ashby *et al.,* 1990) and did not produce mutations in *Escherichia coli* WP2 (Dunkel *et al*., 1984). It transformed mammalian cells *in vitro* (Pienta *et al*., 1977; DiPaola and Casto,1979; Dunkel *et al*., 1981) and produced sister chromatid exchanges (Larramendy *et al*., 1981). It produced conflicting results in tests for chromosomal aberrations (Paton and Allison, 1972; Larramendy *et al*., 1981; Brooks *et al*., 1989; Ashby *et al*., 1990) and did not produce mutations in mammalian host-mediated *Salmonella typhimurium* mutagenesis tests (Simmon *et al*., 1979).

Beryllium oxide did not produce mutations in the *Salmonella typhimurium* mutagenesis test and did not inhibit growth in the *Bacillus subtilis* spore *rec* assay (Kuroda *et al*., 1991). Beryllium oxide did produce DNA strand breaks in rat tracheal epithelial cells and transformed mammalian cells *in vitro* (Steele *et al*., 1989). It did not produce sister chromatid exchanges in Chinese hamster V79 cells (Kuroda *et al*., 1991).

Interpretation of *in vitro* tests for genotoxicity of beryllium salts is complicated by the low solubility of beryllium phosphate. Because phosphate is the source of the essential element phosphorus in these tests, addition of a beryllium salt may result in inadequate concentrations of bioavailable phosphate (Rosenkranz and Poirier, 1979).

Toxicological Effects in Humans

Noncarcinogenic Effects

Oral

No reports documenting human beryllium poisoning following exposure to beryllium or beryllium compounds by the oral route have been identified.

Inhalation

Acute exposure to the soluble beryllium compounds beryllium sulfate and beryllium fluoride at concentrations greater than 0.1 mg beryllium/m^3 has been associated with pneumonitis (Eisenbud *et al*., 1948). In general, exposure to beryllium can result in two types of non-neoplastic respiratory disease: acute beryllium disease (berylliosis) and chronic beryllium disease (chronic berylliosis; CBD). Acute berylliosis is usually associated with exposure to high concentrations of soluble beryllium compounds like those described by Eisenbud *et al*. (1948). This type of disease is a fulminating

inflammatory reaction of the entire respiratory tract with symptoms ranging from mild nasopharyngitis to a severe chemical pneumonitis (ASTDR, 2002). With the initiation of strict exposure limits in 1950, the syndrome of acute beryllium disease has been practically eliminated in the workplace (ASTDR, 2002).

Chronic beryllium disease (CBD) is a progressive lung disease characterized by formation of non-caseating granulomas that contain beryllium (Rossman, 2001; Newman *et al*., 1996; IARC, 1993). CBD is only observed in individuals who are sensitized to beryllium (usually <15% of an exposed population (ASTDR, 2002). The disease results from a hypersensitivity response to some antigenic form of beryllium (termed beryllium antigen) and the presence of beryllium antigen in the lung. The immune response is mediated by subsets of T-helper cells (CD4+ T cells) that recognize and respond to beryllium antigen by initiating a type IV (delayed hypersensitivity) allergic response (Fontenot *et al*., 2001; Fontenot *et al*., 2000; Fontenot *et al*., 1999; Fontenot *et al*., 1998; Tinkle, Schwitters and Newman, 1996).

Susceptibility to CBD is associated with specific alleles of a class II histocompatibility gene that are expressed on the surface of cells presenting antigens to lymphocytes (Fontenot *et al*., 2000; Wang *et al*., 1999). These alleles have been identified as HLA DP alleles (Fontenot *et al*., 1998) that are part of the major histocompatibility complex (MHC). Furthermore, sensitivity to beryllium is highly associated with the presence of a glutamic acid codon at position 69 of the DPB1 gene: In one study of 25 beryllium-sensitive individuals, 22 possessed a HLA DPB1 allele with a glutamic acid codon at position 69 (Wang *et al*., 1998, 2001). In another study of 25 beryllium-sensitive individuals, all possessed a HLA DPB1 allele with a glutamic acid codon at position 69 (Lombardi *et al*., 2001).

As reviewed by Rossman (2001), a glutamic acid codon at position 69 of the HLA DPB1 gene is present in 30-40 per cent of individuals in control populations. This suggests that 30-40 percent of the U.S. population may be susceptible to beryllium sensitization. Populations of beryllium-exposed individuals with frequencies of beryllium sensitization in this range have not been identified. Frequencies as high as 11.4 and 11.9 per cent were found in beryllium machinists and health physics technicians, respectively, who were formerly employed at a nuclear weapons manufacturing facility (Kreiss *et al*., 1993; Stange *et al*., 2001). The frequency of beryllium-sensitization was 9.4 per cent in workers at a beryllium machining plant (Newman *et al*., 2001) and was 9.9 per cent in workers at a beryllium ceramics plant (Henneberger *et al*., 2001).

More recently, Rossman *et al.* (2002) have suggested that the susceptibility to beryllium hypersensitivity and its progression to CBD may be due to presence of certain alleles (e.g., HLA-DPB1, HLA-DQB1, and/or HLA-DRB1). In their study, Rossman *et al*. (2002) performed DNA-based typing of HLA-DPB1, HLA-DQB1, and HLA-DRB1 loci on 55 subjects with beryllium hypersensitivity and compared this with the results for 82 beryllium-exposed workers with no evidence of beryllium hypersensitivity. Their results suggest that not all individuals with beryllium hypersensitivity will develop CBD.

Carcinogenicity

Oral

Studies regarding the association between cancer incidence and exposure to beryllium in drinking water or food in human populations were not found.

Inhalation

Evidence for carcinogenicity of beryllium in humans was judged by IARC (1993) to be sufficient. The data supporting this conclusion are published in epidemiological studies of workers exposed to beryllium compounds by inhalation (Wagoner *et al*., 1980; Ward *et al*., 1992). The IARC (1993) summary of evidence from the studies states "In an early series of cohort mortality studies of workers at two beryllium extraction, production and fabrication facilities in the USA (Wagoner *et al.*, 1980), a consistent, marginally significant excess of deaths from lung cancer was observed. The excess increased with time since first exposure. In a more recent mortality analysis of some 9000 workers at seven beryllium plants in the USA, including the two plants studied previously (Ward *et al*. 1992), a small but significant excess in mortality from lung cancer was found in the total cohort. The risks for lung cancer were consistently higher in those plants in which there was also excess mortality for nonmalignant respiratory disease. Also the risk for lung cancer increased with time since first exposure, and was greater in workers first hired in the period when exposures to beryllium in the work place were relatively uncontrolled. Mortality from cancers at other sites was not increased. The association between lung cancer risk and exposure to beryllium was judged not to be confounded by smoking."

"Follow-up of deaths among workers entered into the US Beryllium Case Registry (which registered cases of acute beryllium-related pneumonitis and chronic beryllium-related nonmalignant lung disease, including cases from the plants mentioned above) revealed excess mortality from cases of lung cancer; the excess was greater in those who were entered into the Registry with acute beryllium pneumonitis. Potential confounding by smoking was addressed in several ways and did not appear to explain the increased risk for lung cancer. The results of the follow-up of the Case Registry subjects yielded a higher risk for lung cancer than had been found in the previous cohort mortality study of the seven production facilities."

"In a nested case-control study of cancers of the central nervous system among workers at two nuclear facilities in the USA, an increasing risk of cancer of the central nervous system was suggested with longer duration of employment in jobs with more highly ranked exposure to beryllium." However, none of the increased risks associated with potential beryllium exposure is statistically significant. More-detailed information on these studies can be found in the original articles and the IARC review.

U.S. EPA (1998a) concluded that the evidence for carcinogenicity of beryllium in humans is "limited," based on evaluation of the same cohort mortality studies reviewed by IARC (1993). The difference in evaluating the weight of evidence is based on the potential effects of confounding exposures in epidemiological studies of workers exposed

to beryllium: the U.S. EPA concluded that there was insufficient discussion or control of potential confounding exposures including exposure to tobacco smoke.

In a study published after the IARC and U.S. EPA evaluations, Sanderson *et al*. (2001) compared incidence of lung cancer with estimated beryllium exposure in workers at a beryllium alloy production plant. When exposure was calculated as total exposure 10 years or more before occurrence of lung cancer (10-year lag) or 20 years or more before cancer occurrence (20-year lag), the study authors found a statistically significant association between lung cancer incidence and beryllium exposure. The authors examined data on cigarette smoking habits of the workers and concluded that there was a lack of evidence for confounding by cigarette smoking.

Developmental and Reproductive Toxicity

Savitz *et al*. (1989) identified pregnancies in the 1980 U.S. National Survey of Natality and Infant Mortality where there was a maternal or paternal employment with possible exposure to beryllium or beryllium compounds. For the pregnancies with possible paternal exposure or for those with possible maternal exposure, the incidences of stillbirths, preterm births, and low birth weight were not increased above national incidences.

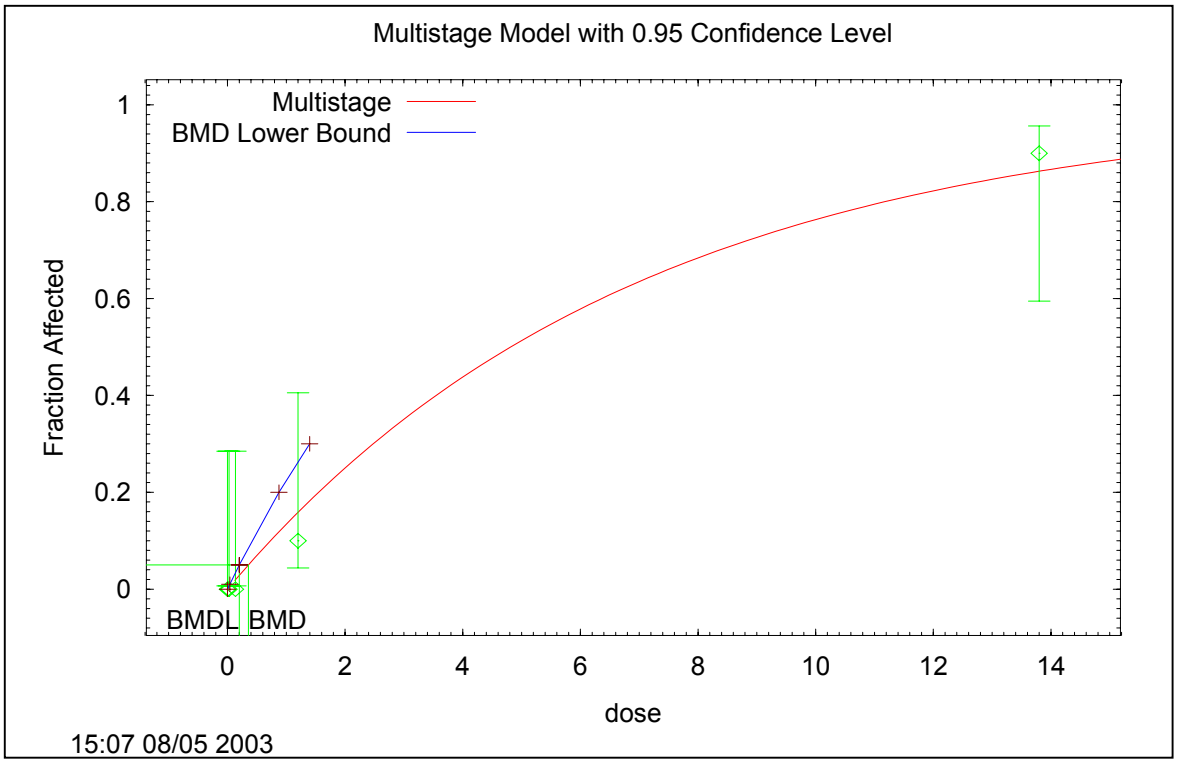
DOSE-RESPONSE ASSESSMENT

Noncarcinogenic Effects

Toxic effects in laboratory animals exposed to beryllium or beryllium compounds in water or food are liver toxicity, osteoporosis, anemia, and ulceration and inflammation of the intestinal mucosa. The most sensitive target identified is the intestinal mucosa where the LOAEL in the chronic feeding study in female dogs was 1.3 mg/kg-day. The NOAEL observed in this study was 0.15 mg/kg-day (Morgareidge *et al.*, 1976). The dataset is described in Table 3.

A benchmark dose was also calculated for comparative purposes using U.S. EPA's Benchmark Dose Software 1.3.2 (U.S. EPA, 2003). The benchmark dose software was developed as a tool to facilitate the application of benchmark dose (BMD) methods. A goal of the BMD approach is to define a starting point for extrapolation to low doses, or point of departure (POD), for the estimation of a public-health protective exposure level. In this case, the calculated BMD reflects a 5 percent increase in the incidence of small intestinal lesions (BMD05), which we consider to be equivalent to a NOAEL. The most appropriate dose-response model (a multistage model) was used for the dataset in Table 3. Figure 1 (below) provides a graphical representation of the dose-response function and its lower 95 percent confidence limit (BMDL). A good fit of the first-degree multi-stage model to the data ($p = 0.9621$) was obtained. The BMDL05 calculated under these conditions was 0.20 mg/kg-day. The U.S. EPA (1998a,b) used the BMDL10 in their risk assessment, which was reported as 0.46 mg/kg-day.

Figure 1. Best fitting dose-response model for Morgareidge *et al*. (1986) data using U.S. EPA's Benchmark Dose software.



In lifetime studies of beryllium administered to laboratory rodents by the oral route, the NOAEL was 37 mg/kg-day for male rats given beryllium sulfate in feed (Morgareidge *et al.*, 1975, 1977), 0.63 mg/kg-day for male Long-Evans rats given beryllium sulfate in drinking water (Schroeder and Mitchener, 1975a), and 1.2 mg/kg-day for male and female Swiss mice given beryllium sulfate in drinking water (Schroeder and Mitchener, 1975b). However, these studies are severely limited for the purpose of defining a NOAEL because no toxic effects were noted.

Carcinogenic Effects

The U.S. EPA (1998b) estimated the carcinogenic potency of inhaled beryllium to be 2.4×10^{-3} $(\mu g/m^3)^{-1}$. The basis for this estimate was the incidence of lung cancer in workers exposed to beryllium aerosol (Wagoner *et al*., 1980). OEHHA has recalculated this as 8.4 $(mg/kg\text{-}day)^{-1}$ (OEHHA, 1999). This inhalation potency factor can be applied to the estimation of beryllium cancer risk from inhalation of aerosol droplets in showering.

The U.S. EPA (1995) estimated an upper bound of 4.3 $(mg/kg\text{-}d)^{-1}$ for the potency of ingested beryllium. This estimate was made using the linearized multistage model and

was based on the incidence of tumors at all sites in male rats of the Schroeder and Mitchener (1975a) study. While it has not been a common practice for U.S. EPA to use a "negative" study as the basis for a potency estimate, there is some support for this procedure. In its proposed guidelines for carcinogen risk assessment, U.S. EPA states that it may be possible to obtain potency estimates from "negative" epidemiologic studies "to provide a check on the plausibility of available estimates based on animal tumor or other responses" (U.S. EPA, 1996). A "negative" animal bioassay can similarly be used to calculate the highest value of carcinogenic potency that is consistent with the data. While the U.S. EPA has not recommended that this be done, using a "negative" laboratory animal study to calculate an upper-bound potency estimate is consistent with the proposed guidelines and can help ensure that all relevant cancer data are considered.

The U.S. EPA has withdrawn its 1995 oral potency factor. In the April 3, 1998 IRIS update for beryllium and beryllium compounds, the U.S. EPA stated "The basis for not using the Schroeder and Mitchener rat study (1975a) is that the incidences of gross or malignant tumors in the control and beryllium-exposed groups were not significantly different." Around the same time, OEHHA prepared a draft document for the Air Toxics program, which included the 1995 U.S. EPA oral potency factor for ingested beryllium. However, the final document (OEHHA, 1999) does not list a cancer potency factor for ingested beryllium. Our review for the PHG development concurs with the 1999 conclusion. There are no available studies that are judged adequate for calculating an oral carcinogenic potency that may be used for regulatory purposes.

CALCULATION OF THE PHG

Calculations of concentrations of chemical contaminants in drinking water associated with negligible risks for carcinogens or noncarcinogens must take into account the toxicity of the chemical itself, as well as the potential exposure of individuals using the water. Tap water is used directly as drinking water and for preparing foods and beverages. It is also used for bathing, showering and washing, resulting in potential dermal and inhalation exposures. Use of tap water in toilets and other household devices may also contribute to inhalation exposure.

Noncarcinogenic Effects

Calculation of a public health-protective concentration (C, in mg/L) for beryllium and beryllium compounds in drinking water for noncarcinogenic endpoints follows the general equation:

$$C = \frac{NOAEL\ (or\ LOAEL) \times BW \times RSC}{UF \times W}$$

where,

NOAEL	=	no-observed-adverse-effect-level, or lowest-observed-adverse-effect-level (LOAEL) if a NOAEL is not available;
BW	=	adult body weight (default value is 70 kg);
RSC	=	relative source contribution (default values are 20, 40 and 80 percent);
UF	=	uncertainty factors (customarily 3-10 to account for interspecies extrapolation, 10 for potentially sensitive human subpopulations, 3-10 for the use of a LOAEL in place of a NOAEL, 10 for subchronic to chronic study extrapolation, and 1-10 for inadequate but suggestive evidence of carcinogenic potential);
W	=	daily drinking water consumption rate (default value of 2 L/day) plus a volume of water accounting for inhalation exposure due to volatilization and dermal uptake.

The NOAEL for beryllium toxicity in the principal study (Morgareidge *et al*., 1975, 1977) is 0.15 mg/kg-day based on ulcerative and inflammatory lesions of the intestine in male and female beagle dogs (Table 3). A benchmark dose calculation on the same data provides a BMDL05 of 0.2 mg/kg-day, which OEHHA considers conceptually equivalent to a NOAEL. The adult human body weight is assumed to be 70 kg, the standard default value. A value of 20 percent for the RSC is used for beryllium to account for the multi-route exposures to beryllium, most of which is derived from food (HSDB, 2002).

It is highly probable that the ulcerative and inflammatory lesions of the intestine produced by beryllium in the diet are the result of direct contact with beryllium in the intestinal lumen. Therefore, a factor of 3 is used for interspecies differences. This factor is based on possible differences in tissue sensitivity and not on possible differences in pharmacokinetics, because the toxicity is a direct effect at the point of contact. A factor of 10 is assumed for differences in sensitivity within the human population. As in the calculation of the federal MCL (U.S. EPA, 1992b, 1998a), additional uncertainty factors are used to account for the database deficiencies (3) and possible carcinogenic potential of ingested beryllium (10).

Because the vapor pressure of beryllium and beryllium compounds is very low, the water volume accounting for inhalation of vapor phase beryllium is assumed to be negligible. The equivalent water volume from inhalation of aerosol droplets is also very small, and has been estimated at 0.027 mL/day in a 10-minute daily shower (Keating and McKone, 1993). This exposure produces a negligible additional exposure for non-cancer effects.

The potential for dermal absorption of beryllium compounds in solution can be assessed using values for the skin permeability coefficient, k_p. While values of k_p for beryllium compounds are not available, a range of plausible values can be estimated from the range of k_p values, $1\times10^{-3} - 9\times10^{-6}$ cm/hr, for other inorganic compounds (U.S. EPA, 1992a). For a 10-minute bathing or showering event, the maximum value in this range corresponds to dermal uptake of the amount of chemical contained in 3 mL of water. This is considered to be negligible. Therefore, the default value of 2 L/day was used as the daily water consumption rate associated with beryllium exposure.

A health-protective water concentration (C) for beryllium and beryllium compounds based on non-cancer effects, using both the NOAEL and the benchmark dose approach, is therefore calculated as follows:

$$C = \frac{0.15 \text{ mg/kg-day} \times 70 \text{ kg} \times 0.20}{1000 \times 2 \text{ L}eq/\text{day}}$$

$$= 0.001 \text{ mg/L} = 1 \text{ µg/L (1 ppb)}$$

$$C = \frac{0.20 \text{ mg/kg-day} \times 70 \text{ kg} \times 0.20}{1000 \times 2 \text{ L}eq/\text{day}}$$

$$= 0.0014 \text{ mg/L} = 1 \text{ µg/L (1 ppb) (rounded)}$$

Carcinogenic Effects

As stated previously, U.S. EPA and OEHHA have concluded that there is not an adequate scientific basis for estimation and application of a carcinogenic potency for ingested beryllium. However, the small exposure to beryllium aerosols by the inhalation route in showering should be considered. A 70-kg adult breathing 20 m^3 of air per day, taking a 10-minute shower (U.S. EPA, 1997) is estimated to inhale 0.027 mL of liquid per shower per day (Keating and McKone, 1993). The concentration of beryllium in water associated with 10^{-6} risk of cancer due to inhalation of water droplets in the shower can be calculated by the following equation:

$$C = \frac{R \times BW}{CPF \times L/day}$$

where

R = a target risk level of one in a million, or $10^{-6;}$

BW = adult body weight, a default of 70 kg;

CPF = cancer potency factor, or 8.4 $(mg/kg\text{-}day)^{-1}$ for beryllium by inhalation

L/day = daily exposure to the contaminated medium, or 0.027 mL/day for inhalation of aerosol droplets in a daily 10 minute shower.

The calculation of cancer risk from inhalation of aerosols results in an estimated health-protective level, C (mg/L), of:

$$C = \frac{10^{-6} \text{ risk} \times 70 \text{ kg}}{8.4 \text{ (mg/kg-day)}^{-1} \times 27 \times 10^{-6} \text{ L/day}} = 0.31 \text{ mg/L} = 310 \text{ ppb}$$

Conclusions:

Two health-protective concentrations were developed, one based primarily on non-carcinogenic effects from ingestion of water containing beryllium, and one for carcinogenic effects from inhalation of aerosol droplets in showering. Although it is not possible to calculate a carcinogenic potency for oral exposure to beryllium, an extra 10-fold uncertainty factor has been included in the oral estimate to account for the potential carcinogenicity by this route. The estimated health-protective level based on beryllium ingestion is much lower than that for inhalation. This is due to the much greater exposure by the ingestion route as well as the relatively high potency for non-cancer effects, with a consideration of possible carcinogenicity by the oral route. The PHG for beryllium is therefore set at 1 ppb, the more health-protective of the two estimates.

RISK CHARACTERIZATION

The PHG of 1 ppb was calculated based on toxicity to the gastrointestinal tract in feeding studies in male and female beagle dogs. Sources of uncertainty in the development of the PHG for beryllium and beryllium compounds in drinking water are also the general issues of uncertainty in any risk assessment, particularly mode of action, inter- and intra-species extrapolation, and extrapolation of higher-concentration effects to lower environmental levels.

For PHGs, our use of the RSC has, with a few exceptions, followed U.S. EPA's drinking water risk assessment methodology. For noncarcinogens, RfDs (in mg/kg-day), drinking water equivalent levels (DWELs, in mg/L) and MCLGs (in mg/L) are calculated using uncertainty factors (UFs), body weights and water consumption rates (L/day), and the RSC, respectively. The RSC defaults are 20, 40, and 80 percent (0.2, 0.4 and 0.8); other values may be used depending on the scientific evidence. In this case, the default value of 20 percent (0.2) is used because the major exposure to beryllium appears to be beryllium in food. Some exposure also occurs via ambient air, particularly in urban areas. Data on relative exposures of California populations to beryllium in food, water, and air are inadequate to accurately estimate the contributions from these different sources.

U.S. EPA follows a general procedure promulgating MCLGs for Group C chemicals (*i.e.*, limited evidence of carcinogenicity). In this procedure, either an RfD approach is used (as with a noncarcinogen), but an additional UF of 1 to 10 (usually 10) is applied to account for the limited evidence of carcinogenicity, or a quantitative method (potency and low-dose extrapolation) is used and the MCLG is set in the 10^{-5} to 10^{-6} cancer risk range. In this case the chemical is a known human carcinogen, based on exposures by the inhalation route, but oral cancer potency cannot be determined. OEHHA has chosen to use the former type of approach, i.e., including an extra uncertainty factor). The same

approach was used by U.S. EPA in the derivation of its MCL for beryllium (U.S. EPA, 1992b).

The PHG of 1 ppb is judged to be adequately protective of infants, children, and the elderly from the critical effect, gastrointestinal lesions, and is also protective against potential carcinogenicity by inhalation of aerosolized beryllium in showering. The adequacy of protection of individuals previously sensitized to beryllium is uncertain, although it should be noted that the major exposure to beryllium for this population (and the population at large) is from food. Minimizing drinking water concentrations will also help protect this pre-sensitized population.

OTHER GUIDANCE VALUES AND REGULATORY STANDARDS

The federal MCL for beryllium and beryllium compounds, established in 1992, is 4 ppb. This is also the federal MCLG (U.S. EPA, 1992b). In 1994, California adopted the federal MCL of 4 ppb for beryllium and beryllium compounds. The MCL was based on the Schroeder *et al*. (1975a) study in which no adverse effects were seen in rats given beryllium (as beryllium sulfate) at the rate of 0.5 mg/kg-day. In calculating the MCL, U.S. EPA used an uncertainty factor of 100 and a drinking water contribution to total intake of 20 percent. U.S. EPA also applied an additional factor of 10 "to account for possible carcinogenic potential of this contaminant via ingestion."

More recently, U.S. EPA established a reference dose (RfD) of 2×10^{-3} mg/kg-day for oral exposure to beryllium and beryllium compounds (U.S. EPA, 1998a,b) based on the study of Morgareidge *et al*. (1976), which was also the basis for the PHG. Both the RfD and the PHG are based on lesions of the GI tract in this study. U.S. EPA used the benchmark dose (BMD) methodology as an alternative to the NOAEL for this effect, but used as their critical value the BMD_{10} (the 95 percent lower confidence limit of the dose that produces a 10 percent incidence of small intestinal lesions), which they estimated as 0.46 mg/kg-day. An uncertainty factor of 300 was used, which is the product of a factor of 100 for intraspecies differences and intraspecies variation, and a factor of 3 for database deficiencies. U.S. EPA noted that "human toxicity data by the oral route are lacking, and reproductive/developmental and immunotoxicological endpoints have not been adequately addressed in animals." The U.S. EPA RfD is based on a benchmark dose that is approximately three times higher than the NOAEL identified in the Morgareidge *et al*. study and the five percent response level, which were used for the PHG calculation. The RfD and the PHG are based on the same study and the same data.

The most recent U.S. EPA summary of the status of regulated chemicals (U.S. EPA, 2002) indicates that the beryllium MCLG is to be re-examined based on the revised RfD and other factors. The document states that "EPA believes that any likely revision to the MCLG for beryllium could range from 0.01 mg/L to 0.001 mg/L, based on the change in the RfD in the 1998 assessment, the inclusion or non-inclusion of the risk management factor [for cancer], and using a 20 percent relative source contribution (RSC)" (U.S. EPA, 2002). The U.S. EPA MCLG is comparable in purpose with the OEHHA PHG, i.e., a health-protective goal.

U.S. EPA (1998a,b) has established a reference concentration (RfC) of 2×10^{-2} μg/m^3 for inhalation exposure to beryllium and beryllium compounds. This was based on an occupational morbidity study demonstrating sensitization to beryllium at a mean concentration of 0.55 μg/m^3 (Kreiss *et al*., 1996). U.S. EPA cited the study of Eisenbud *et al*. (1949) that supports a NOAEL for sensitization in the range 0.01-0.1 μg/m^3. To calculate a point estimate of a NOAEL, the LOAEL was divided by a safety factor of 10. The NOAEL for occupational exposure was adjusted by a factor of (10 m^3)/(20 m^3) for respiratory intake volume and by a factor of (5 days)/(7 days) for duration, to calculate the RfC.

The U.S. EPA (1980) proposed a water quality standard of 11 μg/l for the protection of aquatic life in soft fresh water; 1,100 μg/l for the protection of aquatic life in hard fresh water; and 100 μg/l for continuous irrigation on all soils except 500 mg/l for irrigation on neutral to alkaline lime-textured soils.

Other state drinking water guidelines include 0.007 μg/L for Arizona and 0.08 μg/L for Minnesota (U.S. EPA, 1993).

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Responses to Major Comments on Technical Support Document

Public Health Goal
For
Beryllium
in Drinking Water

Prepared by

Pesticide and Environmental Toxicology Section
Office of Environmental Health Hazard Assessment
California Environmental Protection Agency

September 2003

TABLE OF CONTENTS

INTRODUCTION

The following are the combined responses to major comments received by the Office of Environmental Health Hazard Assessment (OEHHA) on the proposed public health goal (PHG) technical support document for beryllium, based on the pre-release review draft. Changes have already been made in response to these comments, and have been incorporated into the draft posted on the OEHHA website. For the sake of brevity, we have selected the more important or representative comments for responses. Comments appear in quotation marks where they are directly quoted from the submission; paraphrased comments are in italics.

These comments and responses are provided in the spirit of the open dialogue among scientists that is part of the process under Health and Safety Code Section 57003. For further information about the PHG process or to obtain copies of PHG documents, visit the OEHHA Web site at www.oehha.ca.gov. OEHHA may also be contacted at:

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RESPONSES TO MAJOR COMMENTS RECEIVED

Comments from University of California, Davis

Comment 1. "This is a well prepared and well written document. The toxicology of Beryllium (Be) is reviewed with emphasis on studies that mostly are relevant to the overall hazard of Be exposure and in particular to possible ingestion (or inhalation through shower mists) of Be and its compounds from water."

Response 1: Comments noted.

Comment 2. "Data on toxicity, metabolism, modes of action and exposure are presented in a clear and concise manner. It has been recognized for decades that the biggest hazard of Be exposure is by inhalation of fumes and dusts in industrial processes and, to a lesser but nevertheless not negligible degree in the neighborhoods of such facilities. It also has been recognized that Be is not a major contaminant in water and that absorption of ingested Be compounds is for all practical purposes minimal to negligible. The report correctly points this out and focuses on data that provide information on the latter point."

Response 2. Comments noted.

Comment 3. "The report focuses on the toxicokinetics and toxicodynamics of ingested Be; there are very few such data available. The relevant literature is covered by report."

Response 3. Comment noted.

Comment 4. "The key study selected for the development of the PHG is a feeding study in dogs where ingested Be did produce lesions in the gastrointestinal tract. The study also allowed to determine a NOAEL. In view of the fact that some other chronic feeding studies failed to show any effects of toxicity, the selection of the dog study conducted by Morgareidge can be justified."

Response 4. Comment noted.

Comment 5. "However, there is a drawback. The Morgareidge study has only been delivered as a laboratory report to the Be industry and was never published in the open literature. This raises the question how accessible it will be. As it happened, I reviewed two times the new ATSDR draft toxicological profiles on Be and had access to the Morgareidge study which looks reasonably well done and documented in detail. But how will it be possible for other interested parties to get a hold of the original document, if so desired?"

Response 5. A copy of the report has been obtained by OEHHA. The report can be made available upon request.

Comment 6. "I have no comments on the risk assessment methodology that has been used; it follows fairly standard and accepted procedures."

Response 6. Comment noted.

Comment 7. "[A]s mentioned above, there is a new ATSDR document on Be; in March 2002 I reviewed the post-public comment draft. OEHHA might check whether the document has now been published and update the reference list. By definition, the scope of the toxicological profile on Be written by ATSDR is much more extensile than the present OEHHA document and might serve as a useful additional source of information."

Response 7. The latest ATSDR document on Be was obtained and reviewed for new information. The new ATSDR document is referenced in the PHG document.

Comment 8. "Uncertainties, where there are any, are adequately addressed."

Response 8. Comment noted.

Comment 9. "Be is indeed one of the known human carcinogens in cigarettes and cigarette smoke, but do amounts contribute essentially anywhere to human risk (except perhaps in smokers)?"

Response 9. Although it may feasible for Be to contribute to human risk, the issue of Be in cigarettes and cigarette smoke was not addressed or evaluated in this document since it would be not pertinent in the context of the PHG evaluation for Be in drinking water.

Comment 10. "[W]hat is the evidence for the statement that 'some absorbed Be is excreted in the feces'? Is there evidence for biliary excretion or how otherwise would absorbed Be get back into the feces?"

Response 11. Data from Finch *et al*. (1990) was included in the document to support the biliary excretion.

Comment 12. "The study of Furchner needs to be described in more detail (as on page 7, last para), because it makes a notable difference in absorption whether carrier free Be^7 is administered or whether larger amounts are given."

Response 12. The text was revised to provide more detail.

Comment 13. “The issue of low fired and high fired Be oxide is also an old one and it might be appropriate to mention that the two calcined forms do have different solubilities that might impact on absorption and toxicity.”

Response 13. The text was revised accordingly.

Comment 14. “[W]hile it is true that Be compounds are not metabolized, Be compounds inasmuch take part in metabolic reactions as they seem to interfere in a rather specific way with the activity of certain enzymes. Furthermore, Be compounds also form insoluble complexes with phosphate in the serum, a fact that may impinge on their distribution to different organs.”

Response 14. Comment noted.

Comment 15. “[A]ny need to discuss in somewhat more detail the significance that lymphocytes proliferated in the presence of Be compounds? After all, the lymphocyte proliferation test was or, in one form or other, remains a widely used diagnostic tool for the human disease.”

Response 15. Comment noted. However, it did not seem warranted to provide further details in the context of the PHG document.

Comment 16. “[S]hould individual studies, summarized by IARC, be referenced so they could be looked up directly, without having to go to the IARC document?”

Response 16. Many additional studies summarized by IARC are not referenced in the PHG document. Readers are encouraged to go to the IARC document if they are interested in the additional material covered by IARC.

Comment 17. “I am very pleased and gratified by the last para of this section on page 14 (Interpretation of in vitro tests....). The insolubility of Be phosphates was recognized long before 1979 and, whenever work in vitro was attempted, in those times, many tricks were used to keep the metal in solution. With the advent of the mutagenesis tests and the apparent ease with which they could be performed, this knowledge was conveniently overlooked and Be was thrown indiscriminately at whatever system was available. Probably most, if not all in vitro mutagenesis tests are artefacts, not so much perhaps because Be would deprive bioavailable phosphate, as Rosenkranz and Poirier suggest, but because insoluble Be phosphate prevents the Be ion from interacting with critical cellular targets.”

Response 17. Comment noted.

Comment 18. *Several editorial comments were provided.*

Response 18. Changes were made to the document, where appropriate.

Comments from Health and Ecological Criteria Division, U.S. Environmental Protection Agency.

Comment 1. "The MCL and MCLG for Beryllium are 4 ppb (U.S. EPA, 1992). The MCL was based on a RfD of 0.005 mg/kg/day from Schroeder *et al*., (1975) study, in which no adverse effects were seen in rats given beryllium at 0.5 mg/kg-day. In calculating the MCLG, a rsc of 20% was used, and an additional factor of 10 was used for possible carcinogenic potential. U.S. EPA has revised the RfD to be 0.002 mg/kg/day, based on BMD10 of 0.46 mg/kg-day for small intestinal lesions from Morgareide *et al.* (1976) dog dietary study.

California EPA proposed a public health goal for beryllium of 1 ppb based on a NOAEL of 0.15 mg/kg-day for ulcerative and inflammatory lesions of the intestine in male and female dogs in Morgareidge *et al*. (1975) study. An rsc of 0.2, and an uncertainty factor of 1000 (3 for interspecies extrapolation, 10 for intraspecies variation, 3 for database deficiencies, and 10 for possible carcinogenic potential)."

Response 1: Comment noted.

REFERENCES

Finch GL, Mewhinney JA, Hoover MD, *et al*. (1990). Clearance, translocation and excretion of beryllium following acute inhalation of beryllium oxide by beagle dogs. Fundam Appl Toxicol 15:231-241.