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Technical Support Document for

The Determination of Acute Toxicity Exposure Levels for Airborne Toxicants

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Office of Environmental Health Hazard Assessment
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EXECUTIVE SUMMARY

This technical support document presents a uniform, scientifically-based method for deriving acute toxicity exposure levels applicable to the general public for hazardous substances released into the air.

The Air Toxics "Hot Spots" Act (California Health and Safety Code (CH&SC) 44300 *et seq.*) requires facilities to report to their air pollution control districts the amounts of certain chemicals they release into the air, to submit to OEHHA for review their estimate of the human health risks to surrounding communities and to inform exposed persons and communities of any significant health risks. The act also requires OEHHA, in collaboration with the Air Resources Board, to provide regulated facilities with guidance as to how to assess those risks.

Risk assessment is a four step process of hazard identification, dose-response assessment, exposure assessment, and risk characterization. OEHHA, in collaboration with the Air Resources Board, is developing guidance documents which address each step of the process. This technical support document establishes the method for determining the <u>acute</u> (one-hour) inhalation levels for three grades of effect: Level I, the discomfort or mild effect level; Level II, the disability or serious effect level; and Level III, the life-threatening effect level. Other documents are being prepared to address the health hazards associated with longer exposure periods.

The guidelines incorporate recent recommendations of the National Academy of Sciences and the requirements of state legislation. Assembly Bill (AB) 1807 (Statutes of 1983, Chapter 1047; CH&SC Section 39660) and AB 2728 (Stats. 1992, Ch. 1161 CH&SC Sec. 39660) instructs OEHHA to use a margin of safety approach when estimating the levels of exposure that may cause harm. This margin of safety must account for the diversity within human populations and any uncertainty related to the completeness and applicability of the available data. Each acute toxicity level is derived from the most sensitive measure of toxicity and protects identifiable sensitive subpopulations by use of uncertainty factors. The lowest of the three acute toxicity exposure levels is considered the Reference Exposure Level (REL). While health effects are not expected to occur at air concentrations below the REL, the REL may not protect individuals with an idiosyncratic sensitivity.

Appendix C illustrates the application of the methods described in the technical support document, including the acute toxicology summary and the derivation of the REL, for 54 substances of particular concern. Regulated facilities apply these acute RELs in a Hazard Index approach to assess the acute health risks associated with their routine industrial emissions and planned releases. The RELs also have application in characterizing health risks in event of unplanned releases.

INTRODUCTION

Hazardous substances are routinely released into the environment as a result of predictable continuous or short-term emissions from facilities. In addition, industrial accidents or explosions, spills occurring during transportation, or improper storage or disposal of materials can also result in the release of hazardous materials. Workers, emergency responders and the public living or working in communities surrounding such releases are at risk of being exposed to airborne toxicants.

Local air pollution control officers, emergency planners, and industrial facility operators have a need for clear guidance regarding the acute health effects of hazardous substances. Currently there are numerous sources of acute exposure levels developed by various committees for application to occupational and military settings. However, values for acute exposure of the general public are of limited number and of uneven quality. Several methods which are of varying merit relate toxicological information from human data and animal experiments to reference levels for acute chemical exposure. Some of these methods are based upon flawed or inconsistent algorithms or are not designed for the special case of exposure of the public to airborne toxicants (Robinson and Paxman, 1992). Furthermore, there often exist several acute exposure levels for a single compound. These values may differ by more than 100-fold, confounding prudent planning decisions. Consequently, some existing levels reflect sound science and clearly take into account issues such as appropriate endpoints and uncertainties about toxicity to a greater extent than others.

A recent report by the National Academy of Sciences (NAS), titled Science and Judgment in Risk Assessment (NRC, 1994), recommends that the United States Environmental Protection Agency (USEPA) more clearly define, and in some cases change, the methods and assumptions used to estimate the risk of cancer and other health problems from hazardous air pollutants. Specifically, NAS has charged USEPA with developing biologically based quantitative methods for assessing the effects of exposure to a chemical. This includes incorporating information on mechanisms of action and variability among populations and between individuals that might affect susceptibility to toxic insults, such as age, lifestyle, genetic background, sex, and ethnicity. NAS recognizes that there is a continued need to use default options to deal with the uncertainty of underlying mechanisms in risk assessment. NAS has recommended (1) that USEPA explicitly identify each use of a default option in risk assessment; (2) that USEPA clearly state the scientific and policy basis for each default option; and (3) that USEPA articulate criteria for allowing departure from default options. NAS has also recommended that USEPA screen the hazardous air pollutants identified in the 1990 Clean Air Act Amendments to establish

priorities for setting standards, identify data gaps and develop incentives to expedite the generation of data by other governmental agencies.

The Office of Environmental Health Hazard Assessment (OEHHA) has followed the recommendations in the NAS report by establishing uniform, science-based guidelines to be used in the derivation of acute toxicity exposure levels applicable to the general public for hazardous substances released into the environment. By investigating existing exposure guidelines (described below), OEHHA has been able to identify some of the data gaps and inconsistencies of the existing guidelines. The results of this investigation will allow the development of a priority list of chemicals for which acute exposure levels may be calculated using more rigorous and resource-intensive scientific methodology. The use of benchmark dose methodology, described later in this document, is an example of departure from default options as recommended by NAS. Better human dose-response data, for example, improved workplace monitoring, is needed before the departure from default values can be expanded to more substances.

OBJECTIVE

The objective of this document is to present a method for deriving acute (one-hour) inhalation health effect levels for hazardous airborne substances. These health-based acute toxicity exposure levels have applications for risk characterization in two general areas: (1) routine industrial emissions and planned releases and (2) unplanned releases. The guidelines for developing acute inhalation health effect levels will incorporate the recommendations of the NAS' Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances (NRC, 1993).

As defined under the Air Toxics "Hot Spots" Act (California Health and Safety Code Section 44300 *et seq.*), a risk assessment includes a comprehensive analysis of the dispersion of hazardous substances in the environment, the potential for human exposure and a quantitative assessment of both individual and populationwide health risks associated with those levels of exposure. This document establishes a standardized procedure for generating the health based values (acute toxicity exposure levels) used for assessing acute, noncancer risks within the risk assessment process.

In preparing this document, OEHHA is responding to state legislation enacted in 1992. Assembly Bill (AB) 2728 (Statutes of 1992, Chapter 1161; California Health and Safety Code Section 39660) added a mandate to the Toxic Air Contaminants Program that requires OEHHA to use a margin of safety when estimating levels of exposure that may cause adverse health effects. This margin of safety must account for diversity within human populations and uncertainty related to the applicability and completeness of the

available data. Senate Bill (SB) 1731 (Stats. 1992, Ch. 1162) requires OEHHA to develop risk assessment guidelines for implementing the "Hot Spots" Act. To help meet the requirements of AB 2728 and SB 1731, OEHHA is preparing methodology to develop acute toxicity exposure levels and is compiling such levels for specific chemicals. The acute toxicity exposure levels are designed for use in the Air Toxics "Hot Spots" Program but since much of the basic information and methodology comes from other programs, these levels may have a wide variety of applications. For example, a considerable amount of information used comes from the emergency planning field and the California Emergency Planning and Response Commission (CEPRC) has requested that such levels be made applicable to off-site consequence analyses for the Risk Management and Prevention Program.

OEHHA and the Air Resources Board (ARB) have set up a procedure in order to facilitate the extensive public comment and peer review necessary for implementation of AB 2728 and SB 1731 (Figure 1). This process includes consultation with the California Air Pollution Control Officers Association (CAPCOA), the CEPRC and the public. In addition, guidelines, RELs and other acute toxicity exposure levels are required to be reviewed by the Scientific Review Panel on Toxic Air Contaminants administered by the ARB.

All substances compiled by the ARB for the Air Toxics "Hot Spots" list of substances were considered for evaluation and inclusion in this guidance. The substances included on the Air Toxics "Hot Spots" Program List are those substances found on lists developed by the International Agency for Research on Cancer (IARC), the U.S. Environmental Protection Agency (USEPA), the U.S. National Toxicology Program, the ARB (list used in the Toxic Air Contaminant Program), the Hazard Evaluation System and Information Service (State of California), or on the Proposition 65 list of carcinogens and reproductive toxicants (State of California).

Several other exposure guidelines serve as sources for chemicals for which acute exposure levels may be developed. These are: California Ambient Air Quality Standards (CAAQS) developed by the State of California; Emergency Exposure Guidance Levels (EEGLs) and Short-term Public Emergency Guidance Levels (SPEGLs) developed by the National Academy of Sciences (NAS); Emergency Response Planning Guidelines (ERPGs) developed by the American Industrial Hygiene Association (AIHA); or Immediately Dangerous to Life and Health (IDLH) levels developed by the National Institute of Occupational Safety and Health (NIOSH). All of these guidelines were evaluated for the development of acute toxicity exposure levels. The complete list of substances for which these levels will be developed using the methods described in this Technical Support Document is contained in Appendix A.

Other programs or agencies may also require review or development of acute toxicity exposure levels for other mandated or regulatory purposes. The methods described in this Technical Support Document may be used in deriving these levels. For example, the Office of Emergency Services (OES) has requested OEHHA to develop criteria and methods for review and establishment of emergency planning guidelines for acute human exposure.

Priority For Evaluation Of Chemicals

All 32 chemicals for which acute noncancer reference exposure levels (see definition below) appeared in the Air Toxics "Hot Spots" Program Revised 1992 Risk Assessment Guidelines (California Air Pollution Control Officers Association, 1993) were evaluated. In addition, OEHHA developed 22 other chemicals on the list of substances for which emissions need to be quantified. Finally, 6 criteria air pollutants were evaluated. Refer to Appendix C for a list of the 54 chemicals that have already been evaluated with the methods delineated in this Technical Support Document.

CRITERIA FOR DEVELOPMENT OF ACUTE TOXICITY EXPOSURE LEVELS

Toxicological responses to acute exposures can be divided into several categories of severity. OEHHA has chosen to follow the NAS guidelines (1993) to divide these responses into three levels, as detailed below. These levels may have several applications. First, the Air Toxics Hot Spots Program uses the reference exposure levels, derived from the most sensitive endpoint of toxicity, for the risk assessment process. Other acute toxicity exposure levels, derived from more severe endpoints of toxicity, may also be useful for facility planners.

Acute toxicity exposure levels are concentration levels at or below which specified health effects are not expected to occur. This methods document is focused on the development of three categories of acute toxicity exposure levels in accordance with criteria and terminology established by NAS (1993): LEVEL I (the discomfort or mild effect level), LEVEL II (the disability or serious effect level), and LEVEL III (the life-threatening effect level). Each of these three acute exposure levels is determined for a one-hour exposure duration.

ACUTE TOXICOLOGY SUMMARY FOR VINYL CHLORIDE

Molecular formula	Molecular weight	Synonyms	CAS #
C_2H_3Cl	62.50	Chloroethene; chloroethylene; vinyl chloride monomer; VC; VCM	75-01-4

I. Acute Toxicity Exposure Levels (for a 1-hour exposure)

Level I (REL) Discomfort or mild effect level	**82 ppm (210 mg/m^3)**	Exposures to vinyl chloride above this level may result in mild, transient central nervous system disturbances such as dizziness.
Level II Disability or serious effect level	**No recommendation**	
Level III Life-threatening effect level	**No recommendation**	

II. Physical and Chemical Properties
(From HSDB, 1994 except as noted)

Specific gravity	0.91 @ 20°C
Boiling point	-13-37°C
Melting point	-153.8°C
Vapor pressure	2660 mm Hg @ 25°C
Flashpoint	-77.8° C (open cup) (ACGIH, 1993)
Explosive limits	upper = 22% by volume in air (ACGIH, 1993) lower = 4% by volume in air (ACGIH, 1993)
Solubility	soluble in alcohol, ethyl ether, carbon tetrachloride, benzene
Odor threshold	3000 ppm (Amoore and Hautala, 1983)
Odor Description	sweet, ethereal odor
Metabolites	chloroethylene oxide, chloroacetic acid (Antweiler, 1976)
Color	colorless
Conversion factor	1 ppm = 2.56 mg/m^3

III. Major Uses or Sources

The chief use of vinyl chloride (VC) is in the production of polyvinyl chloride (PVC) resins used for plastic piping and conduit (IARC, 1987). It is also used in the manufacture of methyl chloroform (IARC, 1979). Vinyl chloride was used as a propellant until 1974 when this use was banned due to its demonstrated carcinogenicity. The main toxicological concern for vinyl chloride is from exposure to the monomer rather than the polymerized forms (i.e. PVC). Thermal decomposition of VC produces hydrogen chloride, carbon monoxide, and traces of phosgene (ACGIH, 1993).

IV. Acute Toxicity to Humans

The primary acute physiological effect of VC inhalation is CNS depression (Holmberg, 1984). Anesthesia may occur at high concentrations (7000 - 10,000 ppm) for short durations in both animals and humans (Purchase et al., 1987).

Two male volunteers exposed to 25,000 ppm (64,000 mg/m^3) VC for 3 minutes reported the odor as pleasant, but became dizzy and disoriented to the space and size of surrounding objects. The men also reported a burning sensation on the soles of their feet (Patty et al., 1930).

In a controlled exposure, 6 adult volunteers (3 male, 3 female) were exposed to varying concentrations up to 20,000 ppm (51,200 mg/m^3) of VC via a mask covering the nose and mouth. The 5 minute exposures took place twice each day and were separated by 6-hour periods for 3 successive days. No CNS effects were reported at 4,000 ppm (10,240 mg/m^3). Exposure to 12,000 ppm (30,720 mg/m^3) resulted in complaints of dizziness and reeling in 2 subjects (Lester et al., 1963). A clear dose-response was observed in this study, but statistical comparisons were not made by the authors.

Vinyl chloride is known to cause "vinyl chloride disease" upon repeated exposures in workers. This multisystem disorder consists of Raynaud's phenomenon, acro-osteolysis, thrombocytopenia, splenomegaly, portal fibrosis, and hepatic and pulmonary dysfunction (IARC, 1979). This disease is likely an immune complex disorder from the adsorption of VC or a metabolite onto tissue proteins and is unlikely to occur following single acute exposure (Ward et al., 1976).

Predisposing Conditions for VC Toxicity

Medical: unknown

Chemical: Inducers of hepatic cytochrome-P450 enzymes, such as phenobarbital, potentiate the hepatotoxic effects of inhaled VC in rats (IARC, 1979; Jaeger et al., 1974; Kappus et al., 1975). Liver damage was measured by the release of alanine alpha-ketoglutarate, SGOT, and SGPT enzymes.

Ethanol co-administration with VC resulted in greater toxicity to pregnant mice, rats, or rabbits than exposure to VC alone (John et al., 1981).

V. Acute Toxicity to Laboratory Animals

One-hour inhalation LC_{50} values for mice, rats, rabbits, and guinea pigs were 27,000, 48,000, 210,000, and 210,000 ppm, respectively (Prodan et al., 1975). Mastromatteo et al. (1960) reported 1 of 15 deaths in guinea pigs exposed for 30 minutes to 200,000 ppm (512,000 mg/m^3) VC. No deaths were observed with exposure to 100,000 ppm (256,000 mg/m^3), although deep narcosis was observed at this concentration in all animals.

Inhalation of 25,000 ppm (64,000 mg/m^3) vinyl chloride for 2-5 minutes by guinea pigs (sample size unspecified) resulted in deep narcosis without convulsions or twitching; death by respiratory paralysis occurred after 6 hours of exposure. Gross pathological changes included congestion and edema in the lungs, and hyperemia in the liver and kidneys (Patty et al., 1930).

Lester et al. (1963) showed that rats exposed to 50,000 ppm (128,000 mg/m^3) for 2 hours exhibited moderate intoxication with loss of the righting reflex. Loss of the corneal reflex was apparent following a 2-hour exposure to 100,000 ppm (256,000 mg/m^3). Exposure of these rats to 100,000 ppm (256,000 mg/m^3) for two 8-hour periods resulted in mortality from a "pneumonic process".

In mice, inhalation of 1000 ppm (2560 mg/m^3) 6 hours/day for 5 days/week resulted in 5 deaths out of 72 animals within 14 days of exposure (Lee et al., 1977).

A 7-hour exposure of rats to 150 ppm (384 mg/m^3) VC resulted in a reduction of hepatic non-protein sulfhydryl content to 38% of that observed in controls. No effect was seen at 50 ppm (128 mg/m^3) (Watanabe et al., 1976). Depletion of non-protein sulfhydryl groups below 15% of normal physiological levels is considered incompatible with cell viability (Pascoe et al., 1987). The clinical significance of the non-protein sulfhydryl reduction in the Watanabe et al. study is, therefore, unclear.

Rhesus monkeys eliminate VC at approximately half the rate of mice and rats (Buchter et al., 1980). Rodents may therefore be less sensitive than primates to systemic VC toxicity.

VI. Reproductive or Developmental Toxicity

In review of the epidemiological data, Hemminki and Vineis (1985) concluded that there was inadequate evidence of increased t ratogenesis in humans exposed to VC.

Animal studies have also failed to show significant association between VC exposure and teratogenesis. In rats, exposure to VC at a concentration of 1500 ppm (3840 mg/m^3) for 24 hours/day during all three trimesters of pregnancy did not result in an increased incidence of birth defects (13-28 rats per group) (Ungvary et al., 1978). Pharmacokinetic studies showed that VC crossed the placental barrier of these rats, and was present in fetal blood.

John et al. (1981) showed that exposure of pregnant mice, rats or rabbits to 500 ppm (1280 mg/m^3) VC for 7 hours/day during organogenesis did not result in teratogenicity or embryotoxicity. Inhalation of 2,500 ppm (6400 mg/m^3) caused slight ossification changes in the offspring and maternal mortality in the mice. Co-administration of 15% ethanol in drinking water resulted in maternal toxicity, but no elevation in fetal effects above that seen for ethanol exposure alone.

Male mice exposed to 30,000 ppm (76800 mg/m^3) VC 6 hours/day for 5 days were mated to control females, with no resultant increase in spontaneous abortions (Purchase, 1975). However, Bi et al. (1985) showed that inhalation exposure of male rats to 100 ppm VC for 6 hours/day, 6 days/week for 3 months resulted in significant damage to seminiferous tubules compared to controls ($p < 0.05$).

VII. Derivation of Acute Toxicity Exposure Levels (for a 1-hour exposure)

Level I (REL): 82 ppm (210 mg/m^3)

Reference: Lester et al., 1963

Findings: A controlled exposure of 6 adult volunteers (3 male, 3 female) to 6 different successive concentrations of VC via a mask covering the nose and mouth for 5 minutes resulted in no reported CNS effects at 4,000 ppm (10,240 mg/m^3). Exposure

to 12,000 ppm (30,720 mg/m^3) resulted in complaints of dizziness and reeling in 2 subjects (Lester et al., 1963).

Notes: Although statistical comparisons were not performed in the Lester et al. (1963) study, a dose-response relationship was apparent. The recommended Level I was calculated by a benchmark dose (BD) approach, using a log-normal probit analysis (Crump, 1983). The BD is defined as the 95% lower confidence limit of the concentration expected to produce a response rate of 1%. The resulting BD from this analysis was 2968 ppm (7600 mg/m^3). An uncertainty factor (UF) of 10 was used to account for individual variation. An additional modifying factor (MF) of 0.3 was applied since the BD approach accounts for some degree of individual variation.

5-minute REL = BD/(UF X MF)

The intermediate (5-minute) value of 989 ppm (2532 mg/m^3) was adjusted to a 1-hour duration using the formula $C^nT = K$, where n =1. The resulting 1-hour REL is 82 ppm (210 mg/m^3). Refer to section IX of this toxicity summary for the graphic representation of benchmark dose derivation.

Level II: No recommendation

Level III: No recommendation

VIII. References

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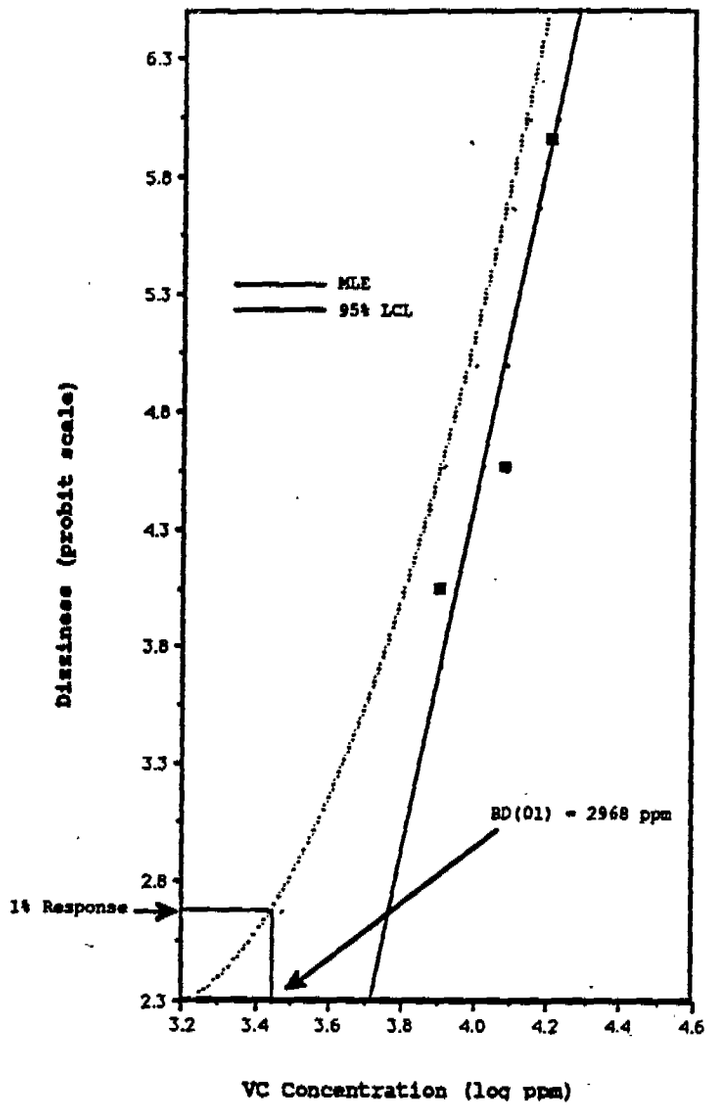
IX. Graphic Representation of Benchmark Dose Derivation for Vinyl Chloride



Dose-response slope of human symptoms of dizziness following 5-minute vinyl chloride exposures from Lester et al. (1963). Each point represents the response of a single treatment group. Equivalent 1-hour exposure concentrations were estimated from the 5-minute data. Log-probit analysis was used to model maximum likelihood estimates (MLE) from these data. The benchmark dose [BD(01)] is the 95% lower confidence limit (LCL) of the MLE for 1% lethality.

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