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A HEALTH RISK ASSESSMENT FOR AIRBORNE VINYL CHLORIDE

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INTRODUCTION

Vinyl chloride, a chemical extensively used in the plastics industry, has been shown to be carcinogenic in both humans and experimental animals. Occupational exposure to vinyl chloride has been linked with the development of liver angiosarcoma (LAS), normally a very rare human tumor. Several other tumor types, including lung and brain cancer, have been associated with occupational vinyl chloride exposure. Evidence for carcinogenicity has been observed in multiple species of experimental animals, including rats, mice and hamsters, and by various routes of exposure, including oral, inhalation, intraperitoneal, and transplacental administration. Tumor types in animals significantly increased above control levels include LAS, hepatocellular carcinoma, lung adenoma and angiosarcoma, mammary gland carcinoma and zymbal gland carcinoma, among others. Vinyl chloride has been classified as a known human carcinogen by the International Agency for the Research on Cancer (IARC)(1), the U.S. Environmental Protection Agency (EPA)(2), and the State of California Dept. of Health Services (CDHS)(3). Vinyl chloride has a relatively low toxicity from acute exposure. However, chronic exposure of humans has been linked with the development of occupational acro-osteolysis and vasospastic disorders of the hands, hepatotoxicity, and impaired pulmonary and central nervous system functioning, in addition to its carcinogenic effects.

Vinyl chloride is genotoxic in both prokaryotic and eukaryotic cells. Enzymatic metabolism of vinyl chloride, leading to the formation of the reactive metabolites chloroethylene oxide and chloroacetaldehyde, is thought to be required for both the genotoxicity and oncogenicity associated with vinyl chloride. Metabolism of vinyl chloride, mediated by cytochrome P-450 and alcohol dehydrogenase, is saturable, and saturation has been estimated to occur at exposure concentrations of approximately 250 ppm. A relatively smaller percentage of vinyl chloride is metabolized at higher exposure concentrations.

Although vinyl chloride has not been detected in the ambient air of California, monitoring in and around certain hazardous waste sites and landfills in California has detected the presence of airborne vinyl chloride. The California Air Resources Board (CARB) has estimated that peak exposure concentrations to vinyl chloride for maximally exposed receptors range from 2 to 10 ppb at the BKK hazardous waste site in West Covina, CA and from 0.6 to 9 ppb at the OII landfill in Monterey Park, CA.

Based on the identification of vinyl chloride in landfill emissions, the known health effects associated with chronic exposure, and at the request of CARB, CDHS has prepared a quantitative risk assessment for vinyl chloride based on both animal carcinogenicity bioassays and an analysis of cancer incidence data for occupationally exposed workers, to determine if vinyl chloride should be considered a toxic air contaminant in the State of California.

METHODS

A number of carcinogenesis bioassays were evaluated in conducting our risk assessment of vinyl chloride. Although all of these studies demonstrated a significant carcinogenic response in the test species, some studies were deemed inadequate for risk assessment purposes due to a variety of reasons.

such as lack of appropriate control groups, insufficient exposure time, or incomplete histopathology of the animals. There were a sufficient number of inhalation studies available so that studies utilizing other routes of administration were used for reference only. The most thoroughly documented inhalation studies with vinyl chloride were the BT series of experiments conducted by Maltoni and associates (4), who, over the course of a decade, examined the carcinogenic potential of vinyl chloride as a function of species, strain, sex, age, and exposure concentration. Sprague-Dawley rats were the best characterized species and strain, with exposure concentrations ranging from 1 to 30,000 ppm. Animals in the Maltoni et al. experiments were exposed 4 hr/day, 5 days/week for 1 year, and then observed for the rest of their natural lifetime.

Several other inhalation bioassays using vinyl chloride were also evaluated, including those of Drew et al. (5) and Bi et al. (6). Drew et al. (5) exposed female Golden Syrian hamsters, F-344 rats, CD-1 Swiss mice, and B6C3F1 mice to 200, 100, 50, and 50 ppm vinyl chloride, respectively (levels previously demonstrated to be carcinogenic in each species), for six hrs/day, five days/week for six, twelve, or eighteen months. Bi et al. (6) exposed male rats to 10, 100, or 3000 ppm vinyl chloride for six hrs/day, six days/week for eighteen months.

It has been suggested that tumor formation may not be strictly a function of administered dose, but may instead be related to metabolized dose (7,8). Because of the potential for metabolic saturation to limit the formation of reactive metabolites thought to be necessary for tumor expression, and because there is a sufficiently large data base at exposure concentrations below the proposed limit of saturation, the staff of CDHS chose to use only bioassay data with exposures of 250 ppm or less to calculate human risks associated with airborne vinyl chloride. This choice preempts the need to adjust for metabolism in the cancer potency calculations. However, for comparison purposes, risk estimates have been calculated for the entire exposure scenario for each bioassay (up to 10,000 ppm), and have been included in Table 1.

There are many inherent difficulties in using animal data to estimate human risk. In an attempt to reduce this uncertainty, risk estimates for vinyl chloride have been calculated using data from different species, sexes, experiments, and tumor types. Several adjustments need to be made to the experimental exposure data to calculate the lifetime average daily exposure levels. Thus, for inhalation exposures, the reported dose must be multiplied by: H/24 x D/7 x Le/L, where H is the hours of exposure per day, D is the number of days exposed per week, Le is the length of the experiment, and L is the lifespan of the animal (the longer of Le or 24 months). This will convert the experimental protocol to a continuous lifetime exposure. Lifetime daily exposures were found to range from 0.0595 ppm (for the 1 ppm group of Maltoni et al.: 1 ppm x 4/24 x 5/7 x 1/2 = 0.0595 ppm) to 595 ppm (from the 10,000 ppm group of Maltoni et al.).

The linearized multistage computer program GLOBAL86 was used to calculate the carcinogenic potency and potential risks associated with vinyl chloride exposure. This model uses bioassay tumor incidence data to compute maximum likelihood estimates and upper 95% confidence limits on risk associated with a particular dose. The 95% upper bound is regarded as the upper limit of the true risk. The true risk is not likely to be higher than the upper limit and

may be lower. The linearized multistage model yields upper bound estimates of risk which are generally regarded as protective of public health.

The linearized multistage model is based on several assumptions about the process of carcinogenesis. It is assumed that cancer is an irreversible process which originates in a single cell, and involves a number of biological events or stages. The rate of occurrence of each stage varies linearly with dose. In addition, it is assumed that the incidences of background and chemically-induced cancer are additive.

The multistage model may be expressed as:

$$P(d) = 1 - \exp -(q_0 + q_1 d + q_2 d^2 + \ldots + q_k d^k)$$

where P(d) is the lifetime probability of cancer for a given dose d of carcinogen, q_0 is a constant that accounts for the background incidence of cancer occurring in the absence of carcinogen, and q_1, q_2, and ... q_k are coefficients that allow the data to be expressed to various powers of the dose of carcinogen to obtain the best fit of the model to the data. Risks are presented as the 95% upper confidence interval of the cancer potency slope as calculated by GLOBAL86. Cancer potency values (q1*) are expressed in units of $(ppb)^{-1}$, and can be converted to risk estimates by the equation: dose x potency = risk. This yields an upper bound lifetime individual cancer risk associated with exposure at that dose. Table I shows the range of cancer potency values for vinyl chloride as calculated from the different sets of animal carcinogenicity bioassays.

Human risk was estimated from the animal data as follows:

$$\text{Estimated Human Risk} = \text{Rodent Risk } [I_R/I_H \times (W_H)^{2/3}/(W_R)^{2/3}]^{-1},$$

where I_R and I_H are the inhalation rates of rodents and humans, and W_R and W_H are the body weights of rodents and humans, respectively. Rodent body weights were derived from data provided by Maltoni et al. (4) and Bi et al. (6); Drew et al.(5) did not provide bodyweight data, and were estimated herein to be 300 g for rats, 30 g for mice, and 92 g for hamsters. Daily inhalation rates were also estimated for each species, following the convention of the U.S. EPA (9). Table II shows the range of human risks associated with vinyl chloride exposure, along with estimated animal body weights and inhalation rates.

A number of epidemiological studies were reviewed to identify the occupational cohort at the greatest risk of developing cancer as a result of vinyl chloride exposure (10). The study conducted by Waxweiler et al. (11) contains the most thoroughly documented information for risk assessment purposes. Eleven cases of LAS were identified among the 1,294 exposed workers, and significant excesses in liver, lung, and brain cancer were also seen. The employment dates for this cohort span 1942-1973, with deaths due to LAS occurring between 1964 and 1973. Stafford (12) has calculated the latency period for LAS among vinyl chloride workers worldwide to be 22.1 years. Individual exposure data for the Waxweiler et al. (11) cohort do not exist, but exposure estimates for the workers based on job classification, existing standards, and literature estimates were made for the purposes of this risk assessment (10). Work histories were analyzed to identify the person-time in each calendar year for the subset who had at least five years employment and who began work (and thus

vinyl chloride exposure) prior to 1964, to correspond to the same restrictions used by Waxweiler et al. (11). It was estimated that the average worktime cohort exposure for the period 1942 to 1964 was a time-weighted average of 647 ppm vinyl chloride. Assuming an 8 hour workday, for 5 days/week and 46 weeks/year, it was determined that the annual overall exposure rate above background for vinyl chloride workers was 1/3 x 5/7 x 46/52 x 647 ppm = 136 ppm vinyl chloride. The adjustment used to extrapolate to lifetime exposure is (in years): duration of employment/(age at first exposure + duration of employment), or, in this study, 11.6/(29.7 + 11.6) = 0.281. Therefore, the average lifetime exposure estimate for the cohort in the Waxweiler et al. (11) cohort was determined to be 136 ppm x 0.281 = 38.3 ppm.

RESULTS

Three separate groups of animal bioassays and one epidemiology study were evaluated to determine the carcinogenic risk from vinyl chloride exposure. Maltoni et al. (4) provided extensive histopathology data for a number of tumor types; Drew et al. (5) reported tumor incidence for tumor types showing a statistically increased incidence; and Bi et al. (6) only reported the incidence of liver and lung angiosarcomas. Risks and cancer potency values were estimated for different tumor types, species, and sex in which a significant increase in tumor formation was observed following exposure to vinyl chloride.

In the Maltoni et al. (4) studies, the most sensitive site, sex, and species observed was the mammary gland in female Sprague-Dawley rats from the BT15 experiment. A human risk of 6.3×10^{-4}/ppb was calculated for this tumor type. Risk estimates for mammary gland carcinomas from other Maltoni et al. experiments which demonstrated a significant increase in tumor formation are lower than that derived from BT15 (Tables I and II). Significant increases in LAS induction were also observed by Maltoni et al. Human risk estimates for LAS range from 1.9×10^{-4}/ppb for female rats in BT15 to 2.4×10^{-6}/ppb for male rats in BT1. Female rats were more sensitive to the oncogenic effects of vinyl chloride than males in all Maltoni et al. experiments. Although risk estimates are provided for the entire dose range of the Maltoni et al. experiments, the tumor incidence and risk estimates derived from the groups exposed to concentrations higher than 250 ppm may not accurately reflect the oncogenic potential of vinyl chloride due to metabolic saturation.

Drew et al. (5) observed increases in tumor incidences at multiple sites in their different test species. Except for female F-344 rats, the authors made no distinction between liver angiosarcoma and angiosarcoma at other sites. The most sensitive tumor sites and associated human risks for different species of female rodents were: angiosarcoma, B6C3F1 mice , 1.2×10^{-4}/ppb; mammary gland carcinoma, CD-1 Swiss mice, 1.8×10^{-3}/ppb; LAS, F-344 rats, 9.7×10^{-5}/ppb; and mammary gland carcinoma, Syrian golden hamster, 1.5×10^{-4}/ppb. Of all studies considered, the most sensitive site, sex and species observed was the mammary gland in the female CD-1 Swiss mouse. Risk estimates for all tumor types from this study are found in Table II.

Bi et al. (6) measured only liver and lung angiosarcomas in male Wistar rats. The human risk estimates for the two tumor types based on the 0-100 exposure range were calculated to be 9.5×10^{-5}/ppb for LAS and 4.2×10^{-5}/ppb for

lung angiosarcoma. Risk estimates calculated for the entire exposure range used by Bi et al. (0 - 3,000 ppm) are listed in Table II.

The occupational epidemiology study of Waxweiler et al. (11) was analyzed to determine the risks associated with actual human exposure to vinyl chloride. A number of epidemiological studies have suggested a causal relationship between vinyl chloride and several different types of human cancer, including liver, lung, and brain cancer. The standardized mortality ratios (SMR) in the Waxweiler et al. study were 1155 for biliary and liver cancer, 333 for brain cancer, and 156 for lung cancer. Historical industrial hygiene data has been used to reconstruct a range of likely exposure scenarios from which risk estimates can be derived. Based on these exposure estimates, the estimated risk for liver cancer was calculated to be 1.0×10^{-6}/ppb, and for liver, lung, and brain cancer combined was 2.1×10^{-6}/ppb.

DISCUSSION

Although vinyl chloride has not been detected in the ambient air of California, the presence of vinyl chloride in the air in and around landfills and hazardous waste sites has led CDHS to evaluate the potential health effects associated with exposure to vinyl chloride. For vinyl chloride, the primary health effect of concern is cancer. Quantitative risk assessments of the relevant animal inhalation studies of vinyl chloride using the linearized multistage model have suggested a range of possible human risks from 1.8×10^{-3}/ppb to 3.9×10^{-6}/ppb (Table III). The human risk from occupational vinyl chloride exposure has been estimated at 2.1×10^{-6}/ppb. Although the time-weighted average exposure was 647 ppm, which is above the expected concentration at which vinyl chloride metabolism saturates, the human exposure estimate was not adjusted for metabolism. Thus, the risk estimates from this exposure is likely to be an underestimate for the workers developing tumors. Although the human risk estimate is based on a historical reconstruction of occupational exposures, it is close to the range estimated from animal studies. The epidemiologic studies were conducted in mature male workers, measuring a tumor (LAS) with a latency period of greater than 12 years. Animal data has suggested that young female animals are at the greatest risk (5); in addition, the mammary gland carcinoma appears to be a more sensitive surrogate indicator of vinyl chloride exposure than LAS. Thus, the occupational cohort does not represent the more sensitive members of the population. The risks estimated herein bound that calculated by the U.S. EPA (2), who derived a risk of 1.8×10^{-5}/ppb. In conclusion, the staff of CDHS believes that the carcinogenic effects associated with vinyl chloride may cause or contribute to an increase in mortality or morbidity, or present a potential hazard to human health, and that animal data need to be used to set levels that will protect the more sensitive members of the population.

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Table 1. Range of animal cancer potency values for vinyl chloride.

Experiment	Species and Sex	Tumor Type	Experimental Exposures (ppm)	LDE[a] (ppm)	q_1^* animal[b] (ppb)$^{-1}$
Maltoni et al.					
BT1	rat, male	LAS[c]	0-10,000	0-595	9.0×10^{-7}
	rat, female	LAS	0-10,000	0-595	2.7×10^{-6}
	rat, female	LAS	0-250	0-14.9	1.5×10^{-5}
BT2	rat, female	LAS	0-200	0-11.9	1.5×10^{-5}
	rat, female	mammary gland	0-200	0-11.9	1.3×10^{-5}
BT9	rat, male	LAS	0-50	0-3	2.6×10^{-5}
	rat, female	LAS	0-50	0-3	6.0×10^{-4}
	rat, female	mammary gland	0-50	0-3	1.6×10^{-5}
BT15	rat, male	LAS	0-25	0-1.5	2.9×10^{-5}
	rat, female	LAS	0-25	0-1.5	7.4×10^{-4}
	rat, female	mammary gland	0-25	0-1.5	2.4×10^{-4}
Bi et al.	rat, male	LAS	0-3000	0-482.1	8.1×10^{-6}
	rat, male	LAS	0-100	0-16.1	3.6×10^{-5}
	rat, male	lung angiosarcoma	0-3000	0-482.1	2.3×10^{-6}
	rat, male	lung angiosarcoma	0-100	0-16.1	1.6×10^{-5}
Drew et al.	rat, female	LAS	0-100	0-17.9	3.7×10^{-5}
	rat, female	mammary gland	0-100	0-8.9	3.1×10^{-5}
	rat, female	hepatocellular carcinoma	0-100	0-17.9	1.7×10^{-5}
B6C3F1	mouse, female	hemangiosarcoma	0-50	0-4.5	4.2×10^{-5}
B6C3F1	mouse, female	mammary gland	0-50	0-2.2	2.5×10^{-4}
CD-1	Swiss mouse, female	hemangiosarcoma	0-50	0-4.5	1.5×10^{-4}
CD-1	Swiss mouse, female	mammary gland	0-50	0-2.2	6.1×10^{-4}
CD-1	Swiss mouse, female	lung carcinoma	0-50	0-4.5	1.2×10^{-5}
	hamster, female	hemangiosarcoma	0-200	0-2.2	2.5×10^{-5}
	hamster, female	skin carcinoma	0-200	0-17.9	2.0×10^{-5}
	hamster, female	mammary gland	0-200	0-17.9	5.3×10^{-5}

[a] LDE = lifetime daily exposure (in ppm) [b] 95% upper confidence interval [c] LAS = liver angiosarcoma

Table II Range of human cancer potency values for vinyl chloride estimated from animal bioassays.

Experiment	Species and Sex	Estimated Body Weight (kg)[a]	Estimated Inhalation Rate (m^3/day)[b]	q_1^* Human ($(ppb)^{-1}$)
Maltoni et al.				
BT1	rat, male	.425	254	2.4×10^{-6}
	rat, female	.275	.190	7.1×10^{-6}
	rat, female	.275	.190	3.9×10^{-5}
BT2	rat, female	.275	.190	3.9×10^{-5}
	rat, female	.275	.190	3.4×10^{-5}
BT9	rat, male	.600	.320	6.8×10^{-4}
	rat, female	.400	.244	1.6×10^{-5}
	rat, female	.400	.244	4.2×10^{-5}
BT15	rat, male	.600	.320	7.6×10^{-4}
	rat, female	.400	.244	1.9×10^{-4}
	rat, female	.400	.244	6.3×10^{-4}
Bi et al.	rat, male	.300	.201	2.1×10^{-5}
	rat, male	.300	.201	9.5×10^{-5}
	rat, male	.300	.201	6.0×10^{-6}
	rat, male	.300	.201	4.2×10^{-5}
Drew et al.	rat, female	.300	.201	9.7×10^{-5}
	rat, female	.300	.201	8.1×10^{-5}
	rat, female	.300	.201	4.5×10^{-5}
B6C3F1	mouse, female	.030	.039	1.2×10^{-4}
B6C3F1	mouse, female	.030	.039	7.3×10^{-5}
CD-1	Swiss mouse, female	.030	.039	4.4×10^{-4}
CD-1	Swiss mouse, female	.030	.039	1.8×10^{-3}
CD-1	Swiss mouse, female	.030	.039	3.5×10^{-4}
	hamster, female	.092	.086	7.0×10^{-5}
	hamster, female	.092	.086	5.6×10^{-5}
	hamster, female	.092	.086	1.5×10^{-4}

[a] Body weights were estimated from data provided or in unavailable, from standard reference values.
[b] See text for discussion of estimating the inhalation rate and human risk.

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Table III. Selected human risk estimates for lifetime exposure to 1 ppb vinyl chloride[a].

Experiment	Species and Sex	Most Sensitive Tumor Site	Risk/ppb
Smith and	human, male	liver	1.0×10^{-6}
Cummings	human, male	liver, lung and brain	2.1×10^{-6}
Maltoni et al. BT1	rat, female	LAS[b]	3.9×10^{-6}
Maltoni et al. BT2	rat, female	LAS	3.9×10^{-5}
Bi et al.	rat, male	lung angiosarcoma	4.2×10^{-5}
Maltoni et al. BT9	rat, male	LAS	6.8×10^{-5}
Bi et al.	rat, male	LAS	9.5×10^{-5}
Drew et al.	rat, female	LAS	9.7×10^{-5}
Drew et al. B6C3F1	mouse, female	hemangiosarcoma	1.2×10^{-4}
	hamster, female	mammary gland	1.5×10^{-4}
Maltoni et al. BT9	rat, female	LAS	1.6×10^{-4}
BT15	rat, female	LAS	1.9×10^{-4}
BT15	rat, female	mammary gland	6.3×10^{-4}
Drew et al CD-1	Swiss mouse, female	mammary gland	1.8×10^{-3}

[a] Estimates were selected on the basis of the most sensitive species, sex, and tumor site for experimental exposure scenarios of less than 250 ppm. Cancer risks are presented as the 95% upper confidence limits of risk for a particular dose.

[b] LAS = liver angiosarcoma