NO SIGNIFICANT RISK LEVELS (NSRLs) FOR THE PROPOSITION 65 CARCINOGEN BENZENE

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SUMMARY OF FINDINGS

The inhalation cancer potency of benzene was estimated from observations of leukemia among U.S. rubber hydrochloride workers exposed to benzene (Pliofilm Cohort) (Rinsky *et al.*, 1987; Paxton *et al.*, 1994) and benzene-exposed workers from various industries in China (Chinese Worker Cohort) (Hayes *et al.*, 1997). In estimating potency, observations were assumed to follow a Poisson distribution. Relative risk was assumed to increase linearly with cumulative exposure, and leukemia onset was assumed unaffected by benzene exposure after 30 years. Cancer potency estimates, obtained from the occupational data, were adjusted using lifetable analyses to those expected for the California population from constant exposure to benzene.

Studies in human volunteers, workers, and animals suggest that humans retain approximately 50 percent of inhaled benzene and absorb 100 percent of ingested benzene at environmentally relevant levels of exposure (OEHHA, 2001a). Based on these differences in absorption of benzene by route of exposure, the oral cancer potency was derived from the inhalation cancer potency.

The Proposition 65 "no significant risk level" (NSRL) is defined in regulation as the daily intake level posing a 10^{-5} lifetime risk of cancer. Cancer potency estimates and the corresponding NSRLs are given in Table 1.

Table 1. Cancer Potencies and NSRLs for Benzene.

Chemical	Cancer Potency $(mg/kg\text{-}day)^{-1}$	NSRL (μg/day)
Benzene		
Oral exposures	0.11	6.4
Inhalation exposures	0.054	13

INTRODUCTION

This report describes the derivation of cancer potency values and no significant risk levels (NSRLs) for benzene (CAS number 71-43-2, molecular weight 78.11). "Benzene" was listed on

February 27, 1987 as known to the State to cause cancer under Proposition 65 (California Health and Safety Code 25249.5 *et seq*.).

Benzene is one of the top 20 production chemicals in the U.S. (ATSDR, 1997). More than 12 billion pounds were produced in the U.S. in 1993, nearly all of which is derived from petroleum (ATSDR, 1997; HSDB, 1997). Benzene is used to produce ethylbenzene, an intermediate in the synthesis of styrene that is used to make plastics and elastomers (ATSDR, 1997). Benzene also is used as a feedstock in the production of phenolic resins, acetone, nylon resins, detergents, pesticides, solvents, and other organic chemicals (ATSDR, 1997). Gasoline is also a major source of benzene. Past formulations of gasoline contained about one to two percent benzene (CARB, 1997). In California, current formulations of gasoline are required to contain no more than one percent benzene by volume. Benzene is also found in tobacco smoke.

OEHHA recently reevaluated the cancer potency of benzene for California's Drinking Water Program (OEHHA, 2001a), which went through a process of peer review and public comment (OEHHA, 2001b). The methods and findings of that assessment are summarized here and form the basis of the cancer potency estimates and NSRLs for the Proposition 65 Program.

STUDIES SUITABLE FOR DOSE-RESPONSE ASSESSMENT

Of the more than 20 epidemiological studies of benzene, two studies were judged to be superior and were selected for analysis (OEHHA, 2001a). The first was a study of 1868 U.S. rubber hydrochloride (Pliofilm) workers, conducted by the U.S. National Institute of Occupational Safety and Health (NIOSH) (Paxton *et al.*, 1994). The second was a study of 74,828 exposed and 35,805 unexposed workers in China, conducted jointly by the U.S. National Cancer Institute and the Chinese Academy of Preventive Medicine (Hayes *et al.*, 1997; Yin *et al.*, 1996; Dosemeci *et al.*, 1994). Each study was evaluated separately.

Pliofilm Cohort

NIOSH conducted a retrospective cohort study of benzene-exposed workers in two production facilities in Ohio that were exposed from 1940 to 1965. Paxton *et al.* (1994) reported the most recent follow-up data, which reflected the mortality experience of the workers through 1987. A full study description of the Pliofilm Cohort is given in OEHHA (2001a).

The mortality, work history and exposure data for each individual in the Pliofilm Cohort (1868 workers total) were kindly provided to OEHHA by NIOSH. Follow-up data on 1212 non-black male '"wetside" workers, *e.g.*, those workers employed in the rubber hydrochloride processing sections of the plant that involved direct benzene exposures, were analyzed. Three separate estimates of cumulative exposure are available for the Pliofilm Cohort: Rinsky *et al.* (1981, 1987); Crump and Allen (1984), and Paustenbach *et al.* (1992) (see OEHHA, 2001a,b for detailed discussion). For comparison purposes, all analyses of the Pliofilm Cohort were repeated using each of the three exposure matrices (OEHHA, 2001a).

Data on the individual worker histories from the Pliofilm Cohort were read by the data transformation and tabulation program DATAB, which is part of the EPICURE software package (Preston *et al.*, 1993). DATAB calculates cases and person-years at risk, and it

estimates expected deaths based on U.S. age-sex-race-year-cause-specific mortality rate tables. Summary information and relative risks (observed/expected) for categories of cumulative exposure for Pliofilm "wetside" workers are provided in Table 2.

Table 2. Summary Information and Relative Risk Estimates for Leukemia among White Male Pliofilm Cohort Workers by Exposure Category.

Exposure Matrix	Categories of Mean Cumulative Exposure (ppm-years)		Person-years	Cases	Expected Number of Cases	Relative Risk	95 % CI
Rinsky *et al*.	0-39	15.9	29648	5	2.228	2.24	0.73-5.24
	40-199	93.3	7209	4	0.677	5.91	1.61-15.13
	200-399	260.8	2476	2	0.232	8.64	1.03-31.12
	≥ 400	530.1	1059	3	0.086	34.76	7.21-101.98
Crump and Allen	0-39	15.5	24907	4	1.842	2.17	0.59-5.56
	40-199	108.0	9358	3	0.801	3.74	0.77-10.95
	200-399	279.0	3100	4	0.280	14.29	3.89-36.57
	≥ 400	808.4	3026	3	0.320	9.39	1.94-27.41
Paustenbach *et al*.	0-39	16.7	20354	3	1.405	2.14	0.44-6.24
	40-199	108.9	9827	2	0.816	2.45	0.29-8.85
	200-399	290.9	3587	2	0.349	5.73	0.69-20.69
	≥ 400	745.3	6623	7	0.673	10.41	4.18-21.43

Chinese Worker Cohort

U.S. National Cancer Institute in collaboration with the Chinese Academy of Preventive Medicine conducted a large retrospective cohort study of 74,828 benzene-exposed workers and 35,805 unexposed control workers (Hayes *et al.*, 1997). Workers enrolled in the study were employed from 1949 to 1987 in various industries from 712 factories in 12 Chinese cities. A full study description of the Chinese Worker Cohort is given in OEHHA (2001a).

The individual data from the Chinese Worker Cohort were not available to OEHHA. Summary data grouped by four exposure categories from Hayes *et al.* (1997) were utilized. Hayes *et al.* (1997) summarized the cases, person-years and relative risks for various hematological neoplasms using several different metrics for exposure. Exposure metrics were cumulative exposure (ppm-yr), average exposure (ppm), "constant" exposure (ppm) and duration of exposure (yr). The "constant" exposure group represents a subset of the full cohort (representing about 76 percent of the total person-years at risk) in which exposures remained relatively constant over their work experience. There is increased confidence in the exposure assignment for this subset of workers and thus only data from the constant exposure group were used for calculation of the potency estimates. Mean exposure estimates and cumulative exposure estimates for each exposure group were kindly provided by the National Cancer Institute (Dr. Hayes, personal communication) and are shown in Table 3.

Table 3. Summary Data for the Chinese Worker Cohort (Hayes et al., 1997).

Neoplasm	Referent group	Exposure Groups[1] *Exposure Range, ppm* Average Exposure, ppm (Cumulative Exposure, ppm-yr) *<10* 1.2 (6.7)	*10-24* 15 (67)	*≥25* 60 (299)
ANLL/MDS				
Cases	4	10	4	8
RR		3.2	5.1	7.1
ANLL				
Cases	4	6	4	5
RR		1.9	4.9	4.4
Leukemia				
Cases	9	12	7	7
RR		1.7	4.0	2.8
NHL				
Cases	3	7	0	3
RR		3.0	--	3.5
Person-years	405,000	324,000	88,000	121,000

Abbreviations: ANLL, acute non-lymphocytic leukemia; MDS, myelodysplastic syndrome; NHL, non-Hodgkin's lymphoma; RR, relative risk.
[1] "constant" exposure groups (see text)

APPROACH TO DOSE RESPONSE ANALYSIS

The evidence regarding the shape of the exposure-response curve for benzene-induced leukemia supports the use of linear risk models to extrapolate to low doses (U.S. EPA, 1998; OEHHA, 2001a,b). Saturation of metabolism and formation of reactive compounds may result in non-linearity at high exposures. Benzene and its metabolites are clearly genotoxic, causing chromosomal damage and mutations in short-term systems *in vitro*, in animals *in vivo*, and in humans exposed occupationally (ATSDR, 1997; OEHHA, 2001a). Despite extensive research, identifying a mechanism of benzene carcinogenesis has been elusive, likely because benzene causes cancer through multiple mechanisms of action (OEHHA, 2001a). At a workshop co-sponsored by OEHHA in 1996, leading researchers in the fields of benzene toxicity and leukemia research found that the understanding of leukemia etiology and benzene's carcinogenic mode of action are insufficient to develop a biologically based model of benzene-induced cancer at this time (Smith and Fanning, 1997), and more recent data have not overcome this insufficiency.

OEHHA (2001a) reviewed the scientific evidence for associations of benzene and various human cancers. The strongest association is for acute non-lymphocytic leukemia and myelodysplastic syndromes (ANLL/MDS). MDS, if not fatal, often progresses to ANLL. Evidence suggests that benzene causes other forms of leukemia as well. Total leukemia (*e.g.*, all subtypes of leukemia as a related class of diseases) was judged to be appropriate as the basis of risk assessment. Benzene exposure also may be associated with non-Hodgkin's lymphoma and multiple

myeloma, but causal associations have not been established and were not used for estimation of cancer potency (*i.e.*, lifetime unit risk). It is important to stress that use of either ANLL/MDS or total leukemia yields similar potency estimates; for example, cancer potencies based on ANLL/MDS (Chinese Worker Cohort) (Hayes *et al.*, 1997) or ANLL (Pliofilm Cohort) (Crump, 1994) differed by approximately 20 to 25 percent from those based on total leukemia (OEHHA, 2001a). No significant new findings have been published since OEHHA's 2001 assessment that would alter the analysis.

Poisson regression of linear relative risk models was utilized to analyze the data. Poisson regression, a procedure that uses maximum likelihood estimation, assumes that the observed cases follow a Poisson distribution. The relative risk model assumes that rates of leukemia in the exposed workers relative to the unexposed referent group increase linearly with increasing cumulative exposure. The model also assumes that increased rate of leukemia among the benzene-exposed workers is a multiplicative function of the background rate of leukemia. Individual exposure and worker history data were used in the analysis of the Pliofilm Cohort. Grouped summary data as published by Hayes *et al.* (1997) were used in the analysis of the Chinese Worker Cohort.

Pharmacokinetic information including studies in human volunteers, workers, and animals were reviewed (OEHHA, 2001a). Available evidence suggests that at lower exposure concentrations (*e.g.*, < 10 ppm), humans retain 50 percent of inhaled benzene and absorb 100 percent of ingested benzene. Since adequate human cancer data are not available for oral exposures to benzene, cancer potency estimates derived from inhalation studies were adjusted to those expected from oral exposures utilizing the information on differential absorption by route of exposure. Metabolism of benzene does not differ substantially based on route of exposure.

DOSE-RESPONSE ASSESSMENT

Cancer potency estimates were derived from the studies described above. The cancer potency estimates are summarized in Table 4 for the Pliofilm Cohort and in Table 5 for the Chinese Worker Cohort.

Cancer potency estimates were derived for all exposures and after removal of workers with the highest cumulative exposures. Highly exposed workers were removed from the analysis because of reduced confidence in their exposure assignments or because of observed non-linearity of response at higher exposures. Three sets of estimates of cumulative exposure are available for the Pliofilm Cohort by: Crump and Allen (1984), Rinsky *et al.* (1981, 1987), and Paustenbach *et al.* (1992). The Paustenbach *et al*. exposure estimates are likely to be high (Utterback and Rinsky, 1995; see detailed discussion in OEHHA, 2001b) and potency estimates derived from them are not presented here. The Crump and Allen estimates differed from those of Rinsky *et al.* mainly in how these authors handled the estimation of early exposures when few measurements were made. Potencies were calculated using both the Crump and Allen and Rinsky *et al.* exposure estimates, first for all exposure categories and second for workers whose exposures were less than 400 ppm-yr. Interestingly, the cancer potency estimates were essentially the same for the both of these exposure estimates after removal of the highly exposed workers (Table 4). For the Chinese Workers Cohort (Hayes *et al.*, 1997), the exposure-response relationships appear

to be nonlinear, *i.e.*, relative risk is less than a linear relationship with increasing cumulative exposure. The basis for this non-linearity is not clear, but may reflect competitive or saturable metabolism at higher exposure levels (OEHHA, 2001a,b). Indeed, recent studies in humans, in which external exposure levels were measured and biological monitoring data were collected, suggest that the primary metabolic pathway (cytochrome P4502E1) begins to saturate at occupational exposures of approximately one ppm benzene (Rappaport *et al.*, 2002). Inclusion of highly exposed workers may significantly underestimate the risks at lower exposures (OEHHA, 2001a; Rappaport *et al.*, 2002).

Cancer potency estimates for total leukemia obtained from the occupational studies were adjusted to those expected from continuous exposure of the general population, since benzene is present in indoor and outdoor air. Cancer potency estimates for the California population from constant exposure to benzene were calculated using lifetable analyses (OEHHA, 2001a). The background rates of leukemia in the California population were used in the lifetable. Also, the pattern of changing leukemia risk following exposure to benzene appears consistent with that observed for radiation and chemotherapeutic agents (OEHHA, 2001a; Finkelstein, 2000). That is, excess relative risk of leukemia increases significantly within 10 to 15 years after exposure and then declines towards background levels in subsequent years. Changing leukemia risk over time was incorporated into the lifetable calculations by estimating age-specific risk of developing leukemia from benzene exposures occurring in the prior 30 years of life (OEHHA, 2001a). It should be noted that the exposure estimates of the workers were not adjusted to reflect this changing pattern of risk following exposure, which may result in underestimation of potency. However, removing highly exposed workers from the analysis likely reduces the impact of this underestimation, since workers with the highest cumulative exposures tended to be the ones whose exposures began in the early years of Pliofilm production.

Table 4. Cancer Potency Estimates for Benzene, Based on the Pliofilm Cohort.

Dataset and Exposure Matrix	**Cancer Potency $(ppm)^{-1}$**	
	Mean	**Upper 95 % CI**
<u>All Data Points</u>		
Rinsky *et al.*	0.039	0.048
Crump and Allen	0.018	0.022
<u>Exposures < 400 ppm-yr</u>		
Rinsky *et al.*	0.034	0.044
Crump and Allen	0.036	0.045

Table 5. Cancer Potency Estimates for Benzene, Based on the Chinese Worker Cohort.

Exposure Categories	Cancer Potency $(ppm)^{-1}$	
	Mean	Upper 95 % CI
All Exposure Groups	0.0084	0.011
Highest Exposure Group Removed	0.045	0.056

Upper-bound estimates of cancer potency from Pliofilm Cohort or Chinese Worker Cohort were very similar after removal of the workers with the highest exposures from each cohort. Cancer potency estimates in units of ppm^{-1} were converted to units of $(mg/kg\text{-}d)^{-1}$ using default intake parameters of 70 kg body weight and 20 m^3/d for breathing rate:

$$\text{Potency}/(mg/kg\text{-}d) = (\text{upper-bound potency}/ppm)*(ppm/3.19\ mg/m^3)*(70\ kg)*(1/20\ m^3/d).$$

Thus, inhalation cancer potency estimates from the Pliofilm Cohort based on the Rinsky *et al.* or Crump and Allen exposure estimates are 0.048 and 0.049 $(mg/kg\text{-}day)^{-1}$, respectively, resulting in a geometric mean of 0.048 $(mg/kg\text{-}day)^{-1}$ after rounding. The cancer potency estimate based on the Chinese Worker Cohort is 0.061 $(mg/kg\text{-}day)^{-1}$. The geometric mean estimate of these two cohort studies is 0.054 $(mg/kg\text{-}day)^{-1}$ (Table 6). Cancer potency estimates from inhalation exposures were converted to those expected from oral exposures by applying a factor of two since 50 percent of inhaled benzene is absorbed and 100 percent of ingested benzene is absorbed (OEHHA, 2001a). The resulting oral cancer potency estimates are also given in Table 6.

Table 6. Human Cancer Potency Estimates for Benzene.

Cohort	Cancer Potency Estimate $(mg/kg\text{-}day)^{-1}$	
	Inhalation	Oral
Pliofilm Cohort		
Rinsky *et al.* Exposure Estimates	0.048	0.096
Crump and Allen Exposure Estimates	0.049	0.098
Chinese Worker Cohort	0.061	0.12
Geometric Mean of Two Studies	**0.054**	**0.11**

Bolding indicates values selected as the basis of the NSRL for benzene.

The cancer potency estimates obtained from the Pliofilm Cohort and Chinese Worker Cohort are consistent with estimates obtained from animal cancer bioassays of benzene, other epidemiological studies of benzene-exposed workers, and epidemiological studies of leukemia and cigarette smoke (of which benzene is a constituent) (OEHHA, 2001a).

NO SIGNIFICANT RISK LEVEL

The NSRL for Proposition 65 is the intake associated with a lifetime cancer risk of 10^{-5}. The cancer potency estimates derived above (Table 6) were used to calculate NSRLs for benzene, which are 13 μg/day for inhalation exposures and 6.4 μg/day for oral exposures.

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