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Cancer Risk Assessment for the Inhalation of 1,3-Butadiene Using Physiologically Based Pharmacokinetic Modeling

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Annual worldwide and US production of 1,3-butadiene (BD) are about 12 billion pounds and 3 billion pounds, respectively (Morrow 1990). Annual emissions of BD in the US are estimated at 12 million pounds. Low levels (< 1 ppb to 10 ppb) have been measured in ambient urban air in the US (Cote and Bayard 1990). The USEPA considers BD to be a probable human carcinogen (i.e., there is sufficient evidence of carcinogenicity in animals but inadequate evidence in humans). About 65,000 workers potentially are exposed to BD. Workplace exposures range from 0.06 to 39 ppm and generally are less than 10 ppm (Melnick et al 1988). The current OSHA permissible exposure limit (PEL) is 1,000 ppm (2212 mg/m^3); OSHA has proposed a lower PEL of 2 ppm (OSHA 1990).

A previous paper evaluated worker and general population cancer risks using a non-PBPK model (Hallenbeck 1990). PBPK refers to physiologically based pharmacokinetic models (Ramsey and Anderson 1984). A non-PBPK model accounts for exposure concentration, intake rate, time of exposure, life expectancy, latency, and body weight in the estimation of dose. A PBPK model accounts for alveolar ventilation, cardiac output, blood flow in tissues, V_{max}, K_m, KF, partition coefficients, body weight, and tissue volumes. This paper compares estimates of environmental and occupational risks using both non-PBPK and PBPK methods.

MATERIALS AND METHODS

Estimates of cancer risks were derived from animal and/or epidemiology studies. Epidemiology studies of workers who were exposed to BD have shown statistically significant excess mortality due to lymphohematopoietic cancer (Hallenbeck 1990). However, these epidemiology studies cannot be used quantitatively in risk assessment

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because of the lack of historical exposure information, multiple chemical exposures, and the small numbers of excess mortality cases due to lymphohematopoietic cancer. Hence, animal studies were reviewed for use in this risk assessment. The mouse (B6C3F1) study by Melnick et al (1988) was utilized because a statistically significant malignant lymphoma response was produced. This response is similar to that observed in the epidemiology studies.

The non-PBPK model used is discussed in Hallenbeck and Cunningham (1986). Data for the PBPK model were obtained from Ramsey and Anderson (1984), Bolt et al (1984), and personal communication (Keller 1991). The area under the BD concentration/time curve for the lung (AUCLU) was used as the tissue dose surrogate. It would have been preferable to formulate a PBPK model for one or more of the reactive metabolites of BD, e.g. butadiene monoxide (BMO). However, available biochemical and partition coefficient data were insufficient. The PBPK model for BD was executed using the Advanced Continuous Simulation Language program (ACSL 1991).

RESULTS AND DISCUSSION

The mouse lymphoma dose/response data from Melnick et al (1988) were used to calculate the cancer (lymphoma) risk factor (in units of risk/ppm) shown in Table 1. This risk factor was derived using non-PBPK methodology and is characterized by dose rate, fraction of lifetime exposed, and dose.

Also, the mouse lymphoma dose/response data from Melnick et al (1988) were used to calculate a cancer (lymphoma) risk factor (in units of risk/(mg x hr/L) shown in Table 2. This risk factor was derived using PBPK methodology and is characterized by lung exposure and fraction of lifetime exposed. The exact mechanism of pathology induced by inhalation of BD is unknown for animals or humans. The assumption was made that the lung exposure of BD in units of mg x hr/L (AUCLU) can be related to the frequency of occurrence of pathology. When the mechanism becomes known, this assumption may change. Currently, there are insufficient data to estimate tissue doses of BD metabolites.

Applications of the risk factors are shown in Table 3. The two air concentrations, 2 ppm and 0.01 ppm, refer to the proposed OSHA PEL for BD and a relatively high ambient level, respectively. The detailed non-PBPK calculations are discussed in Hallenbeck, 1990. It is interesting to note that the theoretical lifetime excess lymphoma risks are similar for these quite different methods.

Table 1. Lymphoma risk factor for 1,3-butadiene inhalation (derived using non-PBPK methodology and the mouse lymphoma response at 625 ppm)

Risk factor characteristics			Risk factor (risk/ppm)	
Dose rate (mg/kg/day)	Fraction of lifetime exposed	Dose (mg x 10^7)	Workers[a]	General Population[b]
43	0.2	1.5	0.014	0.054

[a] Assumes an intake of 10 m^3/day of contaminated air over 250 days and 45 years. The air intake of an adult engaged in light activity for 8 hours is about 10 m^3 (Hallenbeck 1986).

[b] Assumes an intake of 20 m^3/day of contaminated air over 365 days/year for a 74-year lifetime. The daily air intake of an adult engaged in light activity for 16 hours/day is about 20 m^3 (Hallenbeck 1986).

Table 2. Lymphoma risk factor for 1,3-butadiene inhalation (derived using PBPK methodology and the mouse lymphoma response at 625 ppm)

Risk factor characteristics		Risk factor for workers or the general population
Lung exposure (mg x hr/L)[a]	Fraction of lifetime exposed	[risk/(mg x hr/L)]
2,330[b]	0.2	2 x 10^{-4}

[a] AUCLU for BD.

[b] Datum obtained from Presperin (1991).

Table 3. Cancer (lymphoma) risks for butadiene inhalation (derived from non-PBPK and PBPK methodology)

	Workers	General population
Concentration (ppm)	2	0.01
Non-PBPK methodology		
Dose (mg)	5×10^5	1.2×10^4
Fraction of lifetime exposed	0.4	1
Dose rate/kg (mg/kg/d)	0.63	0.0063
Risk factor (risk/ppm)	0.014	0.054
Risk[a]	0.03	5×10^{-4}
PBPK methodology		
Lung exposure (mg x hr/L)[b]	95[c]	1.63[c]
Fraction of lifetime exposed	0.4	1
Risk factor [risk/(mg x hr/L)]	2×10^{-4}	2×10^{-4}
Risk[d]	0.02	3×10^{-4}

[a] The conditions of exposure (dose and dose rate) at 2 ppm and 0.01 ppm are much lower than those in Table 1. Hence, linear interpolation was used to calculate theoretical lifetime risk, e.g. risk at 2 ppm = 2 x 0.014 = 0.03.

[b] AUCLU for BD.

[c] Data obtained from Presperin (1991).

[d] The lung exposures at 2 ppm and 0.01 ppm are much lower than that in Table 2. Hence, linear interpolation was used to calculate theoretical lifetime risk, e.g. risk at 2 ppm = 95 x (2×10^{-4}) = 0.02.

The accuracy of PBPK risks will improve as the mechanism of pathology for BD becomes better defined. Also, PBPK and non-PBPK risks will become more accurate as lower dose animal studies become available. This will reduce the error caused by high to low dose extrapolation. However, the extrapolation method selected (linear interpolation in this paper) is likely to remain arbitrary for some time. Finally, it is important to note that usually there is no way to validate theoretical PBPK or non-PBPK risks. Validation is only possible when there are human dose/response data available. Epidemiology studies of worker exposure to BD have provided response data but not accurate exposure

information. Until PBPK or non-PBPK risks can be validated, they should be used with caution in the standard setting process.

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