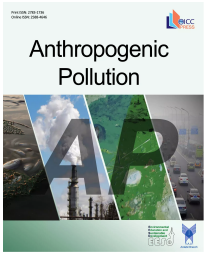

Volume 7, Issue 2, 072325 (1-6)

Anthropogenic Pollution (AP)

https://dx.doi.org/10.57647/j.jap.2023.0702.25

Occupational exposure limits for 1, 3-butadiene based on carcinogenic effects: a comparison of the threshold and non-threshold approaches

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Received 9 May 2023; Accepted 9 November 2023; Published Online 30 November 2023 ORIGINAL RESEARCH

Abstract:
1, 3-Butadiene (BD) is primarily used for the production of synthetic rubbers and polymers, which are found in many industrial and consumer products. BD is suspected to be both carcinogenic and genotoxic to humans. This study aims to compare occupational exposure limits (OELs) based on BD's carcinogenic effects using threshold and non-threshold methods in industrial settings. A review of published literature was carried out to find the most suitable in vivo carcinogenic data. Selection criteria included the number of dose levels considering more than three dose level and chronic exposure through the lung route. Studies of the National Toxicology Program (NTP) and Melnick et al. met the criteria for this study. The U.S. Environmental Protection Agency (EPA)'s BMD software, version 3.2.0, was utilized to estimate BMDL10. In the threshold approach, OELs were calculated using BMDL10 divided by uncertainty factors. The margin of exposure (MOE) method was used as a non-threshold approach. In the threshold approach, an OELI of 2.3 ppm and 3.8 ppm was estimated in males and females, respectively. In the non-threshold approach, the OELII of 0.008 ppm and 0.014 ppm was calculated for males and females, respectively, which were substantially lower than those found using the threshold method. Examining and comparing the results of this study to the threshold limit values (TLVs) and carcinogenic risk values determined by the EPA revealed that the threshold values are closer to the safe workplace concentrations (concentrations where no carcinogenic effects have been detected). Consequently, the use of non-threshold approaches results in an inaccurate estimation of carcinogenic risk.

Keywords: 1, 3-Butadiene; Benchmark dose; Threshold; Non-threshold; Carcinogen, OEL

1. Introduction

1,3-Butadiene (BD), a colorless gas, is primarily used as an intermediate in the production of polymers, elastomers, and other chemicals (EPA 2002). It is produced in significant quantities by the petrochemical industry (Chen and Zhang 2022). This chemical is primarily employed in the production of styrene-butadiene rubber and thermoplastic polymers (Cote and Bayard 1990). Approximately 75% of the BD is used to produce synthetic rubber. Exposure to BD is prevalent in the rubber, plastic, and resin industries (Albertini et al. 2003; NTP 1993).
Acute inhalation of BD causes irritation of the eyes, nasal passages, throat, and lungs in humans. At very high exposure levels, neurological effects such as impaired vision, fatigue, headaches, and vertigo have also been reported (NTP 1993). Many agencies have classified BD as a carcinogen or potential carcinogen in humans (ACGIH 2021; Albertini et al. 2003; IARC 2008; NTP 2021). The Environmental Protection Agency (EPA) classified BD as carcinogenic to humans via inhalation based on epidemiological studies, revealed an increase in lympho-hematopoietic cancers among exposed workers, as well as animal carcinogenicity studies (EPA 2002).
BD is carcinogenic in mice and rats by the inhalation route

and induces tumors at multiple sites (EPA 2002; Miller et al. 1989; NTP 1993). However, mice are more sensitive to the carcinogenic effects of BD than rats (Melnick and Sills 2001). In addition, BD is genotoxic in rodent somatic and germ cells (Albertini et al. 2010). Low concentrations of this compound have adverse effects on the reproductive organs of female rodents (Kirman et al. 2022).

There are two different types of dose-response relationships in chemical risk assessment, including threshold and non-threshold models. In threshold models, it is presumed that all doses below the threshold cause no effect, while doses above the threshold cause effects that increase in incidence or severity as a function of dose. Non-threshold dose-response models are used to assess carcinogen risk. In these models, it is assumed that any low dose above zero has the potential to induce an adverse effect, and the risk of developing cancer exists at any dose (Nohmi 2018; Roberts et al. 2022). Different organizations calculate cancer risk in non-threshold models using distinct methodologies (SWA 2018). In these models, the points of departure (POD) are BMDL, TD50, or T25 (BAuA 2014; ECETOC 2002; USEPA 2005). From the POD, a linear or nonlinear extrapolation is undertaken to determine the excess lifetime cancer risk, or the margin of exposure (MOE) (SWA 2018).

The EPA has determined the cancer slop factor for environmental exposures using the benchmark dose (BMD) method (USEPA 2005), which can be extrapolated to occupational exposures (SWA 2018). However, the use of these approaches in the risk assessment of carcinogenic substances is questionable, and it appears that non-thresholds are incapable of providing a realistic estimate of the risk (Costantini and Borremans 2019). Currently, some studies recommend the use of threshold approaches in the risk assessment of carcinogens (Blum et al. 2023; MacGregor et al. 2015). They assert that there are thresholds for the precursor effects of carcinogenesis and neoplasia (Kobets and Williams 2019; MacGregor et al. 2015). This study aims to determine and compare the occupational exposure limits (OELs) using threshold and non-threshold approaches for the carcinogenic effects of BD in industrial settings, given that threshold levels are not provided for many carcinogenic chemicals. Due to the fact that mice are the most sensitive to the carcinogenicity of BD, the BMD was determined using data from valid animal studies on mice. Finally, OELs were established and compared using mathematical relationships in each approach.

2. Materials and methods

Dataset and endpoint selection

A review of published literature was carried out to find the most suitable in vivo carcinogenic data in mice. Selection criteria included the number of dose levels (considering more than three dose level) and chronic exposure through the lung route. In occupational epidemiology studies, the incidence of lympho-hematopoietic malignancies in the workers exposed to BD has been reported. Therefore, animal studies reporting this malignancy following chronic inhalation exposure were chosen. The National Toxicology Program (NTP) study (NTP 1993) and Melnick et al. (Melnick et al. 1990) met the criteria for inclusion in this research.

In study conducted by the NTP, there was evidence of multiple organ carcinogenicity in male and female mice exposed to $6.25-625$ ppm BD. 70 male and 70 female mice were exposed to concentrations of 0, 6.25, 20, 62.5, or 200 ppm for 6 hours per day, 5 days per week, for up to 2 years; 90 male and 90 female mice were exposed to 625 ppm BD for the same duration. There was a statistically significant increase in the incidence of malignant lymphoma.

In the study of Melnick et al., the carcinogenicity of inhaled BD was assessed in mice exposed to concentrations of $6.25-625$ ppm. Groups of 70 to 90 male and female mice were exposed to BD for 6 hours per day, 5 days per week. In 2-year inhalation studies, a potent multisite carcinogenic response was observed. Early and extensive development of lethal lymphocytic lymphomas in mice exposed to 625 ppm decreased the number of animals for the expression of developing neoplasms at other sites (Melnick et al. 1990).

BMD estimation

Due to the advantages of the BMD approach over the no-observed-adverse-effect level (NOAEL) (Haber et al. 2018), it has been proposed as an alternative method for calculating human health guidance values by many organizations (ECHA 2012; USEPA 2005). US-EPA's BMD software, version 3.2.0, was utilized. To account for experimental uncertainty, the lower 95% confidence bound for the benchmark dose (BMDL) was used. According to the EPA's recommendation, a BMR of 10% extra risk was considered (USEPA 2005). After determining the BMDL for male and female rodents separately using quantal models (log-probit, probit, log-logistic, logistic, gamma, exponential, Weibull, and Hill), the lowest BMDL value was selected from each data set while considering other model acceptance criteria (USEPA 2012).

Deriving OEL values using the threshold method

OELs were calculated using BMDL10 divided by uncertainty factors.

Uncertainty factor values for BD are described below:

Intra-species variation: based on the assumption that the variability in the general population, including children, the elderly and diseased individuals, is higher than that in workers, A default value of 5 for workers was applied (Blum et al. 2023; ECHA 2012).

LOAEL to NOAEL extrapolation: the BMDL10 is considered a LOAEL since the biological effect was a 10% increase in cancer incidence. A maximum factor of 10 is used when deriving an OEL from a LOAEL, instead of a NOAEL; a factor of 3 was used in this study (Blum et al. 2023).

Interspecies variability: a 3-fold factor was used when extrapolating from valid results of long-term inhalational studies in animals (Lipscomb and Ohanian 2007).

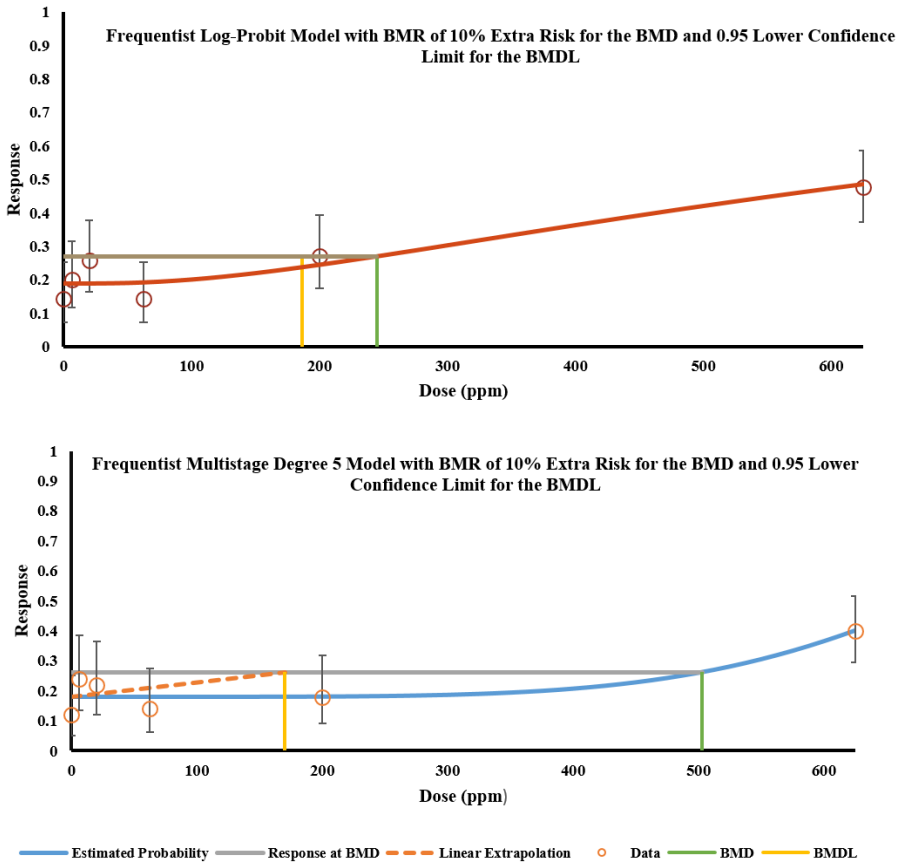

Figure 1. Dose-response curves in female mice based on carcinogenic effects in the study of NTP and Melnick et al.

A total uncertainty factor of 45 was obtained from multiplication of intra-species variation, LOAEL to NOAEL extrapolation and interspecies variability.

Deriving OEL values based on the MOE

The MOE was used as a non-threshold approach. The BMDL10 was divided by 10,000 to provide a 1 in 100,000 margin, which is typically calculated for a lifetime (SCOEL 2003; SWA 2018). An adjustment of working-lifetime (WLT) was applied (Eq. 1) with eight working hours per day, 240 working days per year, and 40 working years per lifetime.

$$\mathrm{WLF} = \frac{40\ \text{years}}{70\ \text{years}} \times \frac{8\ \text{h}}{24\ \text{h}} \times \frac{240\ \text{day}}{356\ \text{day}} = 0.125 \qquad (1)$$

The standard working lifetime was calculated as 12.5% of the whole lifetime, resulting in a margin of exposure of 1 in 12,500 excess risks (SWA 2018).

3. Results

Figure 1 and 2 depict the dose-response curves obtained from BMD modeling in two studies based on lymphoma malignancies. There were two sets of data for male and female rodents in each study. Various models were applied to the data using BMD software version 3.2.1 (supplementary files 1, 2, 3, 4). In four data sets, among the suitable models with a p-value greater than 0.1, the three models with the lowest AIC were selected for further analysis.

Table 1 displays the BMD, BMDL, and BMDU values for three models, as well as their acceptance criteria. The BMDs and BMDLs obtained from the Melnik study were

Table 1. BMD and BMDL of selected models in NTP and Melnick data set.

Study		Model	BMD (ppm)	BMDL (ppm)	BMDU (ppm)	P-value	AIC
NTP	Male	Weibull	548.0	261.4	562.9	0.50	222.7
	Female	Multistage Degree 5	502.8	170.0	570.0	0.47	347.4
Melnick	Male	Multistage Degree 5	219.5	102.2	379.4	0.16	328.7
	Female	Log-Probit	244.6	186.4	621.1	0.34	479.6

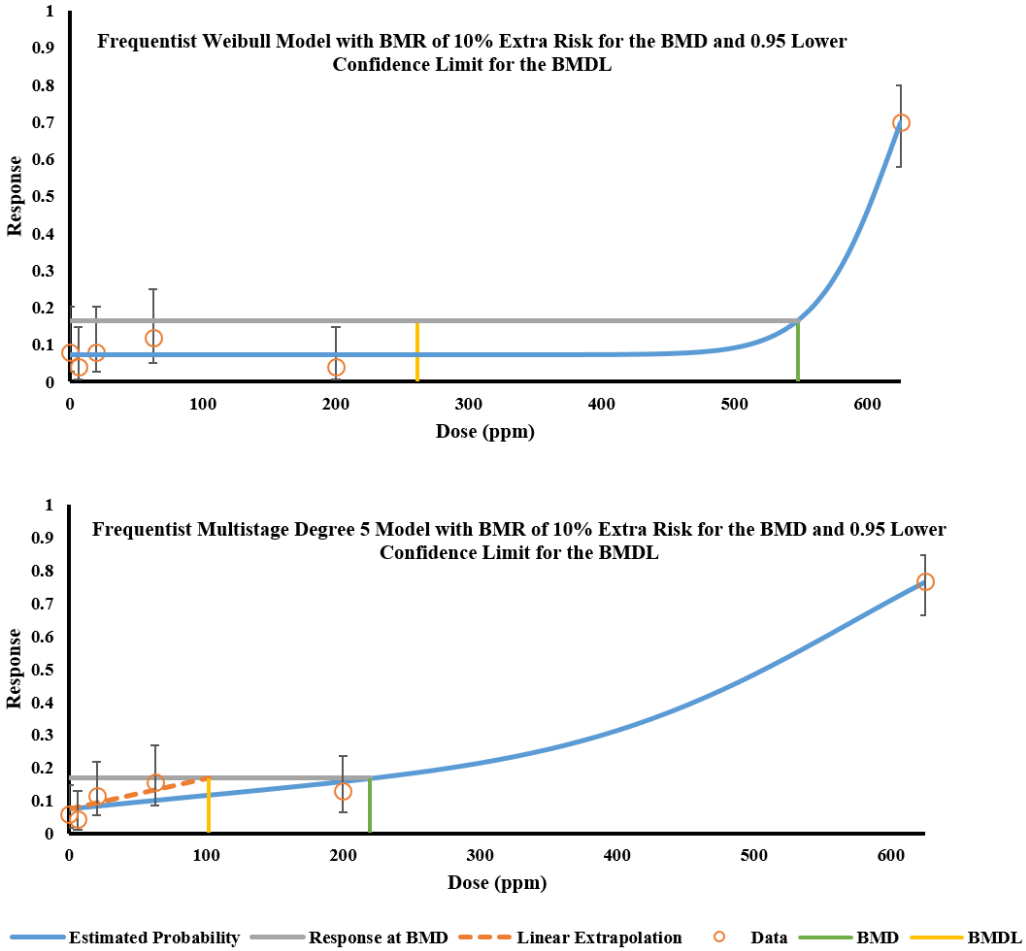

Figure 2. Dose-response curves in male mice based on carcinogenic effects in the study of NTP and Melnick et al.

lower than those obtained from the NTP study. However, the BMDL10 for female mice was lower in NTP. In the NTP study, BMDL10 levels were higher in male than female mice, whereas Melnik's study found opposite findings. By selecting the lowest BMDL10 for male and female mice and using an uncertainty factor of 45 in OELI and a margin of 12500 in OELII, the exposure limits were calculated (Table 2).

4. Discussion

BD is mainly employed in the production of synthetic rubbers and polymers, which are found in an extensive range of industrial and consumer products (Humans, 2008). BD is considered highly likely to be carcinogenic and genotoxic to humans (Hughes et al. 2003). Epidemiological evidence from the styrene-BD and BD monomer industries demonstrates conclusively an increased risk for hematolymphatic cancers (Delzell et al. 1996; Sielken Jr and Valdez-Flores 2001). The genotoxic metabolites 1,2-epoxy-3-butene (EB), 1,2-dihydroxy-3,4-epoxybutane (EBD), and 1,2,3,4-diepoxybutane (DEB) are responsible for the mutagenicity and carcinogenicity of BD. The DNA-reactive compounds EB, EBD, and DEB form a variety of adducts (Albertini et al. 2010). EBD may be an important metabolite and has been indirectly identified by DNA and hemoglobin adducts. (EPA 2002).

For genotoxic carcinogens, it is considered that there is no threshold at the cellular or molecular level. DNA-reactive genotoxic carcinogens may have a practical threshold, primarily as a result of protective mechanisms such as metabolic inactivation and DNA repair (Blum et al. 2023). In this study, this assumption was investigated using threshold and non-threshold approaches. In the threshold approach, using the lowest BMDLs and an uncertainty factor of 45, an OELI of 2.3 ppm in males and 3.8 ppm in females was estimated. This uncertainty factor is close to the uncertainty factor recommended in the Kirman et al.

Table 2. Occupational exposure limits in two approaches.

Sex	BMDL10 (ppm)	UF	OELI (ppm)	OEL II (ppm)
Male	102.2	45	2.3	0.008
Female	170.0	45	3.8	0.014

study (Kirman et al. 2022). In the non-threshold approach, the OELII of 0.008 ppm and 0.014 ppm was calculated for males and females, respectively, which was much smaller than the values obtained in the threshold approach. The non-threshold values are also lower than the recommended OELs by the American Conference of Governmental Industrial Hygienists (ACGIH) (ACGIH 2021) and Occupational Safety and Health Administration (OSHA), which are based on carcinogenic effects. However, the lowest value obtained in the threshold approach (2.3 ppm) was close to the TLV-TWA of ACGIH (ACGIH 2021).

In Albertini et al. study, the NOAEL for mutagenicity (chromosome aberrations and gene mutations) in humans was 0.8 ppm TWA (Albertini et al. 2007). A slightly higher NOAEL of 2.0 ppm has been observed for genotoxicity in exposed Chinese workers (Hayes et al. 2000; Hayes et al. 1996). These results are consistent with our study. In other occupational studies, myelotoxicity was observed in workers exposed to high concentrations of BD (Cheng et al. 2007; Graff et al. 2005).

The corresponding chronic exposure level of BD, resulting in an extra cancer risk of $10-6$ (i.e., 1 in a million) was estimated at 0.01 ppb by the EPA (EPA 2002). Therefore, it can be concluded that the use of threshold approaches can lead to a more accurate prediction of carcinogenic risk. The existence of a threshold value for carcinogenicity in humans shows that the default assumption for low-dose linearity may not be useful for estimating human risk (Kirman et al. 2022), and non-threshold approaches provide an unrealistic estimate of risk.

5. Conclusion

In this study, OELs were estimated based on the carcinogenic effects observed in male and female mice using threshold and non-threshold methodologies. First, the POD for existing animal data was determined using the BMD method, followed by extrapolation to the worker population. Comparing the results with the TLVs and carcinogenic risk values determined by the EPA revealed that the threshold values are closer to the safe workplace concentrations (concentrations where no carcinogenic effects have been detected). Consequently, the use of non-threshold approaches results in an inaccurate estimation of carcinogenic risk.

Conflict of interest statement

The authors declare that they have no conflict of interest.

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