MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

TO: File for n-butyl chloride (CAS# 109-69-3)

FROM: Doreen Lehner, Toxics Unit, Air Quality Division

DATE: January 27, 2017

SUBJECT: n-butyl chloride (CAS# 109-69-3) ITSL change in the averaging time from 24 hours to annual

The initial threshold screening level (ITSL) for n-butyl chloride is 1500 µg/m^3 based on an annual averaging time. The ITSL was originally established on 4/18/2005 and is based on a NTP (1986) 2-year gavage study in mice and rats. The critical effects in the NTP study were significantly increased incidences in cytoplasmic vacuolization in the adrenal cortex in male rats; lung alveoli hemorrhage, hemosiderosis, lymphoid depletion, brain hemorrhage, and multi-organ congestion in both male and female rats. The current file review concludes that the averaging time may appropriately be set at annual, as the key study is a 2-year gavage study. Therefore, the averaging time is being changed from 24 hours to annual.

References:

Act 451 of 1994, Natural Resources and Environmental Protection Act and Air Pollution Control Rules, Michigan Department of Environmental Quality.

NTP. 1986. Toxicology and Carcinogenesis Studies of n-butyl chloride (CAS NO. 109-69-3) in F344/N Rats and B6C3F1 Mice (Gavage Studies). National Toxicology Program. NTP Technical Report Series No. 312.

MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

April 18, 2005

TO: File for n-butyl chloride (CAS #109-69-3)

FROM: Anne Kim, Air Quality Division, Toxics Unit

SUBJECT: Screening Level Derivation

The initial threshold screening level (ITSL) for n-butyl chloride is 1.5 x 10^3 µg/m^3 based on a 24-hour averaging time.

The following references or databases were searched to identify data to determine the screening level: U.S. Environmental Protection Agency (EPA) Integrated Risk Information System, Registry for Toxic Effects of Chemical Substances, American Conference of Governmental and Industrial Hygienists Threshold Limit Values, National Institute for Occupational Safety and Health Pocket Guide to Hazardous Chemicals, Environmental Protection Bureau Library, International Agency for Research on Cancer Monographs, Chemical Abstract Service (CAS) - Online (1967 – 2005), National Library of Medicine, Health Effects Assessment Summary Tables, and National Toxicology Program Status Report. There are no occupational exposure limits for n-butyl chloride. The EPA has not established a reference concentration or reference dose for n-butyl chloride. The molecular weight of n-butyl chloride is 92.57 g. The molecular structure of n-butyl chloride is shown in Figure 1.

Figure 1

Background

n-Butyl chloride is a clear, volatile liquid (vapor pressure is 80 mmHg at 20°C) that releases hydrogen chloride in the presence of water via hydrolysis (ChemFinder.com, 2005; NTP, 1986). This compound also rapidly reacts with oxidizing agents. n-Butyl chloride is mainly used as a solvating and alkylating agent in the process of tin stabilizer manufacture and organic syntheses such as butyl cellulose manufacture (NTP, 1986).

Animal Toxicity

The carcinogenic potential of n-butyl chloride was assessed measuring the appearance of lung adenomas in strain A mice (Poirier et al., 1975). Concentrations of 12.9, 32, and 65 mmol/kg were injected i.p. into groups of ten mice per dose per sex 3 times per week for 8 weeks. Sixteen weeks after the final injection, lungs were examined for the presence of tumors. Control mice developed lung tumors with a mean incidence value of 0.21 per mouse. The positive control mice, treated with a known lung carcinogen, urethan, developed lung tumors at a rate of nearly 1 tumor per mg. The results from lung tumor incidence measures in strain A mice treated with n-butyl chloride were similar to the untreated control; n-butyl chloride did not significantly increase the incidence of lung tumors in mice (Table 1).

Table 1. Lung tumors in male and female mice combined

	0 mmol/kg	12.9 mmol/kg	32 mmol/kg	65 mmol/kg
Lung adenoma	-	3/19	4/19	6/19
Average number of lung tumors per mouse	0.21	0.15 ± 0.04	0.21 ± 0.05	0.31 ± 0.07

An inhalation study was conducted to determine the LC50 value for n-butyl chloride in female Carworth-Wistar rats (Smyth et al., 1954). Six female rats were exposed to a concentration of 8000 ppm n-butyl chloride for 4 hours. Within 11 days, 2 of the 6 rats died resulting in an estimated LC50 value of 2.67 g/kg for n-butyl chloride.

A NTP study (1986) reported the effects of administering n-butyl chloride (>99.5% purity) by oral gavage to F344/N rats and B6C3F1 mice in a series of studies: 14-day, 13-week, and 2-year studies. In the 14-day study, groups of five rats and five mice per sex were exposed daily to 0, 190, 380, 750, 1500, or 3000 mg/kg n-butyl chloride in corn oil. Observations were made twice daily, and weights were recorded daily for rats and on the 1st, 14th, and final day for mice. All rats and mice exposed to 3000 mg/kg, all rats and 3 male and 2 female mice exposed to 1500 mg/kg, and 3 male rats and 1 female rat exposed to 750 mg/kg n-butyl chloride died before the end of the study. Final mean body weights of treated animals were generally lower than control. Convulsions were noted in male rats exposed to 750 mg/kg or more, one female rat exposed to 1500 mg/kg, and 2 male mice exposed to 3000 mg/kg. Hyperactivity was evident in rats exposed to 750 mg/kg or more and in mice exposed to 1500 or 3000 mg/kg. There was no significant reduction in weight that could be attributed to n-butyl chloride administration.

In the 13-week study, groups of ten rats of each sex were given 0, 30, 60, 120, 250, or 500 mg/kg, and groups of ten mice of each sex were given 0, 60, 120, 250, 500, or 1000 mg/kg n-butyl chloride five days per week for 13 weeks. Observations were made twice daily and weights were recorded once a week. Convulsive activity was observed in 5 male rats and 2 female rats exposed to 250 mg/kg, 9 male rats and 8 female rats exposed to 500 mg/kg, and 2 female mice exposed to 1000 mg/kg n-butyl chloride. Final mean body weights showed significant changes between treated and control for rats, but the weights of treated and control mice were comparable. Six male rats in the 500 mg/kg dose group and 1 female in the 1000 mg/kg dose group died before the end of the study from chemical exposure.

The dose regimen for the 2-year study in rats was based on the reduction in weight gain and convulsions observed at 250 mg/kg and deaths in the 500 mg/kg exposure group. Thus, the exposure concentrations of 60 and 120 mg/kg n-butyl chloride were used in the 2-year study in rats. For mice, the doses selected for the 2-year study were based on a lack of effects in male mice and a single death in female mice exposed to 1000 mg/kg n-butyl chloride. Thus, the exposure concentrations of 500 and 1000 mg/kg n-butyl chloride were used in the 2-year study in mice.

In the 2-year study, groups of fifty rats of each sex were given 0, 60, or 120 mg/kg n-butyl chloride, and groups of fifty mice of each sex were given 0, 500, or 1000 mg/kg five days per week for 103 weeks. The mortality rate was excessive in the female mice group treated with 1000 mg/kg n-butyl chloride; all were dead by week 52. Thus, a dose of 250 mg/kg was administered to another group of fifty male and female mice started 13 months after initiation of the original study with another set of control mice. Rats frequently showed symptoms of tremor and convulsion after being gavaged. Survival decreased significantly in the high dose group after week 59 for male rats and after week 41 for female rats, and in the continued male mice group exposed to 1000 mg/kg n-butyl chloride after week 89 for male mice. Male rats showed increased incidence of cytoplasmic vacuolization in the adrenal cortex (vehicle control, 5/50; low dose, 10/50; high dose, 20/50) (Table 2). Female rats, however, did not portray the same dose-related increase (vehicle control, 4/50; low dose, 5/50; high dose, 3/49) (Table 3). The biological significance of this cytoplasmic vacuolization in male rats is not known.

Hemorrhaging of the brain and lung were observed in rats, and these effects were attributed to clinical symptoms commonly associated with death by convulsion. Lymphoid depletion and hemosiderosis of the spleen were other effects seen in high dose rats. Lymphoid depletion is usually apparent in animals kept in prolonged conditions of stress. (Table 2 & Table 3)

Table 2. Male rats nonneoplastic lesions – 2-year study

Toxic Effect	0 mg/kg	60 mg/kg	120 mg/kg
Adrenal cortex – cytoplasmic vacuolization	5/50	10/50	20/50*
Lung alveoli hemorrhage	0/50	2/50	19/50*
Hemosiderosis	6/50	3/50	16/50*
Lymphoid depletion	1/50	1/50	15/50*
Brain hemorrhage	2/49	4/50	18/49*
Multiple organs – Congestion, NOS	2/50	6/50	15/50*

*P≤0.01

Table 3. Female rats nonneoplastic lesions – 2-year study

Toxic Effect	0 mg/kg	60 mg/kg	120 mg/kg
Adrenal cortex – cytoplasmic vacuolization	4/50	5/50	3/49
Lung alveoli hemorrhage	0/50	0/50	26/50*
Hemosiderosis	3/50	3/50	27/50*
Lymphoid depletion	1/50	1/50	24/50*
Brain hemorrhage	1/50	1/50	25/50*
Multiple organs – Congestion, NOS	0/50	1/50	28/50*

*P≤0.01

Mice in high dose groups also convulsed and presented tremors preceded by hyperactivity after dosing by gavage. There were no other significant increases in incidence of toxic effects in mice in the 2-year study.

The NTP report concluded that n-butyl chloride is not carcinogenic in F344/N rats and in B6C3F1 mice chronically exposed to 60 to 120 mg/kg and 250 to 1000 mg/kg, respectively.

Human Toxicity

EPA IRIS (2005) deemed n-butyl chloride as "not classifiable as to human carcinogenicity" based on no carcinogenicity data in humans and inadequate data in animals.

Discussion

Despite the fact that n-butyl chloride is a very volatile liquid, n-butyl chloride has not been extensively studied by the inhalation route. The only inhalation study available came from a range-finding toxicity data list (Smyth et al., 1954), which provided a LC50 value of 2.67 g/kg. n-Butyl chloride was extensively studied, however, in a more robust oral gavage NTP study (1986). The NTP study results can be used to derive a reference dose (RfD) which can then be used to derive an initial threshold screening level (ITSL). The LC50 value obtained from the range-finding study conducted by Smyth et al. (1954) can also potentially be used to derive an ITSL, however, Rule 232(1) lays out the hierarchal resources from which ITSLs should be calculated (Rule 232(1)(a-i). The use of a LC50 value is listed under subrule (f), whereas the use of a RfD is listed under subrule (b). Therefore, the derivation of the ITSL was based on the results of the 2-year NTP study conducted in rats.

The toxic effects of significant increased incidences of cytoplasmic vacuolization in the adrenal cortex in males only, lung alveoli hemorrhage, hemosiderosis, lymphoid depletion, brain hemorrhage, and congestion in multiple organs all occurred at the 120 mg/kg dose level in both male and female rats.

The no-observed-adverse-effect level (NOAEL) is defined by EPA (1994):

> [NOAEL is] an exposure level at which there are no statistically and biologically significant increases in the frequency or severity of adverse effects between the exposed population and its appropriate control. Some effects may be produced at this level, but they are not considered as adverse, nor immediate precursors to specific adverse effects.

Since the biologically significant adverse effect level is 120 mg/kg, the NOAEL for the 2-year NTP study is the lowest exposure concentration of 60 mg/kg.

Note: NOAEL = 60 mg/kg

Derivations of Screening Level

ITSL = RfD x (70 kg)/(20 m^3)

>where RfD = Reference Dose

During the 2-year study, n-butyl chloride was administered 5 days per week for 103 weeks. Therefore, the NOAEL must be adjusted accordingly:

Adjusted NOAEL = 60 mg/kg x (5 days)/(7 days)

Adjusted NOAEL = 42.9 mg/kg

Calculation of RfD:

$$RfD = \frac{NOAEL}{UF}$$

>where RfD = defined above

UF = uncertainty factor

UFs that apply: 1) variation in sensitivity among members of the human population = 10

2) extrapolation from animal data to humans = 10

$$RfD = \frac{42.9\ mg/kg}{10 \times 10}$$

RfD = 0.429 mg/kg

ITSL = 0.429 mg/kg x (70 kg)/(20 m^3)

ITSL = 1.5015 mg/m^3

ITSL = 1501.5 ug/m^3 = 1.5 x 10^3 ug/m^3

Therefore, the ITSL for n-butyl chloride (109-69-3) is 1.5 x 10^3 ug/m^3 based on a 24-hour averaging time.

References

ChemFinder.com – Internet World Wide Web. 2005. Chemical and physical properties for n-butyl chloride. http://chemfinder.cambridgesoft.com/.

IRIS. 2005. 1-chlorobutane CASRN 109-69-3. Integrated Risk Information System. http://www.epa.gov/iris/search.htm.

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Poirier, L.A., Stoner, G.D., Shimkin, M.B. 1975. Bioassay of Alkyl Halides and Nucleotide Base Analogs by Pulmonary Tumor Response in Strain A Mice. *Cancer Research*. 35: 1411 – 1415.

Smyth, H.F., Carpenter, C.P., Weil, C.S., and Pozzani, U.C. 1954. Range-Finding Toxicity Data: List V. *American Industrial Hygiene Association Journal*. 10: 61 – 68.