MICHIGAN DEPARTMENT OF NATURAL RESOURCES & ENVIRONMENT

INTEROFFICE COMMUNICATION

TO: File for 2-N-Dibutylaminoethanol (CAS# 102-81-8)

FROM: Doreen Lehner, Toxics Unit, Air Quality Division

DATE: January 23, 2017

SUBJECT: 2-N-Dibutylaminoethanol (CAS# 102-81-8) change in the averaging time from 24 hours to annual

The initial threshold screening level (ITSL) for 2-N-dibutylaminoethanol is 28 µg/m^3 based on an annual averaging time. The ITSL was originally established on 7/2/2001 and was set at 28 µg/m^3 based on a 24-hour averaging time. The ITSL is based on a 27 week inhalation study on rats by Cornish et al., (1969). The current file review concludes that the averaging time may appropriately be set at annual, as the screening level was derived from a 27 week inhalation study. Therefore, the averaging time is being changed from 24 hours to annual at this time.

References:

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

Cornish HH, Dambrauskas T, Lee DB. 1969. Oral and inhalation toxicity of 2-N-dibutylaminoethanol. American Industrial Hygiene Association Journal. 30(1):46-51.

MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

July 2, 2001

TO: File for 2-N-Dibutylaminoethanol (CAS No. 102-81-8)

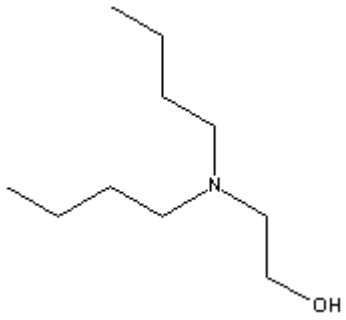
FROM: Michael Depa, Toxics Unit, Air Quality Division

SUBJECT: Development of the Screening Level

The initial threshold screening level (ITSL) for 2-N-dibutylaminoethanol (DBAE) is 28 µg/m³ (24-hour averaging time).

The following references or databases were searched to identify data to determine the screening level: Environmental Protection Agency's (EPA's) Integrated Risk Information System (IRIS), the Registry of Toxic Effects of Chemical Substances (RTECS), the American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Values (TLV), National Institute of Occupational Safety and Health (NIOSH) Pocket Guide to Hazardous Chemicals, Environmental Protection Bureau Library, International Agency for Research on Cancer (IARC) Monographs, Chemical Abstract Service (CAS) Online (1967- May 2001), National Library of Medicine (NLM), Health Effects Assessment Summary Tables (HEAST), and National Toxicology Program (NTP) Status Report. The EPA has not established a reference concentration (RfC) or reference dose (RfD) for dibutylaminoethanol. The ACGIH has established a TLV of 3.5 mg/m³ and NIOSH has established an REL of 14 mg/m³. The molecular weight is 173.3 g, and the molecular formula is $C_{10}H_{23}NO$. The molecular structure is pictured in Figure 1. Dibutylaminoethanol is not water soluble. The boiling point is 224-232^{o} C, and its physical state is a clear colorless liquid. Its vapor pressure in 0.1 mmHg.

Figure 1. Molecular Structure of 2-N-Dibutylaminoethanol (DBAE)



Toxicity Studies

The oral LD50 was determined to be 1.78 g/kg (95% Confidence Interval = 1.33-2.39) (Hartung and Cornish, 1968).

Groups of 5 male Sprague-Dawley rats were gavaged with graded doses of DBAE and observed for 2 weeks (Cornish et al., 1969). At the high dose levels (4 - 8 gm/kg) animals exhibited periods of depression followed by tremors, incoordination, clonicotonic convulsions and death. At lower doses (0.5 - 1.0 gm/kg), animals appeared depressed during the first day. On the day after

dosing, surviving rats appeared normal with the exception of a mild diarrhea. The LD50 value and 95% confidence level of neutralized DBAE was 1.78 (1.33-2.39) gm/kg.

A group of 10 Sprague-Dawley rats was orally exposed to a single dose of 1.2 gm/kg DBAE and the survivors sacrificed 24 hours later (Cornish, et al., 1969). Histopathologic examination included tissue from heart, lung, liver, kidney, adrenal, spleen, duodenum, brain, and testes of surviving animals. The authors stated that there were no differences between control and dosed histopathology.

Groups of 5 male and 5 female Sprague-Dawley rats in each dose group were exposed via drinking water to 0, 0.13, 0.2, or 0.43 mg/kg/day for 5 weeks (Cornish, et al., 1969). Weight loss occurred in both male and female rats during the 1st two weeks of dosing. Drinking water consumption was also decreased. Subsequent growth rates were comparable to control rats although no dose group completely overcame its original weight loss. Liver weights were not significantly affected by DBAE, however, relative kidney weight increased in both male and female rats ($p< 0.01$) at the 0.43 mg/kg/day dose. Relative kidney weight also increased ($p<0.05$) in the 0.2 mg/kg/day males. The authors stated that histopathologic examination of the heart, lung, liver, kidney, adrenal, spleen, and duodenum were not different from controls.

In several inhalation studies, groups of 5 male Sprague-Dawley rats were exposed to 0, 22, 33, or 70 ppm DBAE for 6 hours per day, 5 days per week various exposure durations (Cornish, et al., 1969). The 4 groups dosed with 0 ppm (controls) were exposed for 1, 4, 15, and 27 weeks, after which the animals were sacrificed. The 4 groups dosed with 22 ppm groups were exposed for 1, 4, 15, and 27 weeks, then sacrificed. The 1 group dosed with 33 ppm was exposed for 1 week. The 1 group dosed with 70 ppm was also exposed for 1 week. Hematocrit, white blood cell count, serum bilirubin and organ weights ratios were determined. The tissues were also taken for histopathological examination. RESULTS: Approximately four hours after the beginning of exposure to 70 ppm of DBAE, animals had tremors, in many cases, progressing to convulsive seizure. Eye and nasal irritation was evident, accompanied by a marked chromodacryorrhea. On subsequent days of exposure, mild tremors were evident and one death occurred on the fourth day. Eighteen hours after the fifth exposure, the animals were sacrificed. Body weight was decreased, but relative liver and kidney weight was increased. Statistical analysis was not indicated. The one-week exposure to 33 ppm resulted in essentially a maintenance of original weight but no growth. The authors stated that animals at 33 ppm appeared essentially normal except for some occasional rubbing of the nose, suggestive of mild irritation. The authors stated that liver to body weight ratios were normal, while kidney to body weight ratios were slightly elevated. The authors stated that other findings were not significant. The data obtained during the 6-month (27 weeks) daily exposure to approximately 22 ppm of DBAE showed no clinical symptoms of exposure. Biological endpoints that were recorded included body weight percent change, relative liver and kidney weights, serum bilirubin, clotting time white blood cell count and hematocrit. Kidney to body weight ratios were somewhat elevated at the end of the first week and serum bilirubin levels were higher than controls in 3 of the 5 rats sacrificed at this time. By the end of the 4th week of exposure, total body weight gain was comparable to the controls and all other criteria were essentially normal. However, the kidney to body weight ratio was slightly elevated (0.66 in controls vs. 0.72 in 22 ppm dose group). No further significant changes occurred in these animals throughout the 6-month exposure period, and at sacrifice all biological measurements were comparable to those of the control group. The authors stated that histopathological sections of the organs from animals exposed for 6 months were not different from the controls. It was not evident from reading the report exactly which organs were examined histopathologically. The reporting of organ weights was limited to liver and kidney.

Basis of ACGIH TLV

The ACGIH TLV was based on the Cornish et al. (1969) study cited above. ACGIH stated that,

> In view of the no-observed-effect level (NOEL) of 22 ppm in a 6-month study in rats and considering that DBAE has an approximately tenfold greater toxicity than diethanolamine (DEA), a TLV-TWA for DBAE of 0.5 ppm is recommended. This exposure limit is believed to be sufficiently low to minimize the potential for adverse systemic effect. Information is not available to judge whether 0.5 ppm will protect against irritation.

Derivation of Screening Level

It was determined that the Cornish et al. (1969) study was adequate to derive an RfC. The dose of 22 ppm (155.9 mg/m³) was determined to be a NOAEL. Since DBAE is relative insoluble in water it was determined to be a Category 3 gas. There was no information concerning the blood gas partition coefficient for DBAE, therefore, the human equivalent concentration is the same as the duration adjusted concentration. The RfC was calculated as follows:

$NOAEL_{adj}$ = NOAEL x (6 hours per day)/(24 hours per day) x (5 days per week)/(7 days per week)

$NOAEL_{adj}$ = 155.9 mg/m³ x 6/24 x 5/7

$NOAEL_{adj}$ = 27.8 mg/m³

RfC = $(NOAEL_{adj})/(UF_1 \times UF_2 \times UF_3)$

Where the UF_1 is an uncertainty factor for animal to human extrapolation (interspecies variability), UF_2 is for sensitive individuals (intraspecies variability) and UF_3 is for subchronic to chronic exposure duration extrapolation.

RfC = (27.8)/(10 x 10 x 10)

RfC = 0.0278 mg/m³

RfC = 28 µg/m³

According to Rule 232 hierarchy, specifically subrule (1)(a), the ITSL shall equal the RfC, therefore, the ITSL for 2-N-dibutylaminoethanol (DBAE) is 28 µg/m³ with a 24-hour averaging time.

References

Cornish HH, Dambrauskas T, Lee DB. 1969. Oral and inhalation toxicity of 2-N-dibutylaminoethanol. American Industrial Hygiene Association Journal. 30(1): 46-51.

Hartung R, Cornish H. 1968. Cholinesterase inhibition in the acute toxicity of alkyl-substituted 2-aminothanols. Toxicology and Applied Pharmacology. Volume 12, pages 468-494.

MD:DB
cc: Cathy Simon
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