MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

TO: File for Nitroethane (CAS # 79-24-3)

FROM: Robert Sills, AQD Toxics Unit Supervisor

SUBJECT: Nitroethane ITSL change in the averaging time from 24 hrs to annual

DATE: December 17, 2015

The current ITSL for nitroethane (60 ug/m^3) has a justification (attached) dated January 19, 2005. The averaging time (AT) assigned at that time was 24 hours, as per the default methodology (Rule 232(2)(b)). The current file review concludes that the AT may appropriately be set at annual, based on the nature and duration of the key study and the ITSL value derivation, as allowed under Rule 229(2)(b). Therefore, the AT is being changed from 24 hours to annual at this time.

MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

January 19, 2005

TO: **File for Nitroethane [CAS # 79-24-3]**

FROM: Margaret M. Sadoff

SUBJECT: Derivation of Screening Level

The initial threshold screening level (ITSL) for nitroethane is 60 ug/m3 with a 24-hour averaging time.

INTRODUCTION

A search of the literature and the following databases was performed on June 9, 2004 and updated on January 24, 2005 for information regarding nitroethane: American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Values, National Institute for Occupational Safety and Health (NIOSH) Pocket Guide to Hazardous Chemicals, Integrated Risk Information System (IRIS), CCOHS's Registry of Toxic Effects of Chemical Substances (RTECS), Environmental Protection Bureau Library, International Agency for Research on Cancer (IARC) Monographs, CAS Online (1967 to December 2003), Hazardous Substance Data Bank (HSDB), National Library of Medicine/Toxline, Health Effects Assessment Summary Tables (HEAST), and National Toxicology Program (NTP) Study Database.

Nitroethane (NE) is one of four nitroparaffins produced by the vapor phase nitration of hydrocarbons for use as solvents and liquid propellants. 2-nitropropane is the most toxic of the group by all accounts and is a known carcinogen (ACGIH).

ACGIHs TLV documentation for NE advises that the 100 ppm OEL be used with discretion in light of the significantly lower TLVs for the related chemicals as noted below:

Name	CAS No.	TVL-TWA (ppm)	Basis
Nitroethane	[79-24-3]	100	Irritation, narcosis, liver
Nitromethane	[75-52-5]	20	Thyroid
1-nitropropane	[108-03-2]	25	Irritation, liver
2-nitropropane	[79-46-9]	10	Liver, cancer

Source: ACGIH, 2004

1-nitropropane is the most structurally similar compound with similar toxic effects but has a TLV of 25 ppm compared to 100 ppm for nitroethane. Given the lack of confidence in the TLV for NE, it would not be appropriate to utilize Rule 232(c) for deriving a screening level in this instance. In addition, data of sufficient quality exists from which to derive an RfC pursuant to rule 232(a).

Nitroethane **Nitropropane**

PHYSICAL AND CHEMICAL PROPERTIES

NE is a colorless, flammable liquid with a mild fruity odor. It is slightly soluble in water and has a high vapor pressure. Therefore, NE is expected to exist as a vapor in ambient air (ChemFinder.com). The reported odor threshold for NE is 163 ppm (HSDB, last revised 2002, last reviewed 1994).

RESULTS OF RANGE FINDING INHALATION TOXICITY TESTS IN MULTIPLE SPECIES

(from "A Review of Toxicological Studies on the Nitroparaffins with Particular Emphasis on 2-nitropropane, IMC Chemical Group, Inc., 1977, TOSCA Submission OTS0516799.

Species	Concentration NE Vapor (mg/m3)	Survival Time
Rats	13,000 ppm (39,877)	6-7 hrs
Rabbits	2,500 ppm (7,669) 1,000 ppm (3,067) 500 ppm (1,534)	3 hrs 6 hrs 140 hrs
Guinea Pigs	2,500 ppm (7,669) 1,000 ppm (3,067)	3 hrs 6 hrs
Monkey	500 ppm (1,534)	140 hrs

Liver damage was observed in all animals expiring shortly after exposure. Pulmonary congestion accompanied mortality at the larger dose ranges.

The LD50 in Sprague-Dawley rats was reported to be 1625 $\pm$ 193 mg/kg. Liver damage was apparent in all surviving animals at sacrifice 14 days post-exposure.

MUTAGENICITY, GENOTOXICITY & REPRODUCTIVE/DEVELOPMENTAL TOXICITY

Ames tests for mutagenicity are negative. Testing in mammalian cell lines is limited and inconclusive. Teratology studies in Swiss mice (11 days) were to a chemical mixture containing NE but no effects were noted (Toxline/DART). Three generation studies in Swiss mice exposed to the same chemical mixture also produced no adverse effects. RTECS lists NE as a mutagen but only one study reported multinucleated spermatids in mice exposed to 1,000 ppm (the DOW study detailed herein).

CARCINOGENICITY

Information on the carcinogenicity of NE in experimental animals is severely limited, while evidence in humans is non-existent. There is no information for this chemical listed in IARC, IRIS or HEAST. A chronic 2-year inhalation study by Griffin reported no increased incidence of tumors in either male or female Long-Evans rats upon exposure to 100 or 200 ppm (310 or 610 mg/m3) NE vapor. NE has not been reported as carcinogenic in rats, but did induce skin fibrosarcomas in male ICR Swiss mice in one study after inhalation exposure to a mixture of diethylhydroxylamine, nitroethane, and diethylamine hydrogen sulfite. (HSDB).

METABOLISM

Distribution studies in experimental animals show rapid elimination of NE, partially via the lungs. Nitroethane is readily converted by glucose oxidase to acetaldehyde, nitrite, nitrate, hydrogen peroxide and dinitroethane (HSDB). NE absorption via inhalation occurs in both the upper and lower respiratory tract producing respiratory and mucous membrane irritation, as well as remote effects (methemoglobinemia, narcosis) (Scott & McKenna 1984; Dow Chemical Co., 1982). Therefore, NE classifies as a Category 2 gas (EPA RfC manual, 1994).

A study was conducted to assess the absorption & excretion of chemical vapors by the upper, lower and intact respiratory tract of male Fischer 344 rats (Stott and McKenna, 1984). The authors report a blood:air partition coefficient for NE as 21 at an exposure concentration of 1,000 ppm with an obligate nose-only breathing apparatus set to deliver vapor at the normal average respiratory minute volume of rats (53+/- 3 ml/min). Percent absorption reported for the upper, lower and intact rat respiratory tract, respectively, was 64.8%, 71% and 58%. The percent excreted by the upper and lower respiratory tract was 2.8% and 2.0%, respectively. It was reported that NE did not appear to undergo extensive metabolism in the upper respiratory tract and its absorption was linear over a 10-fold exposure concentration range (up to 1,000 ppm).

ACUTE AND SUBCHRONIC EFFECTS FROM INHALATION EXPOSURE TO NE

The following acute effects in experimental animals exposed to high concentrations of NE (1,000 to 4,000 ppm) have been reported by various groups: methemoglobinemia, cyanosis, narcosis, liver damage, eye and respiratory irritation, dyspnea and coughing.

The recommended NIOSH REL and OSHA PEL for NE is 100 ppm (310 mg/m3) and is a value derived to minimize the potential for skin, mucous membrane, and upper respiratory tract irritation. Repeated inhalation by humans in excess of 500 ppm (1530 mg/m3) has been

reported to produce narcosis and liver damage. (ACGIH, 2004). Additionally, NIOSH has set an IDLH value at 1,000 ppm. Clinical case studies have reported methemoglobinemia in children who accidentally ingest artificial nail remover which contains NE.

DOW range-finding toxicity tests of the nitroparaffins have reported varying degrees of methemoglobin found in blood, with 2-nitropropane being most toxic for the effect (up to 80% found), followed by 1-nitropropane (4-10%), then nitroethane (< 3%) and nitromethane (< 1%) (DOW TsCA submission). Rats exposed to NE via inhalation to 500-550 ppm for 6 hour intervals for 2-3 weeks were not found to be methemoglobinemic. This finding is in contrast with the subchronic study (detailed later), which found minimal changes in methemoglobin levels in rats at 100 ppm after 13 weeks of exposure. However, differences in the timing of the blood collection post-exposure or strain of rat utilized could account for this discrepancy. Dow reported that the timing of the blood extraction for methemoglobin testing (e.g., directly after exposure vs. several hours after exposure) can influence results and lead to erroneous conclusions about effect levels.

CHRONIC INHALATION STUDIES IN EXPERIMENTAL ANIMALS

There are no reports of chronic exposure to NE in humans. In general, chronic inhalation studies have shown inflammation and degenerative changes in the olfactory epithelium of rats, at exposure concentrations above the OEL of 100 ppm (HSDB).

There are two studies of sufficient quality from which a reference concentration could be derived pursuant to Rule 232(a).

1) (TOSCA submission EPA OTS0539250, Dow Chemical Co., submitted 4/21/92)

A subchronic inhalation study was conducted in male and female rats (M/F Fischer 344) and mice (M/F B6C3F1) exposed to 0 ppm (0 ug/m3), 100 ppm (300 mg/m3), 350 ppm (1000 mg/m3), or 1,000 ppm (3,000 mg/m3) NE for 6 hrs/day, 5 days/wk for 13 weeks (15/sex/exposure group). Only the rat results will be reported here since rats were the more sensitive species in this study. Five animals/sex/exposure group were sacrificed and examined after 30 days of exposure (interim kill) while the remaining 10 animals/sex/exposure group were exposed for a full 13-week period from which 5/sex/exposure group were sacrificed and examined (terminal kill). The test material was relatively pure (97%+) but did contain traces of paraldehyde, 2-nitropropane (1.5% max) and nitromethane (1% max). Clinical observations as well as the following parameters were reported: body weights, organ weights, blood parameters including methemoglobin determination, clinical chemistry (enzyme levels), urinalysis, gross pathology and histopathology.

Rats exposed to 1000 ppm exhibited multiple adverse effects including decreased weight gain, elevated methemoglobin levels associated with cyanosis, changes in various blood parameters and blood synthesis (secondary to methemoglobinemia), hepatocellular vacuolization, splenic congestion, degenerative and inflammatory changes in the nasal epithelium, and cellular changes in renal and salivary gland epithelium. Rats exposed to 350 ppm NE exhibited similar but less severe effects in body weights, methemoglobin levels, spleen, nasal turbinates and salivary glands. It should be noted that the animal randomization procedure used in this study did not assure equal group mean body weights prior to the study initiation, however, the authors report obvious growth retardation among males and females in the 350 ppm and 1,000 ppm groups. Rats in the 100 ppm group exhibited minimal changes (not statistically significant) in

methemoglobin levels, spleen, and nasal turbinates and transient effects on salivary gland epithelium. Methemoglobin levels in all treatment groups and both sexes were observed to be dose-dependent. Blood for this parameter was collected 19 hours post-exposure prior to the interim kill and at timed intervals prior to the terminal kill (immediately post-exposure, 4 hours post-exposure and 19 hours post-exposure). At 19 hours post-exposure, only rats in the 1,000 ppm exposure group showed statistically significant increased methemoglobin levels as compared to controls. There were no spontaneous deaths of rats during the 13 week study.

A LOEL of 100 ppm (300 mg/m3) was reported in this study for rats and mice.

Methemoglobin formation and minimal changes in salivary gland epithelium were the most sensitive effects in rats inhaling 100 ppm NE. Both effects were reversible. Mice exhibited similar effects at the corresponding exposure levels but the changes were much less severe. The only unique finding in mice was in the 1000 ppm exposure group in which multinucleated spermatids in the testes were present. No other studies have reported reproductive or genotoxic effects in any species from inhalation exposure to NE.

2) Griffin et al. (1988) Chronic Inhalation Exposure of Rats to Vapors of Nitroethane. ECOTOXICOLOGY & ENVIRONMENTAL SAFETY 16, 11-24.

A chronic inhalation study was performed in which 121 male and 119 female Long-Evans rats (approximately 40/sex/group) were exposed to vapors of nitroethane at concentrations of 0, 100, or 200 ppm (**0, 263, 525 mg/m3***), 7 hrs/day, 5 days/wk for 2 years via whole body inhalation. The test material was 97.9% pure containing traces of nitromethane (0.01%) and 2-nitropropane (2.07%). The animals were observed daily for general appearance and signs of pharmacologic, behavioral, or other general toxic effects of NE. Animals were weighed weekly during the first 6 months of the study and bi-weekly thereafter. At terminal sacrifice, an array of tests on blood parameters and blood chemistry were performed on 10 animals of each sex. Notably absent from this panel was a methemoglobin determination.

(*Concentrations in mg/m3 are slightly different from the straight conversion because they were adjusted to account for the altitude of the experimental site in New Mexico)

Full necropsies were performed on all animals found dead or sacrificed moribund during the study and on all animals surviving the two year study period. A thorough gross examination was performed and the following organs were weighed: brain, liver, kidneys, lungs and heart. Microscopic examination of numerous tissues was performed including reproductive organs. The liver was scrutinized since it is a common target organ of related nitroparaffins and a known target organ of high-level 2-nitropropane exposure. Appropriate statistical tests were used to interpret test results.

Animals displayed no overt signs of toxicity as noted by general observations during the study period and survival was approximately equal among the control and exposed groups. Oddly, the highest percentage of survival for both sexes was in the highest exposure group (M = 50% control, 47.5% 100 ppm, 58.5% 200 ppm and F= 42.5% control, 42.5% 100 ppm, 64.1% 200 ppm). Mean body weights of exposed animals were generally lower than control animals; however, the lack of a well-defined dose-response relationship makes it difficult to attribute this finding to a treatment-related effect. The authors cite the fact that control animals were not housed in exposure chambers during the exposure periods as a possible explanation for the weight differences observed (stress-related effects of experimental animals being placed in exposure chambers).

Results of hematology showed no effect of exposure to 100 or 200 ppm in either male or female rats at the selected probability level of 0.05. Serum chemistry findings revealed a slight but significant elevation of total protein in the female high exposure group as compared to controls and a statistically but not biologically significant difference in BUN between females in the high exposure group and controls.

A statistically significant difference (at p=0.05) in relative kidney weights was found between females in the low exposure group and controls but not between the high exposure group and controls. Likewise, in males, absolute but not relative brain weights displayed statistically significant differences (at p=0.05) between the low exposure and control group but not between the high exposure and control group. Relative brain weights in females displayed statistically significant differences (at p=0.05) between controls and both exposure groups. These differences in relative female brain weights were attributed to differences in total body weight among females. Overall, the authors conclude that NE does not have any biologically significant effect on organ weights.

There were no significant dose-related pathology findings. Only age-associated endocrine tumors and nodular hyperplasia of the liver were noted, though rarely, and these changes occurred in all groups. Emphasis of the histopathological examination was on neoplastic changes in all tissues. Liver tissue and enzymes were also scrutinized. Notably, there were no effects of NE at the tested concentrations on gross and microscopic pathology of the liver nor were there changes in liver weight. In addition, there was no elevation of serum transaminases which is an indication of chemically induced liver injury. This seemingly complete lack of toxicity on the liver was a surprising finding since a related compound, 2-nitropropane, is known to cause liver toxicity and carcinogenicity and nitroethane at acutely high concentrations has been reported to cause liver damage.

Griffin et al. did not study nor report effects on olfactory epithelium or on blood methemoglobin levels. In contrast, the DOW study reported olfactory effects (reversible changes in nasal turbinates) and increased methemoglobin levels (also reversible) at similar exposure concentrations.

<u>Summary Findings in both sexes exposed to 100 or 200 ppm NE:</u>

- No pharmacologic effects
- No effect on mortality
- Likely no effect on body weights since there was no discernible dose-relationship
- No effect on blood parameters (however, methemoglobin levels were not determined)
- No biologically significant differences in serum chemistry parameters
- No biologically significant difference in organ weights
- No significant differences in neoplastic or non-neoplastic pathology

Therefore, the authors report a free-standing NOEL of 200 ppm (525 mg/m3).

EVALUATION OF THE DATA

The DOW study yielded a LOEL of 100 ppm (300 mg/m3) while the Griffin study yielded a NOEL of 200 ppm (525 mg/m3). Normally a chronic study with a NOEL would take precedence over a subchronic study with a LOEL. However, the Griffin study has certain limitations such as leaving out a key parameter in NE toxicity – namely, increased blood methemoglobin levels. An increase in blood methemoglobin level may not be considered strictly as an "adverse" effect since a) it is reversible and b) a threshold methemoglobin level would need to be exceeded in order for any adverse overt clinical effect (e.g. methemoglobinemia, narcosis) to be manifested. Changes in blood methemoglobin levels would be considered a "pre-clinical" sign of potential adverse effect. Such transient effects are generally not the subject of chronic studies.

In addition, Griffin et al. (1988) report a NOEL even though there were statistically significant findings (though slight) with regard to certain parameters. They concluded that there were no effects based on the fact that these differences had no biological significance, coupled with the lack of a dose-response relationship. Although this chronic study seems to have merit and is frequently cited by other researchers, the absence of a known important parameter, coupled with the fact that there were no biologically significant effects noted throughout the entire two-year period makes it less informative. The Dow study reported effects (minimal) at a lower exposure level than the Griffin NOEL, therefore, it is the more conservative study on which an ITSL should be based.

The Dow study is a 13-week subchronic inhalation study that examined important parameters such as blood methemoglobin levels and changes in the olfactory nasal epithelium. Dow used three exposure levels (as opposed to Griffin's two) and reported effects in both rats and mice at the 100 ppm exposure level. It should be noted that these studies utilized different rat strains, which may account for the differences in toxicity results. The Dow study used Fischer 344 rats while the Griffin study used Long-Evans rats. The Dow study is more appropriate because its test animal strain was more sensitive and it utilized a broader range of exposure concentrations above the TLV. Calculations using both studies' results are presented below for comparative purposes.

The following equation is used to calculate a human equivalency concentration (HEC) for the extrarespiratory effects of Category 2***** gases:

NOAEL [HEC] (mg/m3) = NOAEL (adj)/ UF

NOAEL (adj) =

exposure level (mg/m3) X # of hours per day (h/24 hr) X # of days per week (days/7 days) X $\frac{(Hb/g)\ A^{**}}{(Hb/g)\ H}$

***Since the default equation for extrarespiratory effects of Category 2 gases in EPA's RfC Manual is incorrect, the default equation for Category 3 gases is used as a surrogate equation for the extrarespiratory effects of Category 2 gases.**

****Refers to the ratio of animal to human blood:gas partition coefficients for the chemical which, when unknown, defaults to 1. Although the blood:air partition coefficient for NE in rats has been reported, the partition coefficient in humans has not.**

A) Calculated ITSL Using Dow LOEL of 300 mg/m3:

$\frac{300 \times 6/24 \times 5/7}{900}$ = 0.0595 mg/m3 or 59.5 ug/m3 **≈60 ug/m3**

UF = 3 for LOEL to NOEL because the effects noted were minor and reversible and not reported in the chronic study.
10 for animal to human
10 for human to sensitive human
3 for subchronic to chronic because the subchronic study reported effects whereas the chronic study reported a free-standing NOEL without evaluation of the critical effect.

B) Calculated ITSL Using Griffin NOEL of 525 mg/m3:

$\frac{525 \times 7/24 \times 5/7}{300}$ = 0.365 mg/m3 (rounded) or **365 ug/m3**

UF = 10 for animal to human
10 for human to sensitive human
3 for lack of methemoglobin & olfactory epithelium parameters

The RfC derived by method "A" was used to establish the ITSL, pursuant to Rule 232(1)(a).
The ITSL for nitroethane is 60 ug/m3 with a 24 hour averaging time.

REFERENCES

Primary

1) ToSCA Initial Submission: Nitroethane: A 4-day and 13-week inhalation study in rats and mice with cover letter dated 042192, USEPA/OPTS Public Files, Microfiche # OTSO539250, Produced 02/09/82, Received 04/30/92, Dow Chemical Company.

2) Griffin TB, Stein AA & Coulston F. (1988). Chronic Inhalation Exposure of Rats to Vapors of Nitroethane. Ecotoxicology and Environmental Safety 16, 11-24.

Secondary

1) Stott WT and McKenna MJ. (1984). The comparative absorption and excretion of chemical vapors by the upper, lower and intact respiratory tract of rats. Fundamental & Applied Toxicology 4: 594-602.
2) ToSCA Submission: A Review of Toxicological Studies on the Nitroparaffins with Particular Emphasis on 2-Nitropropane. USEPA/OPTS Public Files, Microfiche # OTS0516799, Produced 4/22/77, Received 6/5/89, IMC Chemical Group, Inc.