MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

TO: File for Nitromethane (CAS # 75-52-5)

FROM: Robert Sills, AQD Toxics Unit Supervisor

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

DATE: September 9, 2015

The current ITSL for nitromethane (70 ug/m^3) has a justification (attached) dated May 29, 2008. 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

TO: Memo to File for Nitromethane [CAS# 75-52-5]

FROM: Margaret M. Sadoff, Toxics Unit

DATE: May 29, 2008

SUBJECT: Update of Interim ITSL and IRSL/SRSL Development

A search of the literature and the following databases was performed for information regarding nitromethane: American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Values, National Institute for Occupational Safety and Health (NIOSH) Pocket Guide to Hazardous Chemicals, EPA Integrated Risk Information System (IRIS), EPA High Production Volume Information System, Registry of Toxic Effects of Chemical Substances (RTECS), Environmental Protection Bureau Library, International Agency for Research on Cancer (IARC) Monographs, CAS Registry Online, Hazardous Substance Data Bank (HSDB), National Library of Medicine/Toxline, National Library of Medicine ToxSeek, Health Effects Assessment Summary Tables (HEAST), National Toxicology Program (NTP) Study Database, Entrez PubMed, Scirus, IPCS Intox Databank and CalEPA's Toxicity Values Database

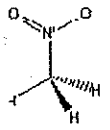
General Information
(Source: ChemInfo, Toxline HSDB, Report on Carcinogens, 11th ed.)

Nitromethane is a colorless, oily liquid with a moderately strong disagreeable odor which falls into the class of chemicals known as nitroparaffins. It has a vapor pressure of 27.8 mmHg at 20C and, therefore, will rapidly volatilize. It is slightly soluble in water (95 mL/L at 20C), acetone, carbon tetrachloride, ethanol, and diethyl ether. Nitromethane is highly flammable with a flash point of 35C and reacts with alkalis, strong acids, oxidizers, and metallic oxides. Hazardous decomposition products are nitrogen oxides. In the atmosphere, nitromethane will degrade by photolysis with a half-life approximately of approximately 4-9 hrs.

Nitromethane (NM) is used as a chemical intermediate in the synthesis of many useful compounds such as pesticides, fumigants, and even an anti-ulcer drug. It is also used as a stabilizer and a solvent in other industrial processes. It is a component of rocket and racing car fuels and has been used in explosives and propellants by the military (e.g. RDX). When produced commercially by high temperature vapor-phase nitration of propane, the reaction yields a mixture of nitromethane, nitroethane, 1-nitropropane and 2-nitropropane.

Exposure to NM may cause eye and respiratory tract irritation, CNS depression, lung edema, and narcosis at higher concentrations. Human exposure occurs largely in occupational settings by inhalation and dermal contact. The general population is exposed

primarily by inhalation from auto exhaust and cigarette smoke. The odor threshold has been reported as 100 ppm (250 mg/m^3) and the irritation threshold at 200 pm (500 mg/m^3).



MW = 61 1 ppm = 2.49 mg/m^3

General toxicity

Noted human health effects include respiratory and mucous membrane irritation, CNS depression, dermatitis, anorexia, nausea, vomiting, diarrhea, cough, dizziness, and headache. Experimental animals have developed focal necrosis of the liver and kidney, depressed hemoglobin and hematocrit concentrations, decreased weight gain, weakness, ataxia, and seizures. Methemoglobinemia and anuria are rare effects of exposure to both nitromethane and nitrocellulose. Evolved oxides of nitrogen may cause acute bronchiolitis or pulmonary edema.

Lethal Values as reported in RTECs	Species	Value
	rat LD50	940 mg/kg
	rat LC50	12,750 mg/m^3 (1 hr)
	mouse LC50	18,000 mg/m^3 (2 hr)
	monkey LC50	2,500 mg/m^3 (48 hr)
	rabbit LC50	12,500 mg/m^3 (6 hr)
	guinea pig LC50	12,500 mg/m^3 (3 hr)

A probable human oral lethal dose is between 0.5 and 5.0 g/kg (ACGIH, 2001).

Human Toxicity and Occupational Values

Occupational Case Studies Reported Effects: peripheral neuropathy, allergic contact dermatitis.

Odor Threshold – close to OSHA PEL, 100 ppm (250 mg/m^3)
Irritation Threshold – 200 ppm, (500 mg/m^3)

Like most nitroparaffins, nitromethane is a weakly narcotic respiratory irritant that may produce liver damage after prolonged exposure. A TLV-TWA of 20 ppm (50 mg/m^3) is recommended for occupational exposure to nitromethane to reduce the potential for adverse thyroid effects (as reported in rats and rabbits) and degeneration/metaplasia of

olfactory and respiratory epithelium (as reported in mice). This value should also minimize other risks observed in humans and experimental animals subjected to higher concentrations including blood dyscrasias, peripheral neuropathy (humans), decreased sperm counts and decreased sperm motility. The TLV is based on the weight of evidence from several studies including a 1997 NTP bioassay (key study in this report) and a subchronic inhalation study by Lewis et al., 1979. Sufficient data were not available to recommend Skin or SEN notations or a TLV-STEL. *(Source: ACGIH. Documentation of the threshold limit values and biological exposure indices Vol:7th Ed (2001) 7 p).*
Note: this would put the OEL based ITSL at 500 ug/m^3 (8-hr avg) as opposed to the current interim ITSL of 2500 ug/m^3 (8-hr avg). This TLV was not available in 1992 when the interim ITSL was set. It was adopted in 2000.

Dermal Exposure

NTP reports that dermal absorption is negligible, but that conclusion is in contrast with case reports of contact dermatitis and peripheral neuropathy in exposed workers (although these studies are confounded by multi-chemical exposures).

Case Study: Two relatively young, otherwise healthy workers presented with severe peripheral neuropathy 2-6 weeks after employment in a headlight subassembly plant. Their job was to inspect the headlights and wipe off excess glue with nitromethane, which was sprayed onto the headlight. Workers wore aprons and safety glasses, but no gloves or respiratory protection was worn. Loctite Prism 401® is a rapidly drying glue composed of 90-95% ethyl cyanoacrylate, 5-10% methyl methacrylate, and 0.1-0.5% hydroquinone. Symptoms persisted after exposure ceased, which is fairly typical of toxic neuropathies where recovery is slow and sometimes incomplete. Environmental sampling was performed for nitromethane (4 workers) and ethyl cyanoacrylate (6 workers) but not methyl methacrylate. Personal breathing zone concentrations of nitromethane ranged from 10 to 20 ppm as an 8-hour TWA with a mean of 12.75 ppm. The OSHA PEL is 100 ppm and the ACGIH TLV is 20 ppm. Although the measured exposure concentrations do not exceed the OELs, the OELs are based on a 40-hour work week whereas the employees in question worked an average of 55-60 hours per week. Personal breathing zone concentrations of ethyl cyanoacrylate ranged from 0.04 to 0.16 ppm as an 8-hour TWA with a mean of 0.9 ppm. The TLV is 0.2 ppm. Factors which complicate the link between symptoms and nitromethane exposure include: 1) the possibility of mixed exposure to ethyl cyanoacrylate and methyl methacrylate; and 2) the possibility of multipathway exposure (particularly inhalation and dermal absorption). In addition, it is noted that nitromethane is widely used in industry by over 134,000 workers in the U.S. alone, but peripheral neuropathy has never before been reported in association with its occupational use. In any event, the ACGIH includes neuropathy in its list of critical effects of nitromethane as well as irritation, narcosis, liver, thyroid toxicity, and blood dyscrasias. *(Source: Page et al. (2001) Peripheral neuropathy in workers exposed to nitromethane. American Journal of Industrial Medicine, 40: 107-113.)*

Case Study: 4 case studies of female workers aged 24 to 47 at an automobile parts manufacturer who handled an adhesive solvent containing nitromethane, apparently without the use of gloves. All had developed hand dermatitis to varying degrees which resolved

upon cessation of exposure. *(Source: Webb, KG & Fowler JF. (2002) Occupational allergic contact dermatitis to nitromethane. American Journal of Contact Dermatitis, 13(4): 201-202.)*

Occupational Expsure Values:
OSHA PEL = 100 ppm (250 mg/m^3)
ACGIH TLV = 20 ppm (50 mg/m^3)
NIOSH IDLH = 750 ppm (1875 mg/m^3)

Short-Term Exposure in Experimental Animals
(as reported in IARC 77, 2000)

Non-cancer effects from inhalation exposures to M/F Fischer 344/N rats and B6C3F mice at 7 weeks of age for 6 hr/day, 5 days/wk, 12 days (0, 235, 470, 938, 1875, 3750 mg/m^3).

Generally seen in all animals: Hyperactive behaviors (excessive grooming, rapid breathing) were displayed early in the study, while hypoactivity and loss of hind limb coordination was observed toward the end of the study in both sexes. Concentration-related increase in absolute and relative liver weights and minimal to mild degeneration of the olfactory epithelium were observed in noses of rats and mice. Male and female rats in the two highest exposure groups showed sciatic nerve degeneration (reduced myelin around sciatic axons).

Male rats in the highest exposure group showed a slight but statistically significant decrease in mean body weight gain.

Subchronic Inhalation Toxicity in Experimental Animals

M/F Fischer 344/N rats and B6C3F1 mice, 6 wks old, 6 hrs/day, 5 days/wk, 13 wks to evaluate cumulative toxic effects of repeated exposure (0, 235, 470, 938, 1875, 3750 mg/m3 NM). Clinical pathology and neurobehavioral parameters were evaluated. Male rats in the highest exposure group exhibited significantly decreased body weights and body weight gain. Hindlimb paralysis was noted in rats in the two highest exposure groups. Exposure-related microcytic, responsive anemia was also noted in male and female rats. Transient decreases were noted in male and female rats for serum levels of T3, total and T4. Exposure-related minimal to mild hyperplasia of the bone marrow was also noted. Both rats and mice exhibited olfactory epithelial degeneration Main effects: Blood, neurological, and thyroid effects. (Source IARC 77, 2000)

Sub-chronic inhalation toxicity was evaluated in groups of 50 male Sprague-Dawley rats exposed to NM vapor at 1, 100 and 750 ppm for 7 hr/day, 5 day/wk, for 6 months. High dose rats had decreased body weight gain, increased thyroid weights, decreased hematocrit and hemoglobin, slightly increased erythrocyte count, and elevated serum ornithine carbamyl transferase (liver enzyme). (Source: TSCATS Abstract from Huntingdon Research Center, EPA document no. 86-890001529, Fiche no. OTS0520658, 1977.)

Fifty M Sprague-Dawley rats and 15 male rabbits exposed to 0, 98 or 745 ppm (0, 244 or 1859 mg/m3) NM (96.5% pure) and 0, 27 or 207 ppm 2-NP, 7 hrs/day, 5 days/wk, up to 24 wks. Ten rats from each exposure group were sacrificed after 2 days, 10 days, 1 month, 3 months and 6 months. Given that the purpose of this study was to assess the adequacy of the OSHA standards for these two chemicals (NM = 100 ppm), there seems to be a rather wide gap between the low and high exposure groups. Several blood parameters were collected including methemoglobin count. Clinical chemistry included 2 indicators of liver damage and one for thyroxin. All animals that died or were sacrificed underwent a complete necropsy. All organs were observed macroscopically. Liver, kidney, lungs plus trachea, brain and thyroid were weighed. Tissues examined microscopically included adrenals, bronchi, cerebellum, cerebral hemispheres, eyes, kidneys, liver, lung, spleen, thyroid, and trachea. Significant results were: decreased body weight gain in rats after 8 weeks of exposure at highest exp level, increased thyroid weights and decreased serum thyroxine levels (thyroid effects were most notable in rabbits). No exposure related gross or microscopic alternations were noted in any tissues examined in rats and rabbits at any exposure concentration of NM. (Source: Lewis et al, 1979. J Env Path & Tox 2: 233-249. Subchronic Inhalation toxicity of nitromethane and 2-nitropropane).

Chronic Inhalation Studies in Experimental Animals

Griffin TB, Coulston F & Stein AA. (1996) Chronic inhalation exposure of rats to nitromethane. Ecotoxicology & Environmental Safety, 34: 109-117.

Forty M/F Long-Evans rats/sex/group were exposed at 0, 100 or 200 ppm NM vapors for 7/24 hours, 5/7 days for 2 years. Test material contained 96.26% NM, 2.79% NE, and 0.62% 2-NP. Concentrations in the exposure chamber were measured by infrared gas analyzer 3-4 times per day. The grand means for the 100 and 200 ppm exposure concentrations were 99.5 and 199.3 ppm, respectively. At site elevation (New Mexico at 1350 meters) these concentrations equate to 213 and 427 mg/m^3. Note these values are slightly lower than from a straight conversion (1 ppm NM = 2.49 mg/m^3).

Animals were observed daily for appearance, behavior and other general signs of toxicity. Body weights were recorded weekly during the first 6 months and then at 2-week intervals to the end of the study. At terminal sacrifice, 10 male and 10 female rats were tested for a variety of hematology and serum chemistry parameters. Complete necropsies were performed on all animals found dead or sacrificed moribund and on all animals surviving to terminal sacrifice. Absolute and relative organ weights were recorded for brain, liver, kidney, lungs and heart. Histopathology was performed on all major vital and reproductive organs. The liver results were especially scrutinized since hepatocarcinomas have been reported in male rats exposed to 100 and 200 ppm of 2-nitropropane.

No significant differences in mortality were reported. Body weights of exposed male rats did not differ significantly from controls throughout the experiment. For females, decreases in body weight gain in both dose groups became statistically different from controls after 1 year of exposure. However, data is only presented graphically so this endpoint cannot be used for ITSL calculation. No effects on hematology were noted at the 0.05 significance level for either dose group or either sex. There was a statistically significant difference in serum creatinine levels in the 200 ppm group. However, the authors note that the values

appear to be within the normal range for this parameter. In addition, the assay method utilized the Jaffe reaction, which has been reported in the literature to artificially inflate creatinine levels. No significant increases in absolute or relative organs weights were found. The histopathology revealed the usual age-associated degenerative diseases and age-related endocrine target organ response to pituitary hyperplasia.

The incidence of benign tumors was reported to be similar to that generally found in populations of aging laboratory rats. The numbers of individual malignant tumor types were described as being "very small" and "neither the incidence nor distribution was indicative of any relationship to NM exposure." There was no more than an incidence of 2 for any tumor type in males and females and no increase of response with increasing dose. Therefore, this data would not provide a good dose-response curve.

Other Non-Cancer Toxicity Information

Repro/Developmental Toxicity: No developmental toxicity studies are available. There is limited reproductive evidence in rats and mice at high concentrations. A 13-week inhalation study with M/F 344/N rats and B6C3F1 mice, 6 hrs/day, 5 days/wk (938, 1875, 3750 mg/m^3) reported dose related decreases in sperm motility. These results were significant for the two highest exposure groups in rats and all exposure levels in mice. In the highest rat dose group, decreased body weights, cauda, epididymis, and testis were also observed. Female mice had dose-related increases in estrous cycle at all dose levels.
(Source: IARC 77, 2000)

Mutagenicity/Genotoxicity: Negative results have been reported in bacterial mutagenicity tests, *in vitro* mammalian chromosome tests, Drosophila tests, and *in vitro* and *in vivo* micronuclei tests in mammals. A positive response at high concentration (not stated) was observed in a cell transformation assay in Syrian hamster embryo cells.
(Source: IARC 77, 2000)

Dayal et al, (1989) compared the hepatoxic and mutagenic potential of 2-nitropropane, nitromethane and nitroethane and concluded that the primary nitroalkanes are much less hepatotoxic and mutagenic than 2-nitropropane. NM was reported to be not mutagenic or genotoxic based on the weight-of-evidence. Source: Dayal R, Gescher A, Harpur ES, Pratt I, Chipman JK. (1989). Comparison of the hepatoxicity in mice and the mutagenicity of three nitroalkanes. Fundam Appl Toxicol, 13(2): 341-8.

Nitromethane was not mutagenic *in vitro* or *in vivo*. In general, the primary nitroalkanes (nitromethane, nitroethane, 1-nitropropane, 1-nitrobutane and their nitronates have not been observed to be mutagenic while the secondary nitroalkanes tend to be mutagenic.

Evidence of Carcinogenicity

Source: Report on Carcinogens, Eleventh Edition; U.S. Department of Health and Human Services, Public Health Service, National Toxicology Program .

ACGIH classifies as A3, known animal carcinogen with unknown relevance to humans.
IARC classifies as 2B, probable human carcinogen.
NTP lists as "reasonably anticipated to be a human carcinogen."

In the NTP study, clear evidence of carcinogenic activity in rats and mice was observed based on mammary gland fibroadenomas, Harderian gland adenomas and carcinomas, and liver neoplasms, warranting an A3 notation: Confirmed Animal Carcinogen, with Unkhown Relevance to Humans.

Results Summary:

Mice M/F: Lung tumors; Harderian gland tumors (an accessory to the lacrimal gland on the inner side of the orbit in reptiles and birds but degenerate in many mammals (facilitates movement of the third eyelid. Functions of the Harderian gland are: pheromone synthesis and release, photoprotection and thermoregulation, osmoprotection and immune-endocrine.)

Mice F: Liver

Rats (F344/N) F: Mammary gland neoplasms

Rats (F344/N) M: No tumors

Long Evans Rats M/F: No tumors (at similar exposure concentrations to above) Griffin et al 1996.

(From IARC Vol 77, 2000) – A synopsis of the NTP 1997 Inhalation Studies:

1) M/F Fischer 344/N rats, 7 wks old, 98% purity NM (0.25% ME; 0.03% 2-NP), 6 hrs/day, 5 days/wk, 103 wks. (NTP, 1997).

	Exposure Concentrations (mg/m3)			
	0	135	470	938
Female				
Mammary Gland Fibroadenomas (benign)	19/50*	21/50*	33/50*	36/50*
Mammary Gland Carcinomas	2/50**	7/50**	1/50**	11/50**

* $p < 0.001$ logistic regression test
** $p < 0.05$ logistic regression test

2) M/F BLU:(LE)BR Long Evans rats exposed to 0, 250, 500 mg/m3 NM (96.26% pure with 2.79% NE, 0.62% 2-NP), 7 hrs/day, 5 days/wk, 2 yrs. Weight gain in experimental F as slightly decreased as compared to controls. No significant increase in tumor incidence related to test chemical reported (NTP, 1997).

3) M/F B6C3F1 mice, 7 wks old, 98% pure NM (0.25% NE, 0.03% 2-NP), 6 hrs/day, 5 days/wk, 103 wks (NTP, 1997).

	Exposure Concentrations (mg/m3)			
	0	470	938	1875
Males				
Harderian gland adenoma	9/50	10/50	19/50*	32/50**
Harderian gland carcinoma	1/50	1/50	6/50	5/50
Harderian gland adenoma or carcinoma	10/50	11/50	25/50**	37/50**
Alveolar/bronchiolar adenoma	11/50	10/50	9/50	12/50
Alveolar/bronchiolar carcinoma	2/50	3/50	3/50	11/50**
Alveolar/bronchiolar adenoma or carcinoma	13/50	13/50	12/50	20/50
Females				
Harderian gland adenoma	5/50	7/50	16/50**	19/50**
Harderian gland carcinoma	1/50	2/50	4/50	3/50
Harderian gland adenoma or carcinoma	6/50	9/50	20/50**	21/50**
Hepatocellular adenoma	14/50	24/49**	17/49	35/50**
Hepatocellular carcinoma	10/50	14/49	8/49	12/50
Hepatocellular adenoma or carcinoma	19/50	34/49**	22/49	40/50**
Alveolar/bronchiolar adenoma	3/50	3/50	2/49	9/50
Alveolar/bronchiolar carcinoma	0/50	3/50	5/49*	3/50
Alveolar/bronchiolar adenoma or carcinoma	3/50	6/50	7/49	12/50*

* $p \leq 0.05$, logistic regression test
** $p \leq 0.01$, logistic regression test

KEY STUDY:
National Toxicology Program (1997) Toxicology and Carcinogenesis Studies of Nitromethane (CAS No. 75-52-5) in F344 Rats and B6C3F$_1$ Mice (Inhalation Studies). Technical Report Series No. 461, NIH Publication No. 97-3377, Research Triangle Park, NC.

Only significant findings are reported here.

16-day Study in Rats & Mice

Five/sex/group M/F F344/N rats and B6C3F1 mice were exposed to 0, 94, 188, 375, 750, or 1,500 ppm NM via whole body inhalation 6 hrs/day, 5 days/week for 16 days. All rats and mice survived to the end of the study. Mean body weights between control and experimental groups were similar. Notably, there were no exposure-related lesions in the lungs of exposed male or female rats. In rats, minimal to mild degeneration of olfactory epithelium and sciatic nerve degeneration was noted at 375ppm or greater. In male rats, increased absolute and relative liver weights were also observed. Results were nearly identical in mice, with the addition that female mice exhibited absolute and relative liver weights in all dose groups.

13-Week Study in Rats & Mice

Ten/sex/group M/F F344/N rats and B6C3F1 mice were exposed to 0, 94, 188, 375, 750 or 1500 ppm NM via whole body inhalation 6 hrs/day, 5 days/wk for 13 weeks. Additional

groups of 10 M/F rats were similarly exposed for clinical pathology examination on days 3 and 23.

All rats and mice survived to the end of the study. There were no significant differences in mean body weights between exposed and control mice or female rats. Significant results in rats and mice were reported as follows:

	All Doses	94 ppm	188 ppm or greater	375 ppm or greater	750 ppm or greater	1,500 ppm or greater
Male Rat				Minimal increases in methemoglobin; Transient hypothyroid state	Lower sperm motility; Minimal to mild hyperplasia of the bone marrow	Decreased mean body weight and body weight gain; Decreased testes weight
Female Rat			Minimal to mild hyperplasia of the bone marrow		Minimal increases in methemoglobin; Transient hypothyroid state	
Both				Olfactory epithelial degeneration; Decreases in hematocrit and and hemoglobin consistent w/ anemia; Minimal to mild degeneration of spinal cord and sciatic nerve	Hyaline droplet nephropathy & goblet cell hyperplasia	Hindlimb paralysis

	All Doses	94 ppm	188 ppm or greater	375 ppm or greater	750 ppm or greater	1,500 ppm or greater
Male Mice	Increased relative right kidney weights Increased absolute right kidney weights (except 1500 ppm) Decreased epididymal sperm motility			Increased relative liver weights	Increased absolute liver weights	
Female Mice	Increased estrous cycle		Increased absolute right kidney weights		Increased relative right kidney weights	
Both			Olfactory epithelium degeneration (minimal to mild) Respiratory epithelium hyaline droplets (minimal to moderate)			Minimal extramedullary hematopoiesis of the spleen

The most significant effect in rats was neurotoxicity at the highest dose group as evidenced by hind limb paralysis, loss of grip strength and sciatic nerve and spinal cord lesions. Also notable were olfactory, spinal cord and sciatic nerve degeneration at 375 ppm. In mice, the most significant effect was incidence and severity of nasal lesions at 188 ppm. These effects were used to determine dosing concentrations for the two year studies.

2-Year Study in Rats and Mice

Fifty M/F F344/N rats per group were exposed via whole-body inhalation to 0, 94, 188 or 375 ppm NM 6 hrs/day, 5 days/wk for 103 weeks. There were no significant differences in survival rates or mean body weights between control and experimental groups.

*Mammary Gland Neoplasms In Female Rats: Incidence of combined mammary gland neoplasms (fibroadenoma, adenoma, carcinoma) increased with increasing exposure concentration and incidences in the 188 and 375 ppm groups were significantly greater than controls (21/50, 25/50, 34/50, 41/50). Additionally, incidences of fibroadenoma and carcinoma exceeded the ranges of incidences for these neoplasms in historical, untreated, NTP chamber controls.

There were no tumors of biological or statistical significance in male rats at any site.

Fifty M/F B6C3F1 mice per group were exposed by inhalation to 0, 188, 375 or 750 ppm NM 6 hrs/day, 5 days/wk for 103 weeks. Survival rates and mean body weights were similar between exposed and control groups. Clinical findings were swelling around the eyes and exophthalmos (protrusion of eyeballs from the socket) in exposed M/F mice, consistent with harderian gland neoplasms.

Harderian Gland Neoplasms: Although not relevant to humans, incidence of harderian gland adenoma and adenoma/carcinoma combined increased with increasing exposure and were significantly greater in M/F mice at 375 ppm and 750 ppm. The incidences of these neoplasms in all exposed groups were greater than historical controls.

Liver Neoplasms: Female mice in the 188 and 750 ppm dose groups had significantly increased incidence of hepatocellular adenoma, hepatocellular adenoma/carcinoma combined, and multiple hepatocellular ademonas than controls. These incidences also exceeded historical controls but the lack of a consistent dose response relationship renders these findings less meaningful.

Lung Neoplasms: The incidence of alveolar/bronchiolar carcinoma in male mice in the 750 ppm group was significantly greater than experimental and historical controls. The incidence of alveolar/bronchiolar adenoma and alveolar/bronchiolar adenoma/carcinoma combined in female mice in the 750 ppm group were greater than experimental and historical controls.

Non-neoplastic Lesions of the Nose: Increased degeneration and metaplasia of olfactory epithelium were noted in both M/F exposed mice (minimal to mild). Hyaline degeneration of the respiratory epithelium was also observed.

Weight of Evidence from all NTP Studies: Short-term target organs are nasal epithelium, nervous tissue, thyroid and blood. Results of carcinogenic activity were reported as follows:

Male rats: No evidence
Female rats: Clear evidence of mammary gland fibroadenomas and carcinomas

*Male mice: Clear evidence of harderian gland adenomas and carcinomas
*Female mice: Clear evidence of liver neoplasms (adenomas);
harderian gland adenomas and carcinomas

*Increased incidences of alveolar/bronchiolar adenomas and carcinomas in male and female mice were considered to be related to chemical exposure but were not given a carcinoneginc activity rating.

Chronic non-neoplastic effects in male and female mice were degeneration and metaplasia of nasal and olfactory epithelium at 188 ppm. No significant chronic non-neoplastic effects were noted in male or female rats.

Screening Level Derivation

ITSL
Non-cancer effects identified from both the 13-week and 2-year NTP studies converged on a LOAEL of 188 ppm; most notably, olfactory and respiratory epithelium degeneration in male and female mice. This endpoint was not amenable to benchmark dose methodology since all animals in the two highest dose groups developed lesions, which resulted in an uninformative dose-response curve. The traditional RfC NOAEL/LOAEL approach was used to derive the screening level:

LOAEL = 188 ppm = 468 mg/m^3

LOAEL Adj = 468mg/m^3 x 6hr/24hr x 5d/7d = 84 mg/m^3

LOAEL HEC = 84 mg/m^3 x RDGR mice (0.24) = 20 mg/m^3
Extrathoracic adjustment = RGDR for category 1 gases
$(V/SA)_{mice}$ / $(V/SA)_{human}$
(0.05 L/min / 3cm2) / (13.8 L/min / 200cm2) = 0.24

ITSL = 20 /300 = 0.067 mg/m^3 = ~ **70 ug/m^3, 24 hour**

Total UF 300 =
10 (intraspecies)
3 (interspecies – reduced due to use of RDGR)
10 (lack of NOAEL)

IRSL
Mammary gland tumors in female rats was chosen as the appropriate cancer endpoint since these tumors gave the clearest dose/response curve and also were significant at lower exposure concentrations.

Benchmark dose Values with a BMR of 0.1 are:
BMDL = 60
Multistage Cancer Slope Factor = 0.00164085

1 E-06
1.6 E-03 = 6.25 E-04 x 6/24 x 5/7 = 1.1 E-04 mg/m^3 = 0.1 ug/m^3

IRSL = **0.1 ug/m^3, annual** for Frat mammary neoplasms (combined fibroadenoma, adenoma, carcinoma). See attached BMD printout.

MS:lh