MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

TO: File for Isobutyraldehyde (CAS # 78-84-2)

FROM: Robert Sills, AQD Toxics Unit Supervisor

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

DATE: December 22, 2016

The ITSL for Isobutyraldehyde is 160 ug/m^3, with annual averaging time.

The ITSL for isobutyraldehyde (160 ug/m^3) was established on March 11, 2005 (see attached). The averaging time (AT) assigned to the ITSL at that time was 24 hours, as per the default methodology at that time (Rule 232(2)(b)). The ITSL was based on a 2-year chronic inhalation bioassay. A total uncertainty factor (UF) of 300 was applied, which consisted of a UF = 3 for interspecies extrapolation, UF = 10 for intraspecies variability, and UF = 10 for LOAEL-to-NOAEL conversion. The current file review concludes that the AT for the ITSL 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 averaging time is being changed from 24 hrs to annual.

MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

March 11, 2005

TO: File for Isobutyraldehyde (CAS #78-84-2)

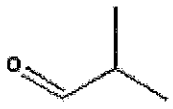
FROM: Anne Kim, Air Quality Division, Toxics Unit

SUBJECT: Screening Level Derivation

The initial threshold screening level (ITSL) for isobutyraldehyde is 160 ug/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 – 2004), National Library of Medicine, Health Effects Assessment Summary Tables, and National Toxicology Program Status Report. There are no occupational exposure limits established for isobutyraldehyde. The EPA has not established a reference concentration or reference dose for isobutyraldehyde. The molecular weight of isobutyraldehyde is 72.1 g. The molecular structure of isobutyraldehyde is shown in Figure 1.

Figure 1



Background

Isobutyraldehyde is a branched alkyl aldehyde used as a chemical intermediate and flavoring agent (NTP TR472, 1999). Some uses and appearances in the environment are "cellulose esters, perfumes, plasticizers, synthetic resins, pharmaceutics, and automobile and diesel exhaust" (Auerbach et al., 1977). Isobutyraldehyde is a clear, colorless, nonviscous liquid that is characterized to have a strong, sharp odor (ChemFinder.com, 2004).

Animal Toxicity

In an acute inhalation study conducted by Salem and Cullumbine (1960), mice, guinea pigs, and rabbits were exposed to a series of aldehydes both in aerosol and vapor form for 10 hours or until death. In general, the behavioral changes observed included blinking, closing of their eyes, rubbing their faces with their paws, and delayed calming where respiration was slow and deep. Animals were noted to convulse just prior to death. Isobutyraldehyde (given at 8967 mg/m^3), relative to other aldehydes, was less irritating causing a slower-occurring death. Pathologic changes caused by isobutyraldehyde differed with more irritation damage on the lung tissue compared to other aldehydes' primary effects on the bronchi.

A subacute inhalation study exposed 4 male and 4 female rats 6 times to isobutyraldehyde (92% purity) at an atmospheric concentration of 1000 ppm for 6 hours (Gage, 1970). The only effect attributable to isobutryaldehyde exposure observed was slight nose irritation. Upon autopsy, organs appeared to be normal.

A study focusing on sensory irritation exposed a number of aldehydes, isobutyraldehyde included, to B6C3F1 and Swiss-Webster mice. Steinhagen and Barrow (1984) developed a RD50 value of 4167 ppm and, by extrapolation from the RD50 (0.01 RD50 – 0.1 RD50), recommended a TLV range of 42-417 ppm – there is no currently published TLV for isobutyraldehyde.

Other references:
Two studies done by Zolotov and Svintukhovskii (1972) reported LC50 and LD50 values of 60,000 ppm after 30 minutes exposure and 960 mg/kg bwt both in rats, respectively. (Note: Cited in NTP, 1999 [In Russian])
RTECS (1982) listed a LC50 value of 13,860 ppm after 2-hour inhalation exposure for mice.
(Note: Cited in NTP, 1999)

The National Toxicology Program (NTP) reported results of well-conducted subchronic and chronic studies of (approximately 99% pure) isobutyraldehyde exposure in F344/N rats and B6C3F1 mice (1999). In the 13-week subchronic study, groups of 10 animals were exposed to 0, 500, 1000, 2000, 4000, or 8000 ppm by inhalation, 6 hours/day, 5 days/week. There were significant organ weight changes in the kidney, liver, and thymus of male rats exposed to 4000 ppm (Table 1 – Table 3).

Table 1. 13-week male rat kidney weights and kidney-weight-to-body-weight ratios

ppm	0	500	1000	2000	4000
Absolute (g)	1.276 ± 0.045	1.315 ± 0.029	1.358 ± 0.029	1.390 ± 0.038	1.258 ± 0.022
Relative (mg/g)	3.85 ± 0.07	3.87 ± 0.07	4.01 ± 0.07	4.03 ± 0.10	4.29 ± 0.04**

** P≤0.01

Table 2. 13-week male rat liver weights and liver-weight-to-body-weight ratios

ppm	0	500	1000	2000	4000
Absolute (g)	12.534 ± 0.479	13.220 ± 0.313	12.983 ± 0.363	12.664 ± 0.181	11.203 ± 0.161*
Relative (mg/g)	37.76 ± 0.69	38.80 ± 0.45	38.24 ± 0.58	36.77 ± 0.48	38.18 ± 0.22

* P≤0.05

Table 3. 13-week male rat thymus weights and thymus-weight-to-body-weight ratios

ppm	0	500	1000	2000	4000
Absolute (g)	0.285 ± 0.024	0.291 ± 0.012	0.289 ± 0.017	0.268 ± 0.024	0.211 ± 0.014*
Relative (mg/g)	0.86 ± 0.06	0.86 ± 0.04	0.85 ± 0.04	0.78 ± 0.07	0.72 ± 0.04

* P≤0.05

All rats and mice exposed to 8000 ppm isobutyraldehyde died before the end of the 13-week study. At the 4000 exposure level, 3 male rats, 6 female rats, 9 male mice, and all female mice died before the end of the study. Thus, for the 2-year chronic study, isobutyraldehyde exposure levels were capped at 2000 ppm; the exposure concentrations were 0, 500, 1000, and 2000 ppm. Groups of 50 animals were exposed to these concentrations by inhalation, 6 hours/day, 5 days/week, for 105 weeks. The incidences of three nonneoplastic lesions were significantly greater in exposed animals than in control. The lesions observed in rats included degeneration of the olfactory epithelium, squamous metaplasia of the respiratory epithelium, and suppurative inflammation, while degeneration of the olfactory epithelium alone was observed with greater significance in exposed mice (Table 4 – Table 7). Male and female rats exposed to 2000 ppm had increased incidences of degeneration of olfactory epithelium and suppurative inflammation compared to control. The incidence of squamous metaplasia was significant compared to control in male rats exposed to 2000 ppm and female rats exposed to as low as 500 ppm. Compared to that of control, the incidence of degeneration of olfactory epithelium was significantly greater in mice exposed to 1000 ppm and 2000 ppm.

Table 4. 2-year study in male rats – Incidences of nonneoplastic lesions of the nose

ppm	0	500	1000	2000
degeneration of olfactory epithelium	0/50	0/49	3/49	44/50**
suppurative inflammation	5/50	3/49	6/49	15/50**
squamous metaplasia of respiratory epithelium	1/50	1/49	10/49**	44/50**

** P≤0.01

Table 5. 2-year study in female rats – Incidences of nonneoplastic lesions of the nose

ppm	0	500	1000	2000
degeneration of olfactory epithelium	0/49	0/50	2/49	45/50**
suppurative inflammation	2/49	3/50	5/49	11/50**
squamous metaplasia of respiratory epithelium	1/49	11/50**	9/49*	44/50**

* P≤0.05
** P≤0.01

Table 6. 2-year study in male mice – Incidences of nonneoplastic lesions of the nose

ppm	0	500	1000	2000
degeneration of olfactory epithelium	0/50	0/50	11/50**	45/50**

** P≤0.01

Table 7. 2-year study in female mice – Incidences of nonneoplastic lesions of the nose

ppm	0	500	1000	2000
degeneration of olfactory epithelium	1/50	1/50	27/50**	49/50**

** P≤0.01

NTP also tested isobutyraldehyde for implications of mutagenicity and carcinogenicity. A series of different tests were used to assess the ability of isobutyraldehyde to induce mutations: evidence of mutations in *Salmonella typhimurium* strains; mutations in L5178Y mouse lymphoma cells; sister chromatid exchanges and chromosomal aberrations in cultured Chinese hamster ovary cells; sex-linked recessive lethal mutations in *Drosophila melanogaster*; chromosomal aberrations in mouse bone marrow cells; and induction of micronucleated erythrocytes in bone marrow cells of mice and rats. Isobutyraldehyde gave positive and negative results depending on which test was employed. In terms of the *in vitro* and *in vivo* mammalian cell assays measuring chromosomal damage, the results were positive. Negative results were obtained from *Salmonella typhimurium* and *Drosophila melanogaster* tests. Increases in micronucleated erythrocytes were not observed in either species. Comments on the different doses applied to each test were discussed to explain the contradicting results; "it appears that isobutyraldehyde-induced chromosomal damage *in vivo* is detected only at doses that are highly toxic and are not compatible with long-term survival, and neither neoplasms nor cytogenetic damage is observed at exposure levels that permit long-term survival" (NTP, 1999). The final conclusion stated that there was no evidence of carcinogenic activity since the studies showed no increases in malignant or benign neoplasms that could be attributed to the effects of isobutyraldehyde.

Human Toxicity

Literature and data for toxic effects of isobutyraldehyde in human subjects is scarce. One report prepared by Sim and Pattle (1957) discusses observations made from fifteen men chamber-exposed to 207 ppm isobutyraldehyde for 30 minutes. This study was

part of a series of acute aldehyde screening tests performed to assess tolerable limits for humans. The authors concluded that isobutyraldehyde was not an irritant but noted symptoms of nausea and vomiting in one participant. The significance of this study is questionable due to the possibility of co-exposure to cigarette smoke; subjects' activities (e.g., walking or smoking) were not restricted while in the exposure chamber.

Discussion

The NTP 2-year chronic inhalation study was used as the basis for the derivation of the initial threshold screening level (ITSL). The results of the sensory irritation studies were not considered to be appropriate for this task as stated in EPA's, Methods for Derivation of Inhalation Reference Concentrations of Inhalation Dosimetry (1994): "...the suitability of the sensory irritation test results is limited to serving as an indication of the potential for respiratory tract irritation. Dose-response assessment of the sensory irritation test is not recommended especially for quantitative evaluation of chronic effects." The LC50 values were not used since adequate information was available to derive an RfC.

The lowest adverse effect, increased incidence of squamous metaplasia of respiratory epithelium, was observed in the female rats from the 2-year chronic study at a concentration of 500 ppm isobutyraldehyde. The male rats also showed an increase in incidence of squamous metaplasia of respiratory epithelium, however, this increase was observed at 1000 ppm. The mice from the 2-year study did not show a significant change in the integrity of the respiratory epithelium cells. Instead, degeneration of olfactory epithelium was the adverse effect observed in mice. In both the males and females, this toxic effect was not seen until the level of 1000 ppm isobutyraldehyde was reached. Thus, the lowest-observable-adverse-effect level (LOAEL) concentration was determined to be 500 ppm for the following calculation of the ITSL.

Derivations of Screening Level

The inhalation reference concentration (RfC) was developed using EPA's, Methods for Derivation of Inhalation Reference Concentrations of Inhalation Dosimetry (1994). Although isobutyraldehyde is categorized as slightly soluble (ChemFinder.com, 2004) characterizing it to be a Category 2 gas, the evidence of extrathoracic (ET) effects of irritation mentioned above characterizes it as a Category 1 gas. Since isobutyraldehyde was determined to be a Category 1 gas, or a gas that is rapidly irreversibly reactive in the surface-liquid/tissue of the respiratory tract and does not significantly accumulate in the blood, most all of the toxicity would be limited to the ET region. Thus a regional gas dose ratio (RGDR) was factored in the derivation of the RfC (below). The body weight used in the calculation of the RGDR was provided by the NTP study's listed mean body weights of the animals. The uncertainty factor used for the extrapolation of animal data to human data was a value of 3, even though it is usually 10, because the application of the calculated RGDR accounted for some of the dosimetric adjustment for this extrapolation (below).

Note: 500 ppm was determined to be the LOAEL.

Conversion of concentration units from ppm to mg/m^3:

$$X\ mg/m^3 = \frac{ppm * MWT}{24.45}$$

$$X\ mg/m^3 = \frac{500\ ppm * 72.1\ g}{24.45}$$

$$X\ mg/m^3 = 1474.44\ mg/m^3$$

Calculation of $LOAEL_{[ADJ]}$:

$LOAEL_{[ADJ]}$ (mg/m^3) = E (mg/m^3) * D (hrs/24hrs) * W (days/7days)

$LOAEL_{[ADJ]}$ = the effect level obtained with an alternate approach, adjusted for duration of experimental regimen

E = experimental concentration level

D = number of hours exposed/24 hours

W = number of days of exposure/7 days

$LOAEL_{[ADJ]}$ = 1474.44 mg/m^3 * 6 hrs/24 hrs * 5 days/7 days

$$LOAEL_{[ADJ]} = \frac{1474.44\ mg/m^3 * 6\ hrs * 5\ days}{24\ hrs * 7\ days}$$

$$LOAEL_{[ADJ]} = \frac{44233.2\ mg/m^3}{168}$$

$LOAEL_{[ADJ]}$ = 263.29 mg/m^3

Calculation of $LOAEL_{[HEC]}$:

$LOAEL_{[HEC]}$ (mg/m^3) = $LOAEL_{[ADJ]}$ (mg/m^3) * $RGDR_r$

$LOAEL_{[HEC]}$ = the effect level obtained with an alternate approach, dosimetrically adjusted to an HEC

$LOAEL_{[ADJ]}$ = defined above

$RGDR_r$ = the regional gas dose ratio; a dosimetric adjustment factor for respiratory tract region, r (in this case extrathoracic – ET)

Calculation of $RGDR_{ET}$:

$$RGDR_{ET} = \frac{(V_E/SA_{ET})_A}{(V_E/SA_{ET})_H}$$

V_E = minute volume for animal (A) and human (H)

SA_{ET} = surface area of the extrathoracic region

> where: $V_{E[A]}$: $\ln V_E = b_0 + b_1 \ln BWT$

$\ln V_E = -0.578 + 0.821 \ln 0.270$

$\ln V_E = -1.65$

V_E = 0.19 L/min

$SA_{ET[A]}$: 15.0 cm2

$V_{E[H]}$: 13.8 L/min

$SA_{ET[H]}$: 200 cm2

$$RGDR_{ET} = \frac{\frac{0.19\ L/min}{15.0\ cm^2}}{\frac{13.8\ L/min}{200\ cm^2}}$$

$RGDR_{ET}$ = 0.1836

Using substitution into the $LOAEL_{[HEC]}$ equation:

$LOAEL_{[HEC]}$ = 263.29 mg/m^3 * 0.1836

$LOAEL_{[HEC]}$ = 48.34 mg/m^3

Calculation of RfC:

$$RfC = \frac{LOAEL_{[HEC]}}{UF}$$

$LOAEL_{[HEC]}$ = defined above
UF = uncertainty factor

> UFs that apply: 1) lab animal data to human extrapolation = 3
2) $LOAEL_{[HEC]}$ to $NOAEL_{[HEC]}$ = 10
3) data on effects of average healthy humans to sensitive = 10

$$RfC = \frac{48.34\ mg/m^3}{10 * 10 * 3}$$

$RfC = 0.1611\ mg/m^3 = 160\ ug/m^3$

Pursuant to Rule 232(1)(a), the ITSL is equal to the RfC; therefore, the ITSL for isobutyraldehyde is 160 ug/m^3 based on a 24-hour averaging time.

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