MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

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TO: File for Hexanaldehyde (CAS #66-25-1)

FROM: Anne Kim, Air Quality Division, Toxics Unit

SUBJECT: Screening Level Derivation

The initial threshold screening level (ITSL) for hexanaldehyde is 2 µg/m³ based on an annual 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 for hexanaldehyde. The EPA has not established a reference concentration or reference dose for hexanaldehyde. The molecular weight of hexanaldehyde is 100.2 g. The molecular structure of hexanaldehyde is shown in Figure 1.

Figure 1

Background

Hexanaldehyde is a saturated aliphatic aldehyde that appears in the processes and uses of organic synthesis of plasticizers, rubber chemicals, dyes, synthetic resins, and insecticides (Clayton and Clayton, 1981; NRC, 1981). Hexanaldehyde is a flammable liquid (ChemFinder.com, 2004). Similar to other aldehydes, hexanaldehyde is irritating to the eyes, skin and respiratory tract.

Animal Toxicity

Patty's Industrial Hygiene and Toxicology (1981) provided a chart of results with limited toxicity information. Included was an LD50 value of 4.9 g/kg bwt in rats. Two different inhalation toxicity results were also listed: rats exposed to a concentrated vapor for 1 hour resulted in 0/6 mortality ratio and rats exposed to 2000 ppm for 4 hours resulted in 1/6 mortality ratio. Irritation was reported to be slight on the skin and in the eye of rabbits (Clayton and Clayton, 1981).

In a short-term oral toxicity study performed by Komsta et al. (1988) rats were exposed to hexanal (hexanaldehyde) for 4 weeks. Groups of 10 males and 10 females were subjected to drinking water containing concentrations of 1, 10, 100, or 1000 mg/L. Clinical outcomes were measured daily including body weight gain (Table 1.1). Consumption of food and water were measured weekly (Table 1.2).

Table 1.1 Clinical Outcomes – Body weight

	Clinical Effect	0 mg/L	1 mg/L	10 mg/L	100 mg/L	1000 mg/L
Male	initial wt gain	133±15	136±15	134±18	137±16	136±19
	wt gain	214±14	200±21	197±21	203±23	210±18
Female	initial wt gain	116±10	116±11	116±11	117±12	119±8
	wt gain	88±12	95±13	98±15	102±18	104±23

Table 1.2 Clinical Outcomes – Consumption of water and approximate amount of chemical ingested

	Consumption	0 mg/L	1 mg/L	10 mg/L	100 mg/L	1000 mg/L
Male	water (g/rat/day)	26±3	24±2	24±2	25±3	25±2
	chemical (mg/kg/day)	0	0.1	1.2	12.6	124.7
Female	water (g/rat/day)	18.8±3	21±5	19±3	19±1	22±4
	chemical (mg/kg/day)	0	0.1	0.9	8.6	95.7

In general, all animals survived the study and clinical effects from toxic exposure were not observed. It was noted, however, that after histological examination of tissues exposed to the highest dose, there were mild alterations compared to control tissues. Brief discussion on these morphological changes stated that "[a]lthough treatment-related morphological changes were observed in the highest dose groups; these were considered to be mild and adaptative in nature, and could not be related to any functional changes" (Komsta et al., 1988). Charted below are the results from hexanaldehyde exposure only to the thyroid, liver, and kidney (Table 2.1, 2.2, and 2.3).

Table 2.1 Histological Outcomes – Thyroid*

	Histological Tissue Effect	0 mg/L	1000 mg/L
Male n = 10	Reduced Follicular size	5/0	6/0
	Increased epithelial height	1/0	5/1
	Reduced colloid density	0/0	3/0
Female n = 10	Reduced follicular size	2/0	4/0
	Increased epithelial height	0/0	1/0
	Reduced colloid density	0/0	0/0

* values denote number of animals with minimal to mild changes/number of animals with moderate to severe changes

Table 2.2 Histological Outcomes – Liver*

	Histological Tissue Effect	0 mg/L	1000 mg/L
Male n = 10	Anisokaryosis	0/0	3/0
	Increased cytoplasmic homogeneity	3/0	10/0
Female n = 10	Anisokaryosis	0/0	2/0
	Increased cytoplasmic homogeneity	1/0	0/0

* values denote number of animals with minimal to mild changes/number of animals with moderate to severe changes

Table 2.3 Histological Outcomes – Kidney*

	Histological Tissue Effect	0 mg/L	1000 mg/L
Male n = 10	Glomerular adhesions	6/0	6/0
	Tubular cytoplasmic inclusions	2/0	3/2
Female n = 10	Glomerular adhesions	8/0	5/1
	Tubular cytoplasmic inclusions	0/0	**4/1

* values denote number of animals with minimal to mild changes/number of animals with moderate to severe changes
** P = 0.04; significant results compared to control

Upon autopsy, 5 organs were grossly examined: the brain, heart, liver, spleen, and kidneys. Gross pathology was unremarkable except for unilateral hydronephrosis in 1 female rat at 1000 mg/kg of exposure.

Hexanal-treated female and male rats did show biochemical changes in the reduced activity of serum lactate dehydrogenase (LDH) enzyme, “however, the biological significance of this change is uncertain” (Komsta et al., 1988) (Table 3).

Table 3. Biochemical Outcomes – LDH activity

	0 mg/L	1 mg/L	10 mg/L	100 mg/L	1000 mg/L
Male	892±151	*820±202	*882±208	*840±296	*702±301
Female	1276±248	*1038±205	*893±208	*836±324	*915±197

* significant decrease from control

Thus, the authors concluded that exposure to hexanaldehyde at concentrations as high as 1000 mg/L in drinking water would not cause any significant toxic effects. Exposure to 1000 mg/kg in female mice, however, caused a significant increase in tubular cytoplasmic inclusions in the kidney compared to controls (Table 2.3) indicating this as an adverse effect level.

Genotoxic effects were observed in the highest-concentration-treated rat hepatocytes (isolated from Sprague-Dawley male albino rats) but they were not statistically significant (Martelli et al., 1994). Dosages ranged from 3 to 100 mM with an exposure duration of 20 hours. Human hepatocytes were also treated for comparison, and there was no induction of genotoxic changes. The authors of this study concluded that "the probability of occurrence in humans of genotoxic effects produced by [hexanaldehyde] is negligible" (Martelli et al., 1994).

Discussion

An LD50 value obtained from Patty's Industrial Hygiene and Toxicology can potentially be used to derive an initial threshold screening level (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 LD50 value is listed under subrule (h) whereas the use of a short-term, oral, no-observed-adverse-effect level is listed under subrule (e). Therefore, the derivation of the ITSL was based on the results of the short-term oral exposure study done by Komsta et al. (1988).

Although Komsta et al. concluded that exposure of hexanaldehyde at the highest dose of 1000 mg/L in drinking water did not cause significant toxic effects, the histological findings from kidney cells show a significant adverse effect at 1000 mg/L.

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 1000 mg/L, the NOAEL for the study done by Komsta et al. is the next highest exposure concentration of 100 mg/L.

Derivation of Screening Level

$$ITSL = \frac{NOAEL\ (mg/kg/day)}{35 \times 100} \times \frac{W_A}{I_A} \times \frac{b}{a}$$

ITSL = initial threshold screening level
NOAEL = no-observed-adverse-effect level
W_A = body weight of experimental animal in kilograms (kg)
I_A = daily inhalation rate of experimental animal in cubic meters/day
b* = absorption efficiency by the oral route of exposure
a* = absorption efficiency by the inhalation route of exposure
*In the absence of data on absorption efficiencies, it is assumed that a = b, thus the term equals 1.

Calculation of I_A (daily inhalation rate of experimental animal):

$I_A = 0.8W^{0.8206}$ (EPA, 1988)

Rat average weights from Komsta et al. (1988):

Female rat: 0.200 kg

Females: $I_A = 0.8(.200)^{0.8206}$

$I_A = 0.214\ m^3/day$

Using the value of the amount of chemical ingested in Table 1.2:

Female rat: 8.6 mg/kg/day

Females: $$ITSL = \frac{8.6\ mg/kg/day}{35 \times 100} \times \frac{0.200\ kg}{0.214\ m^3/day} \times \frac{1}{1}$$

$ITSL = 0.00230\ mg/m^3$ = **2 ug/m^3**

Therefore, the ITSL for hexanaldehyde is 2 ug/m^3 based on an annual averaging time.

References

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