MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

August 2, 2000

TO: File for n-Propyl Propionate (CAS #106-36-5)

FROM: Marco Bianchi, Toxics Unit, Air Quality Division

SUBJECT: Initial Threshold Screening Level

The initial threshold screening level (ITSL) for n-propyl propionate is 84 micrograms per cubic meter ($\mu g/m^3$) based on an annual averaging time.

The following references or databases were searched to identify data to determine the ITSL: Integrated Risk Information System-online, Health Effects Assessment Summary Table, National Toxicology Program Management Status Report-online, Registry of Toxic Effects of Chemical Substances (RTECS), Environmental Protection Bureau (EPB)-Chemical Criteria Database, EPB library, Chemical Abstract Service (CAS)-online, National Library of Medicine-online, International Agency for Research on Cancer-online, National Institute for Occupational Safety and Health Pocket Guide, and American Conference of Governmental Industrial Hygienists Guide.

Toxicity information obtained for n-propyl propionate (nPP) was limited to RTECS listings, and a 2-week rat inhalation study provided by DuPont/Haskell Laboratory. The RTECS listed an oral rat lethal dose 50 (LD_{50}) of 10.3 grams per kilogram (g/kg), and a mouse inhalation LC_{50} of 24 g/m^3, but further information about these studies could not be obtained.

In the DuPont/Haskell study, groups of 10 male Crl:CD (SD)IGS BR rats were exposed six hours per day (hrs/day), for a total of nine exposures over a two-week period to design concentrations of 50, 250, or 2000 parts per million (ppm) of n-propyl propionate vapor. A control group of 10 male rats was exposed simultaneously to houseline air. At the end of the exposure period, blood and urine samples were collected for clinical analyses, and five rats per group were sacrificed for pathologic examination. After three-week recovery period, the surviving rats were also given clinical and pathological examinations.

In rats exposed to 2000 ppm of nPP, a diminished or absent alerting response was observed during the daily six-hour exposures. These effects were considered reversible and were not observed in the other test groups. Rats exposed at 2000 ppm showed depressed body weights compared to controls. By the end of the recovery period the mean body weights of rats exposed to 2000 ppm were no longer statistically different from those of the controls.

Clinical laboratory evaluation of rats exposed to nPP showed no effects attributable to the test compound. Similarly, there were no organ weight findings that were considered to be a result of exposure to nPP.

Histologic effects attributable to the test compound were found in the nose of rats mainly in the 2000 ppm group with one rat slightly affected in the 250 ppm group. Olfactory changes observed in the 2000 ppm group were characterized by mild to moderate disorganization and thinning of the olfactory epithelium, and necrosis and loss of olfactory neurons. Lesions primarily occurred in the olfactory epithelium lining of the dorsal septum, the dorsolateral wall, and the more medial extents of the ethmoturbinates. But, only very slight focal changes were observed in one affected rat exposed to 250 ppm.

Following the three-week recovery period, regenerative changes were present in the olfactory epithelium of rats in the 2000 ppm recovery group. These were characterized by more normal thickness but slight disorganization of the olfactory epithelium. Though these changes were not completely reversible after three-weeks of recovery, a full recovery was expected if a longer recovery time would have been allowed. No other histological effects attributable to nPP exposure were observed. The study investigators concluded that the actual no-observed-adverse-effect level (NOAEL) was between 50 and 250 ppm, and was expected to lie near the upper bound of that range, as effects at the low-effect level of 250 ppm were limited to a single animal and were minimal and focal in nature.

In order to determine whether the nasal lesion observed in one test animal at 250 ppm was significant, two statistical tests (Fischer's Exact Test and Cochran-Armitage Tend Test) were conducted.

Table 1: Incidence of microscopic lesions observed in nasal olfactory epithelium of male rats exposed to nPP for two-weeks by inhalation

ppm	Exposed (n)	Lesions observed (n)	Fischer's test (p-value)	Cochran-Armitage (p-value)
0	5	0		
50	5	0		
250	5	1	0.5	0.15
2000	5	5*#	0.004	0.0001

*comparison to control (Fischer's exact test) significant, $p<0.05$
#trend test (Cochran-Armitage) significant, $p<0.05$

Results from both statistical tests showed no significance (<0.05) for focal nasal lesions observed between the control and 250 ppm exposure groups. Additionally, the test animal exposed to 250 ppm had a pathologist's grading of "minimal" for olfactory/degeneration/necrosis. The pathologist's definition of minimal was "the amount of change present barely exceeds that which is considered to be within normal

limits." Therefore, it seems appropriate to use the NOAEL of 250 ppm (1175 milligrams [mg]/m^3) to derive an ITSL. Coupled with a 3500 uncertainty factor, the resulting ITSL concentration should be protective to sensitive individuals.

The ITSL was derived as follows:

NOAEL = 1175 mg/m^3
35 = uncertainty factor (using a NOAEL from a seven-day exposure period to estimate a NOAEL for a lifetime)
100 = uncertainty factor (animal to human; sensitive populations)

$$ITSL = \frac{NOAEL}{35 \times 100} \times \frac{\text{hours exposed/day}}{24 \text{ hrs/day}}$$

$$ITSL = \frac{1175 mg/kg}{35 \times 100} \times \frac{6 \text{ hrs/day}}{24 \text{ hrs/day}} = 0.0839 \ mg/m^3$$

conversion of mg/m^3 to $\mu g/m^3$:

$$0.0839 \ mg/m^3 \times \frac{1000 \ \mu g}{1 \text{ mg}} = 84 \ \mu g/m^3$$

The ITSL for n-propyl propionate = 84 $\mu g/m^3$ based an annual averaging.

References:

1. Kelly DP. 2000. H-24286: Two-week inhalation toxicity study in male rats. Dupont 3626.

2. Fischer, RA. 1985. Statistical methods for research workers, 13th edition. Haffner, New York.

3. Snedecor, GW and Cochran, WG. 1967. Statistical methods, 6th edition, pp246-248 and 349-352. The Iowa State University Press, Iowa.

MB:SLB
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