MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

November 23, 2015

To: File for 2-ethylhexanol (CAS # 104-76-7)

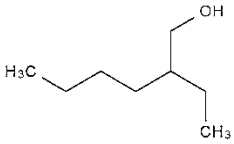
From: Mike Depa, Toxics Unit, Air Quality Division

Subject: Initial Threshold Screening Level

The Initial Threshold Screening Level (ITSL) for 2-ethylhexanol is 130 µg/m^3 with a 24-hour averaging time.

A literature review was performed in order to determine if relevant toxicity data was available for 2-ethylhexanol (2EH). The literature sources reviewed included: Registry of Toxic Effects of Chemical Substances (RTECS), National Toxicology Program (NTP) Management Status Report-online, Provisional Peer Reviewed Toxicity Values for Superfund (PPRTV), Integrated Risk Information System (IRIS)-online, National Library of Medicine (NLM)-online, Agency for Toxic Substances and Disease Registry (ATSDR) and American Conference of Governmental Industrial Hygienists (ACGIH) Guide. The structure is shown below.

Molecular Structure for 2EH:



A number of candidate ITSLs are derived, as shown below.

<u>Occupational Exposure Limit Based ITSL</u>

A candidate ITSL could be derived for 2-ethylhexanol (2EH) based on an occupational exposure limit (OEL) of 1 ppm 2EH (1 ppm = 5.3 mg/m^3; ~ 5000 µg/m^3) (SCOEL, 2011). The OEL (SCOEL, 2011) is based on irritation of human subjects in a chamber for 4 hours at 1.5, 10 and 20 ppm 2EH (2-ethylhexanol). There were significantly increased eye blinks at 10 and 20 ppm. Additionally, there were increased eye blinks at 1.5 ppm but they were not statistically significant. Another human irritation study was performed where volunteers were exposed for 2-hrs to 1 ppm. This dose level produced a no-observed-adverse-effect-level (NOAEL) of 1 ppm (5.3 mg/m^3), which was used as a level protective of sensory irritation, and forms the basis of the occupational exposure limit (SCOEL, 2011).

Candidate ITSL = OEL/100, pursuant to Rule 232(1)(c).
Candidate ITSL = 5.3 mg/m^3/100
Candidate ITSL = 0.053 mg/m^3 x 1000µg/m^3
Candidate ITSL = ~ 50 µg/m^3 (8-hr averaging time).

Subchronic Animal Based ITSL

In a subchronic animal inhalation study, groups of 10 male and female Wistar rats received 0, 15, 40 and 120 ppm 2EH for 6hrs/day, 5 days/week for 90 days (Klimisch et al, 1998). No effects were observed in the following parameters: clinical signs and mortality, body weight and weight gain, food consumption, food efficiency, water consumption, ophthalmo-scopic examination, hematology, clinical chemistry, organ weights, gross pathology, and histopathology (non-neoplastic neoplastic). The highest dose level was identified as a no-observed-adverse-effect-level (NOAEL) at 120 ppm (638 mg/m^3). An RfC protective of long term effects based on the subchronic animal inhalation study would be:

$NOAEL_{adj}$ = 638 mg/m^3 x 6/24 x 5/7
$NOAEL_{adj}$ = 114 mg/m^3

A human equivalent concentration is normally calculated based on the dosimetry of the substance on the target tissue in animals and humans. Yet no effects were observed in the Klimisch et al (1998), so a dosimetric adjustment factor could not be derived. For the purpose of deriving a candidate screening level, in this case, the animal and human doses are considered equivalent.

Candidate ITSL = $NOAEL_{adj}$/(UF1 x UF2 x UF3)
(uncertainty factors of 10 for animal to human, 10 for sensitive individuals and 10 for subchronic to chronic extrapolation).
Candidate ITSL = 114 mg/m^3/(10 x 10 x 10)
Candidate ITSL = 0.114 mg/m^3 x 1000µg/mg
Candidate ITSL = 114 $\mu g/m^3$

Human Chamber Studies And Proposed ITSL

The human studies were summarized by the European Commission's Scientific Committee on Occupational Exposure Level (SCOEL, 2011) as follows:

> The critical effect of EH is irritation of the eyes and airways. The human exposure chamber study by van Thriel and colleagues (van Thriel, Seeber et al. 2003; Kiesswetter, Thriel et al. 2005; van Thriel, Kiesswetter et al. 2005; van Thriel, Kiesswetter et al. 2007) showed concentration-dependent increases in self-rated eye irritation, nasal irritation and annoyance. The effects were seen at all levels tested, 1.5, 10 and 20 ppm, with both constant and variable exposures. The symptoms are supported by objective measurements, namely increased blink frequency at 10 and 20 ppm, and decreased nasal air flow and increased substance P in nasal lavage at 20 ppm. No objective effects were seen at 1.5 ppm and the self-reported irritation symptoms were minimal. Hence, a NOAEL for irritation of 1.5 ppm may be inferred from the study.[1]

[1] See the publication SCOEL, 2011 for additional information, including details of the human studies and references thereof.

Table 1. Human Chamber Study Results After 4-Hour Exposures*

2EH Exposure Level	Effects	Adjusted for Continuous 24-hr Exposure
20 ppm (106 mg/m^3)	▪ ↑ phosphorus in nasal lavage; ▪ ↑ eye blink ▪ ↓ inhalation rate ▪ Subjective odor irritation: "strong"	17.6 mg/m^3
10 ppm (53 mg/m^3)	▪ ↑ eye blink ▪ Subjective odor irritation: "moderate"	8.8 mg/m^3
1.5 ppm (8 mg/m^3)	▪ Subjective odor irritation: "weak"	1.3 mg/m^3

* The results of several human chamber studies, all using the same exposure concentrations (as summarized by SCOEL, 2011).

A candidate RfC was calculated based the NOAEL of 1.5 ppm (8 mg/m^3) 2EH after a 4-hr exposure. Eye blink was elevated at 1.5 ppm, but not statistically significant. A duration adjustment for continuous exposure was made to the 4 hour exposure concentration of 8 mg/m^3:

$NOAEL_{adj}$ = 8 mg/m³ x 4hrs/24hrs
$NOAEL_{adj}$ = 1.3 mg/m³

Candidate Acute RfC = $NOAEL_{adj}$/UF
(UF of 10 for sensitive individuals)
Candidate Acute RfC = 1.3 mg/m^3/10
Candidate Acute RfC = 0.13 mg/m³ x 1000µg/mg
Candidate Acute RfC = 130 µg/m^3

Conclusion

The OEL was not considered the most appropriate basis for developing a screening level because human data was available to derive an RfC. The subchronic animal inhalation exposure study by Klimisch et al (1998) in rats had several shortcomings. After 90 days of exposure to the highest dose (120 ppm 2EH), the rats had no effects at the end of 90 days; the highest dose was considered a free standing NOAEL of ~640 mg/m^3. Also the Klimisch et al (1998) study did not evaluate nasal lavage in the rats for signs of inflammation, which is the critical effect observed in the human studies. The human chamber studies measured statistically significant objective effects in volunteers as low as 10 ppm (increased eye-blink and phosphorus in nasal lavage and decreased inhalation rate). Additionally, subjective ("moderate" odor) effects were elevated at 10 ppm, and "weak" at 1.5 ppm (8 mg/m^3). Since the low-dose of 1.5 ppm (8 mg/m^3) produced no adverse effects it was chosen as the key study upon which to base the ITSL. Therefore, the ITSL was based on the acute RfC of 130 µg/m^3. A 24-hr averaging time was applied based on the nature and duration of the key study and the ITSL value derivation, as allowed under Rule 229(2)(b).

References:

Klimisch HJ, Deckardt K, Gembardt C, Hildebrand B. 1998. Subchronic inhalation toxicity study of 2-ethylhexanol vapour in rats. Food and Chemical Toxicology, 36:165-168.

SCOEL. 2011. Recommendation from the Scientific Committee on Occupational Exposure Limits for 2-ethylhexanol. Scientific Committee on Occupational Exposure Limits (SCOEL). SCOEL/SUM/158. March 2011. Employment and Social Affairs. European Commission.
http://ec.europa.eu/social/BlobServlet?docId=6660&langId=en