



# Recommendation from the Scientific Committee on Occupational Exposure Limits for 2-ethylhexanol

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|                 |              |
|-----------------|--------------|
| 8 hour TWA:     | 1 ppm        |
| STEL (15 mins): | not assigned |
| Notation:       | not assigned |
| BLV:            | not assigned |

### **1. Substance identification:** 2-Ethylhexanol

Synonyms: 2-Ethylhexan-1-ol; Isooctanol; Octyl alcohol

EC No.: 203-234-3

Annex I Index No.: -

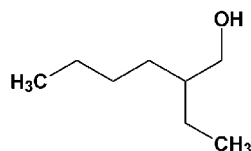
Classification: -

CAS No.: 104-76-7

MWt: 130.20

Conversion factor (20 °C, 101 kPa): 1 ppm = 5.42 mg/m<sup>3</sup>; 1 mg/m<sup>3</sup> = 0.185 ppm

Structural formula:



This evaluation is based on BG-Chemie (1995), ECB (2000), Greim (2000, 2006), WHO (1993) and the references cited in these reviews, along with a literature search in August 2009.

### **Physico-chemical properties**

2-Ethylhexanol (EH) is a colourless liquid with a mild, floral odour. The boiling point of the substance is 183.5 - 185 °C and the vapour pressure is 0.05 - 0.4 hPa at 20 °C. The water solubility of EH is 1 - 27 g/l at 20°C and the log octanol:water partition coefficient (P<sub>ow</sub>) is 2.28. The substance has a density of 0.83 g/cm<sup>3</sup> (BG-Chemie, 1995; ECB, 2000; WHO, 1993).



## 1. Occurrence/use and environmental exposure

EH is used as an intermediate in the production of plasticisers, e.g. diethylhexyl phthalate (DEHP) for polyvinylchloride (PVC) resins, hexyl esters and acrylates such as 2-ethylhexacrylate (Verschuere, 2001; BG-Chemie, 1995; ECB, 2000). EH is further used as a solvent in paint lacquer, inks, rubber, paper, dry cleaning, as a wetting agent in textiles and as a flavouring ingredient in food (WHO, 1993).

EH is emitted from plastic material, including new computers (Bako-Biro, Wargocki et al. 2004). It can also be emitted via alkaline degradation of plasticizers in damp floor constructions (Wieslander, Norback et al. 1999; Putus, Tuomainen et al. 2004; Kamijima, Shibata et al. 2005). Recently, it has been suggested that microbes can degrade phthalate plasticizers (Horn, Nalli et al. 2004), with formation of EH and 2-ethylhexanoic acid (Nalli, Horn et al. 2006). Degradation of plastic building materials may result in formation of EH by a variety of bacteria and fungi (Tuomainen, Seuri et al. 2004; Nalli, Horn et al. 2006). Air samples from a newly completed building showed concentrations up to 0.5 mg/m<sup>3</sup> (Kamijima, Sakai et al. 2002). In a Japanese study the geometric means of measurement in 42 non-domestic buildings was about 0.02 mg/m<sup>3</sup>, the maximum concentration being 2.7 mg/m<sup>3</sup> (Sakai, Kamijima et al. 2006).

## 2. Health significance

### 2.1 Toxicokinetics

EH is a primary metabolite of the plasticiser diethylhexylphthalate (DEHP) and other 2-ethylhexyl compounds in mammals (WHO, 1993).

#### 2.1.1 Human data

No studies on toxicokinetics in humans in vivo are available. In a diffusion experiment by Barber et al. (1992), the absorption rate of human skin in vitro was 38 µg per cm<sup>2</sup> and hour.

#### 2.1.2 Animal data

No quantitative data on the absorption by inhalation exposure are available. The occurrence of systemic toxic effects after inhalation exposure shows the efficient absorption by this route.

The toxicokinetics of EH in female rats were studied by Deisinger et al. (1994). After oral gavage of 50 or 500 mg/kg the absorption rate was about 80%, independent of the administered dose. No differences in absorption were likewise observed following repeated exposures. The dermal absorption rate after exposure to 1000 mg/kg was reported to be about 5% in this study. In a diffusion experiment by Barber et al. (1992), the absorption rate of rat skin in vitro was 215 µg per cm<sup>2</sup> and hour, i.e. about five times higher than in human skin.

In the study by Deisinger et al. (1994), the metabolism of EH was similar after oral and dermal exposure. The main metabolites in urine of orally treated rats were 2-ethylhexanoic acid, 5-hydroxy-2-ethylhexanoic acid, 6-hydroxy-2-ethylhexanoic acid and 2-ethyl-1,6-hexane diacid. Together, they represented 37 - 45% of the administered dose. Minor metabolites were 5-hydroxy-2-ethylhexanoic acid as well as lactones of 5-hydroxy-2-ethylhexanoic acid and 2-ethyl-5-hexanoic acid. They represented 3 - 5% of the administered dose. About 1% of the administered dose was recovered as 2-ethylhexanol. All these compounds were predominantly excreted as glucuronides (Deisinger et al., 1994). Albro (1975) reported the formation of about 50% 2-ethylhexanoic acid following a single oral exposure of rats to 275 mg/kg.



After gavage to rats, 95% of EH was eliminated within 96 h (mostly within 24 h). About 70% of the administered dose was excreted in urine, 13% in faeces and 11% in expired air. A similar elimination pattern was found after dermal exposure, with lower absolute amounts due to lower absorption following dermal exposure.

Older studies in mice and rats support the results of the most detailed study by Deisinger et al. (1994). The metabolism of EH (as a metabolite of DEHP) in monkeys proceeded slower than in rodents (BG-Chemie, 1995; WHO, 1993).

### 2.1.3 Biological exposure monitoring

There are no data available.

## 2.2 Acute toxicity

### 2.2.1 Human data

Human data on effects of acute exposure are not available.

### 2.2.2 Animal data

The inhalation  $LC_{50}$  (4 h) of EH in rats was more than  $890 \text{ mg/m}^3$  ( $> 164 \text{ ppm}$ ) and less than  $5300 \text{ mg/m}^3$  ( $< 978 \text{ ppm}$ ) (BG-Chemie, 1995). A single 6 h inhalation exposure of rats, mice and guinea pigs to  $227 \text{ ppm}$  ( $1230 \text{ mg/m}^3$ ) produced a moderate irritation of the eyes, nose and throat, as well as a decreased motility and dyspnoea. The animals revealed slightly congested lungs with areas of haemorrhages (Scala and Burtis, 1973). When rats were exposed to  $164 \text{ ppm}$  ( $890 \text{ mg/m}^3$ ) for 4 h, there were no signs of irritation, but the animals were hypoactive (Bio/Dynamics, 1989). The oral  $LD_{50}$  in rats was  $2049 - 7000 \text{ mg/kg}$ . The dermal  $LD_{50}$  was  $1980$  to more than  $2600 \text{ mg/kg}$  in rabbits and more than  $3000 \text{ mg/kg}$  in rats. Symptoms of acute intoxication were apathy, dyspnoea, cyanosis, loss of coordination, staggering and ataxia (BG-Chemie, 1995; WHO, 1993).

## 2.3 Irritation and corrosivity

### 2.3.1 Human data

#### *Inhalation exposure*

Reported odour thresholds for EH are  $0.4 - 0.73 \text{ mg/m}^3$  ( $0.08 \text{ ppm} - 0.13 \text{ ppm}$ ) (Ruth, 1986).

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) investigated chemosensory perception, signs of eye (blink frequency) and nasal (air flow, substance P) irritation, and performance in demanding neurobehavioral tasks during exposure to EH under controlled conditions in an exposure chamber. The subjects were either healthy young men with self-reported multiple chemical sensitivity or healthy "controls". Three exposure levels, 1.5, 10, and 20 ppm (corresponding to 8, 54 and  $108 \text{ mg/m}^3$ ), were investigated in randomized sequences. The exposures were either constant or variable (but with same average level). The variable exposures consisted of five peaks evenly spread over the 4-hour exposures, each reaching twice the average level.

The rated intensity of chemosensory perceptions showed a clear concentration dependency. Overall, the average ratings of annoyance corresponded approximately to "moderate" at 1.5 ppm, "strong" at 10 ppm and very strong" at 20 ppm, on the Labeled Magnitude Scale. The corresponding ratings of eye irritation and nasal irritation were



“weak”, “moderate” and “strong”, respectively. Also the acute symptom scores in the SPES (Swedish Performance Evaluation System, (Iregren 1998) ) were clearly concentration-dependent and was increased during the exposures at all three levels. Little difference in ratings was seen between the 27 “normal” and the 19 chemically sensitive men and between constant and fluctuating exposure. (van Thriel, Kiesswetter et al. 2005; van Thriel, Kiesswetter et al. 2007). Overall, as the ratings of nasal and eye irritation were minor at 1.5 ppm, this level is considered as the NOAEL for sensory irritation.

An additional analysis was performed on physiological measurements related to nasal irritation. Concentration-dependent reductions in nasal air flow and increases in substance P in nasal lavage were seen during exposure to EH at the three exposure levels of 1.5, 10 and 20 ppm. The changes were statistically significant only at the highest exposure (van Thriel, Seeber et al. 2003). The measurements suggest a NOAEL for acute irritation/inflammation of 20 ppm.

In addition, eye irritation of EH was assessed by electromyographic eye blink recordings as an indicator of sensory irritation. Each exposure (1.5, 10 and 20 ppm, constant and variable exposure) was carried out with two healthy young men with self-reported multiple chemical sensitivity and age matched controls. Strong concentration-response relationships between airborne solvent concentrations and blink rates were seen, the increases in frequency being statistically significant at the 10 and 20 ppm conditions. During the 40 ppm peak exposures (two 20 ppm) the blink rate increased threefold. In the course of 4 h, exposure blink rates increased significantly showing no adaptation. Subjects with chemical sensitivity revealed no significantly higher blink rates than controls (Kiesswetter, Thriel et al. 2005). The study indicates a NOAEL for eye irritation of 1.5 ppm and a LOAEL of 10 ppm.

The performance in the vigilance test was not affected by the different exposures. Moreover, the results of neurobehavioral tests measuring executive function were neither affected by the exposure level nor by the exposure peaks (van Thriel, Kiesswetter et al. 2007). The study indicates a NOAEL of 20 ppm for neurobehavioral impairment.

The various results in the human volunteer studies by van Thriel et al. described above are consistent with those in a more recent one by Ernstgård et al. (2009). In the latter study, 16 males and 14 females were exposed in random order to 1 mg/m<sup>3</sup> (0.2 ppm) EH or to clean air for 2 h during resting conditions. The subjects performed symptom ratings on 0-100 mm Visual Analogue Scales. The ratings of nasal irritation, throat irritation, headache, dyspnoea, fatigue, dizziness, nausea and intoxication were not significantly affected by exposure to EH. The ratings of smell and eye discomfort were minimally but significantly increased. On average, the ratings of eye irritation increased from “not at all” (0 mm) during exposure to clean air to “hardly” (7 mm) during EH exposure. No exposure-related effects on the measurements of blink frequency by electromyography, eye tear-film break-up time, vital staining of the eye, nasal lavage biomarkers, transfer tests, or by spirometry and rhinometry, were seen. No differences in response were seen between sexes or between atopics and non-atopics (Ernstgård et al. submitted).

#### *Skin exposure*

Exposure with a cotton cloth soaked with EH for 5 h produced slight hyperaemia, but no sensation of irritation or pain in one subject (Mellon Institute, 1940).

In a pilot study to a sensitisation test, EH (4% solution in paraffin oil) was slightly irritating to the human skin (Opdyke, 1979).



## 2.3.2 Animal data

### *Skin*

Undiluted EH was severely irritating to the skin of rabbits (score 6.75 of 8, maximal) in an acute study by Hüls (1987a) according to OECD guideline 404. Results from other studies were similar (BG-Chemie, 1995).

In a developmental toxicity study by Tyl et al. (1992), pregnant rats were dermally exposed for 6 hours to 252, 420, 840, 1680 and 2520 mg of undiluted EH per kg and day on gestation days 6 - 15. Skin irritation was measured before and after each application. Signs of irritation were produced by application of 420 mg/kg per day and above, consisting of mild and included exfoliation, encrustation and erythema.

Signs of irritation (slight reddening and crusting of the skin) were also observed in a study by Schmidt et al. (1973) after repeated dermal non-occlusive exposure of rats to 2 ml (1.67 g) EH per application. Further effects of this study are described in the section "Repeated dose toxicity".

### *Eyes*

Single inhalation exposure of rats, mice and guinea pigs to 227 ppm (1230 mg/m<sup>3</sup>) for 6 h produced moderate irritation of the eyes (Scala and Burtis, 1973). There were no signs of irritation after single exposure of rats to 164 ppm (890 mg/m<sup>3</sup>) for 4 h (Bio/Dynamics, 1989).

Undiluted EH was moderately irritating by instillation into the eyes of rabbits (score 28.6 of 110, maximal) in a study by Hüls (1987b) according to OECD guideline 405. Other studies yielded similar results (BG-Chemie, 1995), while severe eye irritation (according to Draize) was observed in one rabbit study by Scala and Burtis (1973).

### *Respiratory tract*

Single inhalation exposure of rats, mice and guinea pigs to 227 ppm (1230 mg/m<sup>3</sup>) for 6 h produced moderate irritation of the nose and throat (Scala and Burtis, 1973). The reported RD<sub>50</sub> value (concentration causing a 50% depression of the respiratory rate due to sensory irritation of the respiratory tract) in OF1 mice was 44 ppm (238 mg/m<sup>3</sup>) (Alarie et al., 2001, Schaper, 1993).

## 2.4 Sensitisation

### 2.4.1 Human data

There were no indications of sensitising action in workers of an EH production site (BG-Chemie, 1995). EH was tested for sensitisation in 29 subjects in a study by Opdyke (1979), according to the method of Kligman. Skin areas were pretreated with 5% sodium lauryl sulphate for 24 h. The induction was then performed four times for 28 h each with a cotton cloth soaked in a 4% solution of EH in paraffin oil. The challenge was performed with 4% EH for 48 h. None of the subjects showed any allergic reactions.

### 2.4.2 Animal data

Studies on sensitisation in animals are not available.

## 2.5 Repeated dose toxicity

### 2.5.1 Human data

Hollenbach et al. (1972) reported that laboratory workers exposed to EH complained of headaches, dizziness, fatigue and gastrointestinal disorders. The workers also had slightly



decreased blood pressure during the day. Because there was co-exposure to other substances, no definite conclusions can be drawn from these results.

A number of studies indicate respiratory effects of dampness in PVC floor coverings and that EH might be a causative factor (Norback, Bjornsson et al. 1999, Bornehag, Sundell et al. 2005, Janson, Norback et al. 2005, Wieslander, Norback et al. 1999 Norback, Wieslander et al. 2000, Tuomainen, Seuri et al. 2004, Tuomainen, Stark et al. 2006, Putus, Tuomainen et al. 2004, Kamijima, Sakai et al. 2002, Kamijima, Shibata et al. 2005). However, no firm conclusions can be drawn from the above studies with respect to the relation between EH and the reported effects, as the contribution of other agents in the indoor environment is unknown.

## 2.5.2 Animal data

### *Inhalation*

Wistar rats (10 per sex and group) were exposed by inhalation to 0, 15, 40 and 120 ppm (81, 217 and 650 mg/m<sup>3</sup>) on 5 d/w, 6 h/d for 90 days, The test was carried out according to OECD guideline 413 (Klimisch et al., 1998). No signs of irritation were reported. There was no treatment-related toxicity (including peroxisome proliferation) even at the highest exposure concentration (NOAEL 120 ppm).

### *Oral*

The Mellon Institute (1961a, b) exposed DW rats (10 per sex and group) orally for 90 days to EH in feed at concentrations of 100 - 12500 mg/kg (7 - 833 mg/kg per day). At the highest concentration, there were histological lesions of the liver and kidney. The NOAEL of this study was 2500 mg/kg feed (176 mg/kg per day).

F344 rats and B6C3F1 mice (10 per sex and group for each species) were orally exposed for 3 months to EH by gavage on 5 d/w at doses of 0, 25, 125, 250 and 500 mg/kg per day (BASF AG, 1991a, b). In the rat study, effects were observed at doses of 250 mg/kg per day and above, consisting of retarded body weight gain, alterations in clinical chemical and haematological parameters and increased organ weights as well as acanthosis of the mucosa of the forestomach and fatty infiltration of the liver lobules. An increase in peroxisome proliferation (identified by an increased activity of the marker enzyme cyanide-insensitive palmitoyl-CoA-oxidase) was also found. No effects were observed in rats at doses up to 125 mg/kg per day (NOAEL of the rat study). In the mice study, no alterations in clinical chemical and haematological parameters were evident. The stomach weights were increased in males at the 2 higher doses, but the effect was not clearly dose-dependent. Fat deposition in the liver was significantly increased and acanthosis of the forestomach mucosa was observed in some animals of the 500 mg/kg per day group. There were no signs of peroxisome proliferation in mice at all doses tested. The NOAEL of the mice study was 125 mg/kg per day.

Numerous in vitro and in vivo studies were performed regarding the potency of EH to induce hepatic peroxisome proliferation in various species. This effect was observed predominantly in rats and dogs, but only to a low extent in human or monkey cells (BG-Chemie, 1995).

Two studies of Astill et al. (1996) were made with rats and mice, used also as a carcinogenicity studies. In the study with rats, F344 rats received oral doses of 0, 50, 150 and 500 mg/kg per day EH in aqueous emulsion by gavage on 5 d/w for 24 months. Animals of the high dose group showed clinical signs of toxicity, increased mortality, retarded body weight gain and increased organ weights. The animals of these groups revealed congestion of the liver and lung, the males had increased incidences in prostate atrophy. In the mid dose animals, a reduced body weight gain, increased organ weights and clinical signs of toxicity were evident. No effects occurred at the lowest dose (NOAEL





50 mg/kg per day). In the study with mice, animals received oral doses of 0, 50, 200 and 750 mg/kg per day EH in aqueous emulsion by gavage on 5 d/w for 18 months. At the highest dose, there was an increase in mortality and a retardation of body weight gain in both sexes as well as haematological disturbances. No effects could be seen at the two lower doses (NOAEL 200 mg/kg per day).

#### *Dermal*

Repeated dermal exposure of rats to high doses (12 non-occlusive applications of 1.67 g EH each) produced skin irritation, body weight reduction and histopathological alterations in organs (Schmidt et al., 1973).

Bushy Run Research Centre (1988) exposed rats dermally to 0, 417 and 834 mg/kg per day EH (9 occlusive applications for 6 h each within 12 days). Females of the higher dose revealed lymphopenia and decreased spleen weight. Increased triglyceride levels were observed in all exposed females. Histopathological lesions were restricted to the site of application.

## **2.6 Genotoxicity**

### **2.6.1 In vitro**

EH was extensively tested for mutagenicity in bacteria. Studies with *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, TA1538 and TA2637 used the standard or the preincubation assay with and without metabolic activation. Furthermore, bacteria were exposed to urine of EH-treated rats. All of these experiments yielded negative results, except one Ames test by Seed et al. (1982) with TA100, in which a weak mutagenic response was observed without metabolic activation. However, an unusual protocol was used in this test (not the his-gene reversion was analysed, but the azaguanine resistance mutation) and only one strain was tested (BG-Chemie, 1995; ECB, 2000). Studies with *Bacillus subtilis*, strain H17M45 did not show a mutagenic effect (Tomita et al., 1982). DNA repair tests in *E. coli* (polA<sup>+</sup>/polA<sup>-</sup>) yielded conflicting results: EH was positive, when ethanol was used as vehicle, but negative, when DMSO was the vehicle (MRI, 1981).

No gene mutations were observed in L5178Y mouse lymphoma cells and in CHO hamster cells. EH was tested with and without metabolic activation up to concentrations which produced cytotoxicity (Kirby et al., 1983; LBI, 1985).

EH did not induce chromosomal aberrations in CHO hamster cells in vitro (without metabolic activation; Philips et al., 1982) and did not cause unscheduled DNA synthesis in primary rat hepatocytes (Hodgson et al., 1982).

### **2.6.2 In vivo – Human data**

Human data on genotoxic effects in vivo are not available.

### **2.6.3 In vivo – Animal data**

Mice were given either one or two intraperitoneal doses of 456 mg/kg each. The repeated exposure produced a significant increase in micronuclei in polychromatic erythrocytes (LBI, 1982). According to the authors, this should be regarded as a false positive response, as the incidences were within the range of historical control values and the values of the concurrent controls were unusually low.

There was no induction of chromosomal aberrations in the bone marrow of rats treated orally with doses of 16.7 - 167 mg/kg per day on 5 consecutive days. Only 50 metaphases per animal were evaluated (Putman et al., 1983).

A negative result was reported in a dominant lethal test with mice (exposure of male animals to oral doses of 250 - 1000 mg/kg per day for 5 days with subsequent mating with untreated females) (Rushbrook et al., 1982).



EH did not bind covalently to murine liver DNA after oral exposure of mice to diethylhexyl adipate or diethylhexyl phthalate for 4 weeks, followed by a single dose of radioactively labelled EH in doses of 51 - 120 mg/kg (von Däniken et al., 1984).

## 2.7 Carcinogenicity

### 2.7.1 Human data

Human data on carcinogenic effects are not available.

### 2.7.2 Animal data

Two carcinogenicity studies of Astill et al. (1996) were made one with rats and another one with mice. In the study with rats, F344 rats received oral doses of 0, 50, 150 and 500 mg/kg per day EH in aqueous emulsion by gavage on 5 d/w for 24 months. The main study used 50 rats per sex and group, satellite studies were performed with 10 animals per sex and group (examination at 18 months of exposure) and 50 animals per sex and group (18 months exposure to EH, 6 months recovery period). EH was not carcinogenic in rats under the conditions of this study. In the study with mice, B6C3F1 mice received oral doses of 0, 50, 200 and 750 mg/kg per day EH in aqueous emulsion by gavage on 5 d/w for 18 months. The main study used 50 mice per sex and group, satellite studies were conducted with 10 animals per sex and group (examination at 13 months of exposure) and 50 animals per sex and group (13 months exposure to EH, 5 months recovery period). Female mice of the highest dose group of the main study showed a significant increase in hepatocellular carcinomas and of basophilic liver foci compared to the vehicle control. The incidences were not increased compared to the control group with gavage administration of water or to historic control values, when evaluated on the basis of 50 animals. Based on the number of survivors, the adjusted incidences were greater than that for historical control values. Therefore, EH was evaluated by the authors as an equivocal or weak carcinogen.

## 2.8 Reproductive toxicity

### 2.8.1 Human data

No relevant human data reported.

### 2.8.2 Animal data

#### *Fertility*

No studies on reproduction (fertility) with inhalation exposure to EH are available. Adverse effects in relation to this endpoint were not observed in an oral study with exposure of rats to 5 daily doses of 352 mg/kg per day (Sjöberg et al., 1986), but significant increases in prostate atrophy were reported in the study by Astill et al. (1996) in rats after chronic exposure to 500 mg/kg per day (NOAEL 50 mg/kg per day). Histopathological alterations (interstitial oedema, reduced spermiogenesis) were found in the testes of rats after repeated non-occlusive dermal exposure to 2 ml (1.67 g) EH per administration (Schmidt et al., 1973). Further effects of this study are described in section "repeated dose toxicity".

In vitro studies revealed no adverse effects of EH on sertoli cells or seminal vesicles (BG-Chemie, 1995; WHO, 1993).

#### *Developmental toxicity*

Groups of 15 pregnant Sprague-Dawley rats were exposed for 7 h/day to air or to an atmosphere saturated with EH vapour (according to the authors approximately 850 mg/m<sup>3</sup> or 160 ppm) on gestation days 1 - 9 (Nelson et al., 1988, 1989). EH reduced maternal feed intake, but no developmental effects were observed.



Pregnant Wistar rats were exposed to one oral dose of 0, 6.25 and 12.5 mmol/kg (814 and 1628 mg/kg per day) by gavage on day 12 of gestation. Seven litters were examined on day 20 of gestation. The treatment resulted in statistically significant and dose-related increases in malformed foetuses (controls: 0; 6.25 mmol/kg: 2.0%; 12.5 mmol/kg: 22.2%). In addition, foetal weights were reduced at the higher dose (et al., 1987). Because of the administered high doses (about half the LD<sub>50</sub>), maternal toxicity is not unlikely, but no information on maternal toxicity was given in this study.

In a study by Hellwig and Jäckh (1997), pregnant Wistar rats (10 animals per group) were gavaged with doses of 0, 130, 650 and 1300 mg/kg per day on gestation days 6 - 15. No adverse substance-related effects were seen in dams or foetuses at the lowest dose. Exposure to 650 mg/kg per day caused first signs of maternal toxicity (2 animals with piloerection), slightly reduced foetal weights and an increased incidence of skeletal variation and retardation. Exposure to the highest dose resulted in marked maternal toxicity (increased mortality, severe clinical symptoms of toxicity, organ damage) as well as effects in the offspring (increased number of resorptions and post implantation loss, marked reduction of foetal weights, increased number of visceral and skeletal malformations, skeletal variation and retardation). The NOAEL of this study was 130 mg/kg per day for maternal and developmental effects.

Pregnant CD-1 mice (28 animals per group) were exposed to EH via feed at concentrations of 0, 0.009, 0.03 and 0.09% (13, 43 and 129 mg/kg per day) on gestation days 0 - 17. Up to the highest dose, there were neither signs of maternal toxicity nor effects on fertility and development of the offspring (Price et al., 1991).

In a study by Tyl et al. (1992), pregnant F344 rats (8 animals per group in a range-finding study, 25 per group in the main study) were dermally exposed to 0, 252, 420, 840, 1680 and 2520 mg/kg per day undiluted EH on gestation days 6 - 15 for 6 h/d. Exposed animals showed skin irritation (see section "irritation and corrosivity"). Maternal toxicity was evident in form of a significantly decreased body weight gain at doses of 1680 mg/kg per day and above (maternal NOAEL 840 mg/kg per day). There were no developmental effects in all treated groups (developmental NOAEL 2520 mg/kg per day).

### **Methods of exposure monitoring and analysis**

OSHA method PV2033 is only partially validated. Samples are collected by drawing a known volume of air through a charcoal tube. Samples are desorbed with 1 mL of 1:99 dimethyl formamide: carbon disulfide and analyzed by gas chromatography with a flame ionization detector (GC-FID). The overall detection limit is 0.78 ppm based on a 10 L air sample.

## **Recommendations**

### *Systemic toxicity:*

Neurotoxicity is a typical endpoint of short-chained aliphatic alcohols, but there are only few data regarding this action of EH or similar substances. Headache, dizziness and fatigue were reported during occupational exposure to EH and other substances, but no exposure concentration was stated (Hollenbach et al., 1972). Single inhalation exposure of animals to concentrations of 164 ppm and above provoked clinical signs of central nervous depression (Bio/Dynamics, 1989; Scala and Burtis, 1973). No data was found concerning more subtle neurological effects in humans or animals.



EH is a peroxisome proliferator. The most sensitive species for this type of response are rats and dogs. Peroxisome proliferation in mice, humans or monkeys is less pronounced (BG-Chemie, 1995). EH and its main metabolite 2-ethylhexanoic acid were equipotent in this respect (Keith et al. 1992).

Studies with chronic oral exposure revealed NOAEL values of 50 mg/kg per day for rats and 200 mg/kg per day for mice (Astill et al., 1996). Applying route-to-route extrapolation, it is evident that systemic effects are not expected to occur at non-irritating concentrations.

#### *Reproductive toxicity:*

No maternal or developmental effects were observed in rats or mice exposed to concentrations of about 850 mg/m<sup>3</sup> (160 ppm) EH (Nelson et al., 1988, 1989) or oral doses up to 1300 mg/kg per day (Hellwig and Jäckh, 1997; Price et al., 1991). Thus, no developmental effects are to be expected at non-irritating concentrations.

Higher doses were toxic to the dams and produced embryotoxic, foetotoxic and teratogenic effects (Ritter et al., 1987; Hellwig and Jäckh, 1997). The concern for developmental toxicity at higher doses is supported by the observation of marked foetotoxicity and teratogenicity in various studies with 2-ethylhexanoic acid (EHA), the main metabolite of EH. A comparison of the corresponding LOAEL and NOAEL for EHA (Pennanen et al., 1992) with the NOAEL of EH (Hellwig and Jäckh, 1997; Price et al., 1991) showed that developmental risks due to EHA are not substantially higher than those posed by EH.

#### *Genotoxicity and carcinogenicity:*

Most of the available mutagenicity tests in vitro and in vivo yielded negative results. Liver tumours were observed only in mice and not in rats (Astill et al., 1996). As there was no indication of peroxisome proliferation in mice studies (but in rats) at doses higher than those chosen in the carcinogenicity studies (BASF AG, 1991a, b), peroxisome proliferation is probably not causative in the tumour formation. Because the tumourigenic dose in the mouse study exceeded the maximal tolerated dose (reduced body weight gain, increased mortality, liver and stomach lesions), cytotoxicity may have contributed to the carcinogenic effects. Furthermore, the B6C3F1 strain is especially sensitive to carcinogenic effects in the liver (Greim, 2000).

#### *Irritation*

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.

Additional tests were carried out in a human exposure chamber study by Ernstgård et al. (2009) showed a minimal but statistically significant increase in the rating of eye irritation in subjects exposed at 1 mg/m<sup>3</sup> (0.2 ppm) EH for 2 hours. The ratings of nasal irritation, throat



irritation, headache, dyspnoea, fatigue, dizziness, nausea and intoxication were not significantly affected. Further, no exposure-related effects on blink frequency, eye tear film break-up time, vital staining of the eye, nasal lavage biomarkers, transfer tests, or spirometric and rhinometric measures were seen. The negative findings in the Ernstgård et al. study, including several objective measurements, add additional support to the results by van Thriel et al.

No signs of irritation could be detected in rats repeatedly exposed by inhalation to 120 ppm (650 mg/m<sup>3</sup>) or in rats, mice or guinea pigs exposed once to 164 ppm (890 mg/m<sup>3</sup>) (Klimisch et al., 1998; Bio/Dynamics, 1989). Irritation was evident after a single inhalation exposure of rats for 6 h to 227 ppm (1230 mg/m<sup>3</sup>) (Scala and Burtis, 1973).

Based on the referred human exposure chamber studies, the health based 8-h OEL for 2-ethylhexanol is set to 1 ppm.

*Other assignments:*

Skin sensitisation was not observed in a study on 29 volunteers (Opdyke, 1979). Adequate animal studies are not available.

A "skin" notation is not considered necessary since the systemic toxicity of EH is very low.

No measurement difficulties are foreseen at the recommended OEL.



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