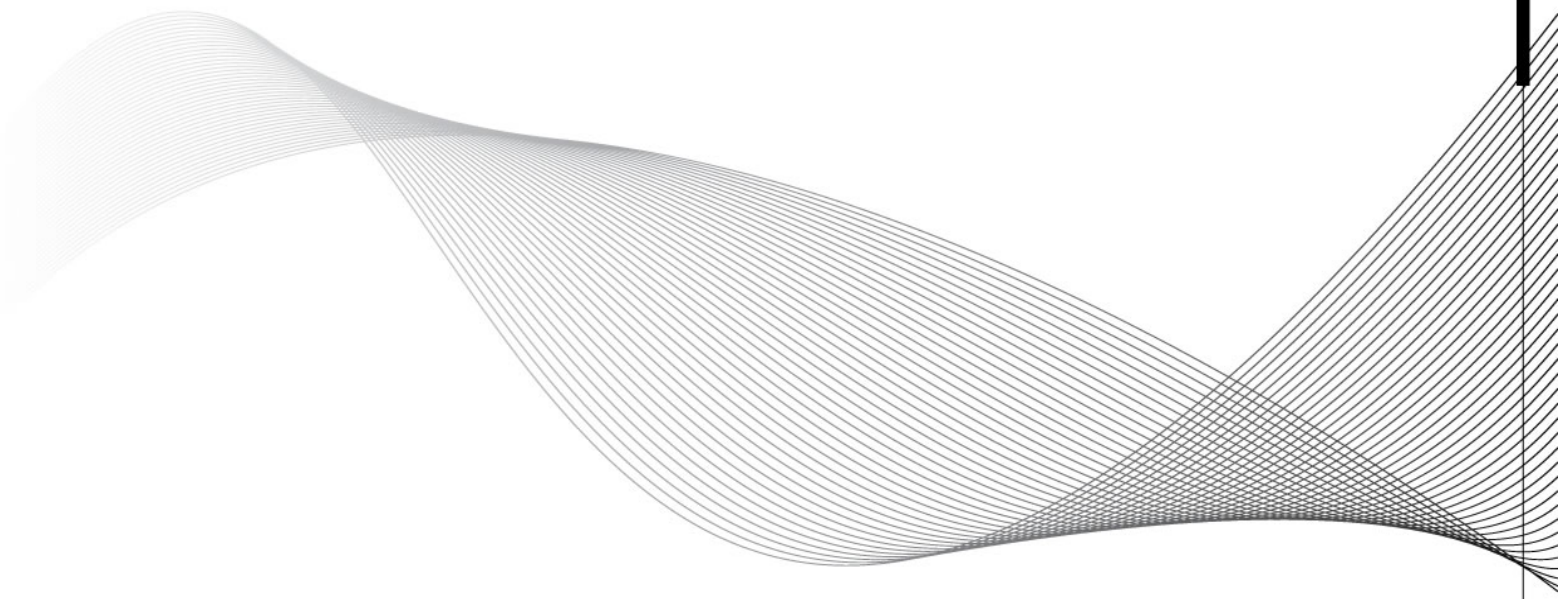
Social Europe



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

SCOEL/SUM/158

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European Commission

Table of Contents

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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.: -

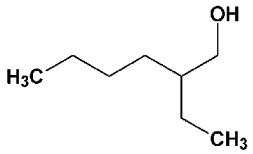
Classification: -

CAS No.: 104-76-7

MWt: 130.20

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

Structural formula:



CH_3-$(CH_2)_3$-$CH(C_2H_5)$-CH_2OH

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_{OW}) is 2.28. The substance has a density of 0.83 g/cm^3 (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-ethyl-hexacrylate (Verschueren, 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 degradate phtalate 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^3 (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^3, the maximum concentration being 2.7 mg/m3 (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^2 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^2 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-hexanoneacid. 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 mg/m³ (> 164 ppm) and less than 5300 mg/m³ (< 978 ppm) (BG-Chemie, 1995). A single 6 h inhalation exposure of rats, mice and guinea pigs to 227 ppm (1230 mg/m³) 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 ppm (890 mg/m³) 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 mg/kg. The dermal LD_{50} was 1980 to more than 2600 mg/kg in rabbits and more than 3000 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 mg/m³ (0.08 ppm - 0.13 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 mg/m³), 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 (twa 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^3 (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^3) 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^3) 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^3) for 6 h produced moderate irritation of the nose and throat (Scala and Burtis, 1973). The reported RD_{50} 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^3) (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^3) 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 resistence 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 ($polA^+/polA^-$) 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^3 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_{50}), 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^3 (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 efect 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^3 (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^3) or in rats, mice or guinea pigs exposed once to 164 ppm (890 mg/m^3) (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^3) (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.

References

Alarie, Y.; Nielsen, G.D.; Schaper, M.M., 2001
Animal bioassays for evaluation of indoor air quality. Chapter 23
In: Spengler, J.D.; McCarthy, J.F.; Samet, J.M., Indoor Air Quality Handbook. McGraw-Hill, 2001, 23.1-23.49

Albro, P.W., 1975
The metabolism of 2-ethylhexanol in rats
Xenobiotica, 10, 1975, 625-636, cited in BG-Chemie, 1995 and WHO, 1993

Astill, B.D.; Gingell, R.; Guest, D.; Hellwig, J.; Hodgson, J.R.; Kuettler, K.; Mellert, W.; Murphy, S.R.; Sielken, R.L.; Tyler, T.R., 1996
Oncogenicity testing of 2-ethylhexanol in Fischer 344 rats and B6C3F1 mice
Fundamental and Applied Toxicology, **31**, 1996, 29-41

Barber, E.D.; Teetsel, N.M.; Kolberg, K.F.; Guest, D., 1992
A comparative study of the rates of in vitro percutaneous absorption of eight chemicals using rat and human skin
Fundamental and Applied Toxicology, **19**, 1992, 493-497

BASF AG, Abteilung Toxikologie, 1991a
Report on the Study of the Oral Toxicity of 2-Ethylhexanol in Rats afterAdministration by Gavage (Aqueous Emulsion) for 3 Months
unveröffentlichter Bericht, Project No 31C0631/87077
im Auftrag der Chemical Manufacturers Association, Washington, USA, cited in BG-Chemie, 1995

BASF AG, Abteilung Toxikologie, 1991b
Report on a Limited Study of the Oral Toxicity of 2-Ethylhexanol in Rats afterAdministration by Gavage (Aqueous Emulsion) for 3 Months
unveröffentlichter Bericht, Project No 31C0631/87082
im Auftrag der Chemical Manufacturers Association, Washington, USA, cited in BG-Chemie, 1995

BG-Chemie, Berufsgenossenschaft der chemischen Industrie, 1995
2-Ethylhexanol (Nr. 114)
Toxikologische Bewertungen, Programm zur Verhütung von Gesundheitsschädigungen durch Arbeitsstoffe
Loseblattsammlung, 12. Erg. Lfg., Heidelberg, 1995

Bio/Dynamics, 1989
An Acute Inhalation Study of C-1257 (2-Ethylhexanol) in the Rat
Project No. 88-8085, im auftrag der Hoechst-Celanese Corporation, NTIS/OTS 0520664, Doc-ID 86-890001535, NTIS, Springfield, VA, USA, 1989, cited in Greim, 2000

Bushy Run Research Centre, Pennsylvania, USA, 1988
2-Ethylhexanol (2EH): Nine-Day Dermal, Oral Gavage, and Drinking Water Probe Studies in Rats
Bericht Nr. 50-614
im Auftrag der Chemical Manufacturers Association, Washington, USA
NTIS/OTS 0516482, cited in BG-Chemie, 1995

Deisinger, P.J.; Boatman, R.J.; Guest, D., 1994
Metabolism of 2-ethylhexanol administered orally and dermally to the female Fischer 344 rat
Xenobiotica, **24**, 1994, 429-440

ECB, EuropeanChemicalsBureau, 2000
IUCLID, International Uniform Chemical Information Database

European Commission, 2000
http://ecb.jrc.it/esis/esis.php?PGM=ora&DEPUIS=autre

Ernstgård L, Norbäck D, Nordquist T, Wieslander G, Wålinder R, Johanson G, 2009?
Acute effects of exposure to vapours of 2-ethyl-1-hexanol in humans. Indoor Air (accepted)

Greim, H., 2000
Gesundheitsschädliche Arbeitsstoffe, Toxikologisch-arbeitsmedizinische Begründungen von MAK-Werten, Loseblattsammlung, 30. Lfg.
DFG, Deutsche Forschungsgemeinschaft, WILEY-VCH Verlag, Weinheim, 2000

Greim, H., 2006
Gesundheitsschädliche Arbeitsstoffe, Toxikologisch-arbeitsmedizinische Begründungen von MAK-Werten, Loseblattsammlung, 41. Lfg.
DFG, Deutsche Forschungsgemeinschaft, WILEY-VCH Verlag, Weinheim, 2006

Hellwig, J.; Jäckh, R., 1997
Differential prenatal toxicity of one straight-chain and five branched-chain primary alcohols in rats
Food and Chemical Toxicology, **35**, 1997, 489-500

Hodgson, J.R.; Myhr, B.C.; McKeon, M.; Brusick, D.J.; 1982
Evaluation of di(2-ethylhexyl)phthalate and ist major metabolites in the primary rat hepatocyte unscheduled DANN synthesis assay
Environmental Mutagenesis, **4**, 1982, 388-389, cited in BG-Chemie, 1995

Hollenbach, K.; Schmidt, P.; Stremmel, B., 1972
Tierexperimentelle Untersuchungen zur Blutdruckwirksamkeit von Thioglykolsäureisooctylester, Thioglykolsäure und 2-Anthylhexanol
Zeitschrift für die gesamte Hygiene, **18**, 1972, 481, cited in WHO, 1993

Hüls AG, Ps-Biologie/Toxikologie, 1987a
Prüfung der akuten Hautreizung von 2-Ethylhexanol
unveröffentlichter Bericht Nr. 1047, 1987, cited in BG-Chemie, 1995

Hüls AG, Ps-Biologie/Toxikologie, 1987b
Prüfung der akuten Augen- und Schleimhautreizung von 2-Ethylhexanol
unveröffentlichter Bericht Nr. 1048, 1987, cited in BG-Chemie, 1995

Keith, Y.; Cornu, M.C.; Canning, P.M.; Foster, J.; Lhuguenot, J.C.; Elcombe, C.R., 1992
Peroxisome proliferation due to (2-diethylhexyl) adipate, 2-ethylhexanol and 2-ethylhexanoic acid
Archives of Toxicology, **66**, 1992, 321-326

Kirby, P.E.; Pizzarello, R.F.; Lawlor, T.E.; Haworth, S.R.; Hodgson, J.R., 1983
Evaluation of di-(2-ethylhexyl) phthalate and ist major metabolites in the Ames test and L5178Y mouse lymphoma mutagenicity assay
Environmental Mutagenesis, 5, 1983 , 657-663, cited in BG-Chemie, 1995

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

LBI, Litton Bionetics, Inc., Kensington, Maryland, USA, 1982
Mutagenicity Evaluation of 2-ethylhexanol (2-EH) in the Mouse Micronucleus Test
unveröffentlichter Bericht LBI Project No. 20996
im Auftrag der Chemical Manufacturers Association, Washington, USA, 1982, cited in BG-Chemie, 1995

LBI, Litton Bionetics, Inc., Kensington, Maryland, USA, 1985
Evaluation of 2-ethylhexanol (2-EH) in the CHO/HGPRT forward mutation assay
Bericht LBI Project No. 20989

im Auftrag der Chemical Manufacturers Association, Washington, USA, 1985
NTIS/OTS 0508498, cited in BG-Chemie, 1995 and ECB, 2000

Mellon Institute of Industrial Research, University of Pittsburgh, 1940
Summary of the toxicity of Octyl Alcohol (2-Ethyl Hexanol)
Bericht, Industrial Fellowship No. 274-3
im Auftrag der Carbide & Carbon Chemicals Corporation. NTIS/OTS 0515545, 1940, cited in BG-Chemie, 1995

Mellon Institute of Industrial Research, University of Pittsburgh, 1961a
Gross Results of Three Months of Inclusion of 2-Ethyl Hexanol in the Diet of Rats – Spezial Report
Bericht Nr. 23-61
im Auftrag der Union Carbide Chemicals Co. NTIS/OTS 0515388, 1961, cited in BG-Chemie, 1995

Mellon Institute of Industrial Research, University of Pittsburgh, 1961b
Results of Three Months of Inclusion of 2-Ethyl Hexanol in the Diet of Rats – Pathology Report
Bericht Nr. 24-8
im Auftrag der Union Carbide Chemicals Co. NTIS/OTS 0515388, 1961, cited in BG-Chemie, 1995

MRI, Midwest Research Institute, Kansas City, USA, 1981
Evaluation of 2-ethylhexanol in the E. coli DANN repair-suspension assay
Bericht, MRI Project No. 4822-E
im Auftrag der Tenneco Chemicals, Inc., Saddle Brook, New Jersey, USA, 1981
NTIS/OTS 0515130, cited in BG-Chemie, 1995 and ECB, 2000

Nelson, B.K.; Brightwell, W.S.; Khan, A.; Hoberman, A.M.; Krieg, E.F., 1988
Teratological evaluation of 1-pentanol, 1-hexanol and 2-ethyl-1-hexanol administered by inhalation to rats
Teratology, **37**, 1988, 479-480, cited in BG-Chemie, 1995

Nelson, B.K.; Brightwell, W.S.; Khan, A.; Krieg, E.F.; Hoberman, A.M., 1989
Developmental toxicology evaluation of 1-pentanol, 1-hexanol, and 2-ethyl-1-hexanol administered by inhalation to rats
Journal of the American College of Toxicology, **8**, 1989, 405-410, cited in BG-Chemie, 1995

Opdyke, D.L.J., 1979
Fragrance raw materials monographs. 2-Ethylhexanol
Food and Cosmetics Toxicology, **17**, 1979, 775-777, cited in BG-Chemie, 1995

Pennanen, S.; Tuovinen, K.; Huuskonen, H.; Komulainen, H., 1992
The developmental toxicity of 2-ethylhexanoic acid in Wistar rats
Fundamental and Applied Toxicology, **19**, 1992, 505-511

Phillips, J.B.; James, T.E.B.; Gangolli, S.D., 1982
Genotoxicity studies of di(2-ethylhexyl)phthalate and ist metabolites in CHO cells
Mutation Research, 102, 1982, 297-304, cited in BG-Chemie, 1995

Price, C.J.; Tyl, R.W.; Marr, M.C.; Myers, c.B.; Morrissey, R.E.; Heindel, J.J.; Schwetz, B.A., 1991
Developmental toxicity evaluation of DEHP metabolites in Swiss mice
Teratology, **43**, 1991, 457, cited in BG-Chemie, 1995

Putman, D.L.; Moore, W.A.; Schechtman, L.M.; Hodgson, J.R., 1983
Cytogenetic evaluation of di(2-ethylhexyl)phthalate and ist major metabolites in Fischer 344 rats
Environmental Mutagenesis, **5**, 1983, 227-231, cited in BG-Chemie, 1995

Ritter, E.J.; Scott, W.J.; Randall, J.L.; Ritter, J.M., 1987
Teratogenicity of di(2-ethylhexyl) phthalate, 2-ethylhexanol, 2-ethylhexanoic acid, and

valproic acid, and potentation by caffeine
Teratology, **35**, 1987, 41-46, cited in BG-Chemie, 1995

Rushbrook, C.J.; Jorgenson, T.A.; Hodgson, J.R., 1982
Dominant lethal study of di(2-ethylhexyl)phthalate and ist major metabolites in ICR/SIM mice
Environemntal Mutagenesis, **4**, 1982, 387, cited in BG-Chemie, 1995

Ruth, J.H., 1986
Odor tresholds and irritation levels of several chemical substances: a review
American Industrial Hygiene Association Journal, **47**, 1986, A142-A151

Scala, R.A.; Burtis, E.G., 1973
Acute toxicity of a homologous series of branched-chain primary alcohols
American Industrial Hygiene Association Journal, **34**, 1973, 493-499

Schaper, M., 1993
Development of a database for sensory irritants and its use in establishing occupational exposure limits
American Industrial Hygiene Association Journal, **54**, 1993, 488-544

Schmidt, P.; Gohlke, R.; Rothe, R., 1973
Zur Toxizität einiger C8-Aldehyde und –Alkohole
Zeitschrift für die gesamte Hygiene, **19**, 1973, 485-490, cited in BG-Chemie, 1995

Seed, J.L., 1982
Mutagenic activity of phthalate esters in bacterial liquid suspension assays
Environmental Health Perspectives, **45**, 1982, 111-114, cited in BG-Chemie, 1995 and ECB, 2000

Sjöberg, P.; Bondesson, U.; Gray, T.J.B.; Plöen, L., 1986
Effects of di-(2-ethylhexyl phthalate and five of ist metabolites on rat testis in vivo and in vitro
Acta Pharmacologica et Toxicologica, **58**, 1986, 225-233, cited in BG-Chemie, 1995

Tomita, L.; Nakamura, Y.; Aoki, N.; Inui, N., 1982
Mutagenic/carcinogenic potential of DEHP and MEHP
Environmental Health Perspectives, **45**, 1992, 119-125, cited in BG-Chemie, 1995 and ECB, 2000

Tyl, R.W.; Fisher, L.C.; Kubena, M.F.; Vrbanic, M.A.; Gingell, R.; Guest, D.; Hodgson, J.R.; Murphy, S.R.; Tyler, T.R., Astill, B.D., 1992
The developmental toxicity of 2-ethylhexanol applied dermally to pregnant Fischer 344 rats
Fundamental and Applied Toxicology, **19**, 1992, 176-185, cited in BG-Chemie, 1995 and WHO, 1993

von Däniken, A.; Lutz, W.K.; Jäckh, R.; Schlatter, C., 1984
Investigation of the potential for binding of di(2-ethylhexyl) phthalate (DEHP) and di(2-ethylhexyl) adipate (DEHA) to liver DNA in vivo
Toxicology and Applied Pharmacology, **73**, 1984, 373-387, cited in BG-Chemie 1995

WHO, World Health Organization, 1993
Ethyl-1-hexanol, 2-
Toxicological Evaluation of Certain Food Additives and Contaminants. Forty-first Meeting of the Joint FAO/WHO Expert Committee on Food Additives. WHO Food Additives Series, No. 32
Geneva, 1993
http://www.inchem.org/pages/jecfa.html

New references

Bako-Biro, Z., P. Wargocki, et al. (2004). "Effects of pollution from personal computers on perceived air quality, SBS symptoms and productivity in offices." Indoor Air **14**(3): 178-87.

Bornehag, C. G., J. Sundell, et al. (2005). "'Dampness' at home and its association with airway, nose, and skin symptoms among 10,851 preschool children in Sweden: a cross-sectional study." Indoor Air **15 Suppl 10**: 48-55.

Horn, O., S. Nalli, et al. (2004). "Plasticizer metabolites in the environment." Water Research **38**(17): 3693-8.

Iregren, A. (1998). Computer-assisted testing. Occupational neurotoxicology. L. G. Costa and L. Manzo. Boca Raton, CRC Press**:** 213-232.

Janson, C., D. Norback, et al. (2005). "Insomnia is more common among subjects living in damp buildings." Occupational & Environmental Medicine **62**(2): 113-8.

Kamijima, M., K. Sakai, et al. (2002). "2-Ethyl-1-hexanol in indoor air as a possible cause of sick building syndroms." J Occup Health **44**: 186-191.

Kamijima, M., E. Shibata, et al. (2005). "[Indoor air pollution due to 2-ethyl-1-hexanol airborne concentrations, emission sources and subjective symptoms in classroom users]." Nippon Koshu Eisei Zasshi - Japanese Journal of Public Health **52**(12): 1021-31.

Kiesswetter, E., C. v. Thriel, et al. (2005). "Eye blinks as indicator for sensory irritation during constant and peak exposures to 2-ethylhexanol." Environmental Toxicology and Pharmacology **19**(3): 531-541.

Nalli, S., O. J. Horn, et al. (2006). "Origin of 2-ethylhexanol as a VOC." Environmental Pollution **140**(1): 181-5.

Norback, D., E. Bjornsson, et al. (1999). "Current asthma and biochemical signs of inflammation in relation to building dampness in dwellings." International Journal of Tuberculosis & Lung Disease **3**(5): 368-76.

Norback, D., G. Wieslander, et al. (2000). "Asthma symptoms in relation to measured building dampness in upper concrete floor construction, and 2-ethyl-1-hexanol in indoor air." International Journal of Tuberculosis & Lung Disease **4**(11): 1016-25.

Putus, T., A. Tuomainen, et al. (2004). "Chemical and microbial exposures in a school building: adverse health effects in children." Archives of Environmental Health **59**(4): 194-201.

Sakai, K., M. Kamijima, et al. (2006). "Indoor air pollution by 2-ethyl-1-hexanol in non-domestic buildings in Nagoya, Japan." Journal of Environmental Monitoring **8**(11): 1122-8.

Tuomainen, A., M. Seuri, et al. (2004). "Indoor air quality and health problems associated with damp floor coverings." International Archives of Occupational & Environmental Health **77**(3): 222-6.

Tuomainen, A., H. Stark, et al. (2006). "Experimental PVC material challenge in subjects with occupational PVC exposure." Environmental Health Perspectives **114**(9): 1409-13.

van Thriel, C., E. Kiesswetter, et al. (2007). "From neurotoxic to chemosensory effects: new insights on acute solvent neurotoxicity exemplified by acute effects of 2-ethylhexanol." Neurotoxicology **28**(2): 347-55.

van Thriel, C., E. Kiesswetter, et al. (2005). "An integrative approach considering acute symptoms and intensity ratings of chemosensory sensations during experimental exposures." Environmental Toxicology and Pharmacology **19**(3): 589-598.

van Thriel, C., A. Seeber, et al. (2003). "Physiological and psychological approaches to chemosensory effects of solvents." Toxicology Letters **140-141**: 261-71.

Wieslander, G., D. Norback, et al. (1999). "Nasal and ocular symptoms, tear film stability and biomarkers in nasal lavage, in relation to building-dampness and building design in hospitals." International Archives of Occupational & Environmental Health **72**(7): 451-61.