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TOXICOLOGICAL EVALUATIONS

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TOXICOLOGICAL EVALUATION

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2-Ethylhexanal No. 113

CAS No. 123-05-7

BG Chemie
Berufsgenossenschaft der chemischen Industrie

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2-Ethylhexanal

In addition to 2-ethylhexanal, Toxicological Evaluations on 2-ethylhexanoic acid (No. 275) and 2-ethylhexanol (No. 114) are available and can be consulted for comparison. Large bodies of data are available on both 2-ethylhexanol and 2-ethylhexanoic acid. Biotransformation studies demonstrate that 2-ethylhexanol is rapidly and quantitatively metabolised to 2-ethylhexanoic acid. The toxic effects of 2-ethylhexanol and 2-ethylhexanoic acid seen after subchronic exposure are nearly identical. 2-Ethylhexanal is formed as the oxidative intermediate during the conversion of 2-ethylhexanol to 2-ethylhexanoic acid, and it can therefore be assumed that 2-ethylhexanal is comparable to those compounds in terms of toxicological profile following systemic administration.

1 Summary and assessment

The acute oral and dermal toxicities of 2-ethylhexanal are low with LD_{50} values > 2000 mg/kg body weight (LD_{50} rat oral: 2630 to 6600 mg/kg body weight; LD_{50} mouse oral: 3550 and 3200 to 6400 mg/kg body weight, depending on the source of information; LD_{50} rabbit, rat and guinea pig dermal > 6830 mg/kg body weight following 24-hour application). Weakness, prostration, ataxia, narcosis, reeling, lying on the abdomen, roughening of the coat, diarrhoea, convulsions and slight tremor have been reported as signs of toxicity following acute oral administration. Dermal application results in erythema and oedema formation in the application area, with one guinea pig study also reporting necrosis with scarring and eschar formation. Necropsy findings in animals which succumbed in oral studies have been reported to include lung congestion and haemorrhage, congestion of the liver and kidneys and congestion and opaqueness of the gastrointestinal tract. Terminal necropsy of survivors was without findings with the exception of 2 out of 5 female rats treated with 2500 mg/kg body weight which exhibited hyperkeratosis of the nonglandular gastric mucosa in one study.

Acute inhalation toxicity is also low. Thus, 4-hour whole-body exposure to the maximum 2-ethylhexanal (97.96% pure) concentration that was technically attainable at 20 °C, approx. 6830 ± 1320 mg/m³, was not lethal to rats

in an acute inhalation study conducted in accordance with OECD guideline No. 403. Clinical signs of toxicity seen in the animals included severe nose and eye irritation, reduced respiratory rate and reduced reaction to external stimuli. Necropsy after the 14-day observation period revealed deep-pink to red mottled areas covering the lung surfaces. When administered intraperitoneally, 2-ethylhexanal is more toxic. For the mouse, LD_{50} values have been reported as approx. 247 (0.3 ml), approx. 329 (0.4 ml) and 1600 to 3200 mg/kg body weight, while for the rat they are given as 500 and 800 to 1600 mg/kg body weight, depending on the source of information.

The potential of 2-ethylhexanal to cause sensory irritation of the upper respiratory tract was assessed in an Alarie test conducted in the Swiss-Webster mouse. 2-Ethylhexanal exposure resulted in concentration-dependent depression of respiratory rate in this test. The investigators evaluated 2-ethylhexanal as a sensory irritant because respiratory rate was depressed due to delayed expiration rather than prolongation of the pauses between individual breaths as in pulmonary irritation. The study was carried out in accordance with the Standard Test Method “American Society for Testing and Materials” designated number E 9/81-84. Classification of 2-ethylhexanal on the basis of the criteria used in analogous studies of 4-chlorobutanoic acid chloride (No. 163) would require that, in respect of sensory irritation, the chemical be placed in a category even below that of a “mild sensory irritant”.

The toxic effects of 2-ethylhexanal following repeated administration were investigated in Fischer-344 rats in an inhalation study conducted in accordance with OECD guideline No. 412. The scope of investigation as specified in OECD guideline No. 412 was expanded to include a comparative study of hepatic peroxisome proliferation against positive controls treated with di-(2-ethylhexyl) phthalate. Treatment at the top concentration level of 250 ppm (approx. 1334 mg/m³) reduced body weight gain and food conversion efficiency, caused a leftward shift in white blood cell count with a decrease in lymphocytes and an increase in neutrophils and, in the absence of macroscopic or histopathological correlates, resulted in changes in organ weights of the testes, adrenal glands, kidneys, liver, lungs and thymus, and in males, also of the heart. Additionally, but only in females, increases were noted in relative adrenal weights at and above the low test concentration of 25 ppm (approx. 136 mg/m³) as well as in relative kidney weights at the intermediate test concentration of 100 ppm (approx. 543 mg/m³). The

high concentration group tested at 250 ppm showed changes in carbohydrate metabolism (decreased fasting levels of blood glucose) and lipid metabolism (increased triglycerides and decreased cholesterol). Increases in plasma alkaline phosphatase activity were noted in all concentration groups except for the 100 ppm group of males, whereas the activity levels of the other marker enzymes of hepatotoxicity, alanine aminotransferase and aspartate aminotransferase, remained unchanged. Compared with di-(2-ethylhexyl) phthalate, 2-ethylhexanal induced very little hepatic peroxisome proliferation. Activity levels of the marker enzymes of peroxisome proliferation, i.e. cyanide-insensitive palmitoyl-CoA oxidase, lauric acid 11-hydroxylase and lauric acid 12-hydroxylase, were only very slightly increased as compared with the positive control. The number and size of peroxisomes and the amount of smooth endoplasmic reticulum were not increased in centrilobular and portal hepatocytes. The investigators evaluated 2-ethylhexanal as a very weak peroxisome proliferator and determined a *no effect level* (NOEL) of 25 ppm (approx. 136 mg/m³) for this effect. A further study, in which male rats were administered 2% 2-ethylhexanal (ca. 1333 mg/kg body weight/day) in their feed over a period of 3 weeks, also showed the chemical to have only a moderate peroxisome proliferating effect.

Application of 2-ethylhexanal to the skin of rabbits and guinea pigs results in reversible marked irritation with erythema, oedema and eschar formation within 14 to 19 days. Furthermore, the treated skin is described as hardened, dry, chapped and/or scaly. Evaluation of 2-ethylhexanal irritancy in rabbit studies conducted in accordance with Directive 84/449/EEC and/or OECD guideline No. 404 encompasses the range from irritant to severely irritant. In a guinea pig skin irritation study in which the chemical was occlusively applied to the depilated abdominal skin for 24 hours, 2-ethylhexanal was evaluated as moderately irritant, but not corrosive.

In the rabbit eye, 2-ethylhexanal causes temporary marked irritation with reddening, oedema formation, iritis, ocular discharge and positive fluorescein test results. 2-Ethylhexanal proved to cause minimal mucous membrane irritation in a study conducted in accordance with Directive 84/449/EEC and evaluated in accordance with Directive 83/467/EEC. The study established the mean numeric irritation indices of 0.0, 0.4, 0.6 and 0.2 for clouding of the cornea, iritis, reddening of the conjunctivae and conjunctival swelling, respectively. All findings were reversible 72 hours after treatment.

2-Ethylhexanal was evaluated as mildly irritating to the eye in a study conducted in accordance with OECD guideline No. 405 in which the effects cleared up to a considerable extent after 72 hours and were fully reversible after 10 to 13 days.

In the Salmonella/microsome assay, 2-ethylhexanal is not mutagenic in *Salmonella typhimurium* strains TA 97, TA 98, TA 100 and TA 1535, either with or without metabolic activation. A mouse micronucleus test with 2-ethylhexanal, administered orally at 500, 1000 or 2000 mg/kg body weight, showed an increase in micronucleated polychromatic erythrocytes 24 hours after administration. The increase was dose-dependent and, in the top dose group, statistically significant, thus indicating a positive response. At 48 hours after administration, the increase in micronucleus frequencies was only slight and statistically nonsignificant. Overall, 2-ethylhexanal thus produced a positive response in this test system.

A maternally nontoxic oral dose of 2-ethylhexanal of 300 mg/kg body weight was administered to CD rats in an embryotoxicity/teratogenicity study conducted in accordance with OECD guideline No. 414. The foetuses showed incomplete ossification, and foetal weights were slightly low. These changes were considered transient in nature, rather than representing permanent lesions; they were not considered to be of toxicological relevance during later development. Following treatment of dams at the maternally toxic dose level of 800 mg/kg body weight (marked clinical signs of toxicity, weight loss or reduced body weight gain, and low food consumption), foetuses were observed to have a large number of visceral and skeletal abnormalities. The *no observed adverse effect level* (NOAEL) for maternal toxicity and developmental toxicity found in this oral embryotoxicity/teratogenicity study in the CD rat was 300 mg/kg body weight.

In a maximisation test carried out in human subjects, 2-ethylhexanal produced no skin sensitisation.

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (“MAK-Kommission”) has listed 2-ethylhexanal in the “Yellow Pages” of the List of MAK and BAT Values 2004 on the suggestion of BG Chemie in order that a MAK value be established for the chemical.

2 Name of substance

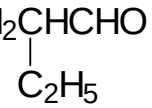
2.1	Usual name	2-Ethylhexanal
2.2	IUPAC name	2-Ethylhexanal
2.3	CAS No.	123-05-7
2.4	EINECS No.	204-596-5

3 Synonyms, common and trade names

2-Äthylcapronaldehyde
2-Äthylhexanal
2-Äthylhexanal-1
Butylethylacetaldehyde
Butylethylethanal
Ethylbutylacetaldehyd
Ethylbutylacetaldehyde
α-Ethylcaproaldehyde
2-Ethylcaproaldehyde
2-Ethylcapronaldehyde
Ethylhexaldehyde
2-Ethylhexaldehyde
α-Ethylhexanal
2-Ethylhexanal-1
2-Ethylhexylaldehyd
2-Ethylhexylaldehyde
3-Formylheptane
Hexanal, 2-ethyl-
β-Propyl-α-ethylacrolein
Secondary Octylaldehyde

4 Structural and molecular formulae

4.1 Structural formula



4.2 Molecular formula $C_8H_{16}O$

5 Physical and chemical properties

5.1	Molecular mass, g/mol	128.21	
5.2	Melting point, °C	< –50	(Creanova, 1998; Hüls, 1995)
		< –60	(Hoechst, 1993; Kohlpaintner et al., 2000)
		–85	(BASF, 1997)
5.3	Boiling point, °C	Ca. 160	(Creanova, 1998; Hüls, 1995)
		162	(BASF, 1997)
		163	(Kohlpaintner et al., 2000)
		163.4	(Sax, 1999)
		168	(Hoechst, 1993)
5.4	Vapour pressure, hPa	2 (at 20 °C)	(BASF, 1997; Creanova, 1998; Hüls, 1995)
		2.4 (at 20 °C)	(Hoechst, 1993)
		7 (at 50 °C)	(BASF, 1988 a)
5.5	Density, g/cm³	0.818–0.821 (at 20 °C)	(Hoechst, 1996)
		0.820 (at 20 °C)	(Creanova, 1998; Hüls, 1995; Kohlpaintner et al., 2000)
		0.8205	(Sax, 1999)
		0.822 (at 20 °C)	(BASF, 1997)
		0.8540 (at 20 °C)	(Lide and Frederikse, 1996)
5.6	Solubility in water	< 0.02% (at 20 °C)	(Falbe et al., 1985)
		0.04 g/100 ml	(Brabec, 1993)
		< 0.2 g/l (at 20 °C)	(Hoechst, 1993)
		Ca. 0.8 g/l	(Creanova, 1998; Hüls, 1995)
		10 mg/l (at 20 °C)	(BASF, 1997)
5.7	Solubility in organic solvents	Soluble in ethyl ether and ethanol but poorly soluble in tetrachloromethane	(Lide and Frederikse, 1996)
5.8	Solubility in fat	log P_{ow}: 2.518 (calculated)	(BASF, 1989)
		log P_{ow}: 2.71 (calculated)	(Hoechst, 1997)
		log P_{ow}: 2.73 (calculated)	(Hüls, 1995; Creanova, 1998; Hoechst, 1994)
		log P_{ow}: 3.07 (determined by experiment at 25 °C in accordance with OECD guideline No. 107)	(BASF, 1988 b)

5.9	pH value	Ca. 4 (Creanova, 1998; Hüls, 1995) Weakly acidic (0.2 g/l water) (Hoechst, 1993)
5.10	Conversion factor	1 ml/m³ (ppm) ≙ 5.32 mg/m³ 1 mg/m³ ≙ 0.188 ml/m³ (ppm) (at 1013 hPa and 25 °C)

6 Uses

Used as an intermediate in the manufacture of 2-ethylhexanol, 2-ethylhexanoic acid and 2-ethylhexylamines. Condensation with aromatic amines yields products which are used as vulcanising agents and antioxidants in the rubber industry (Kohlpaintner et al., 2000).

Combinations with other chemicals are used as surface disinfectants (Eggensperger, 1976; Kohlpaintner et al., 2000).

7 Experimental results

7.1 Toxicokinetics and metabolism

No information available on 2-ethylhexanal.

Metabolisation of 2-ethylhexanol (No. 114) to 2-ethylhexanoic acid (No. 275)

2-Ethylhexanol undergoes oxidative biotransformation to 2-ethylhexanoic acid in a nearly quantitative manner (cf. BG Chemie, 1995; Deisinger et al., 1994). Aldehydes are the oxidative intermediates which form during metabolic transformation of primary alcohols to their corresponding acids. It can therefore be assumed that 2-ethylhexanal also undergoes oxidative biotransformation to 2-ethylhexanoic acid following systemic administration. 2-Ethylhexanoic acid is metabolised by conjugation with glucuronic acid as well as by cytochrome P-450-dependent ω-oxidation and ω-1-oxidation. In addition, 2-ethylhexanoic acid, similarly to fatty acids, is likely to be broken down by β-oxidation, with mitochondrial and, in particular, peroxisomal catabolism ultimately leading to acetyl-CoA. The major metabolites to be

found in urine include the glucuronide conjugate of 2-ethylhexanoic acid as well as 2-ethyl-1,6-hexanedioic acid and 6-hydroxy-2-ethylhexanoic acid and their glucuronide conjugates. Unmetabolised 2-ethylhexanoic acid accounts for only a small percentage of the amounts excreted in urine. With increasing doses, the portion of glucuronidated 2-ethylhexanoic acid increases, while the portion of cytochrome P-450-dependent more strongly oxidised metabolites decreases. Following repeated administration, there is a decrease in total elimination and in the amounts of glucuronidated 2-ethylhexanoic acid and cytochrome P-450-dependent metabolites, compared with single-dose administration. It has been suggested that repeated administration induces β-oxidation of 2-ethylhexanoic acid and results in the compound being incorporated into normal cellular metabolism to a greater extent (cf. BG Chemie, 2000 a; Eastman Kodak, 1987; English et al., 1989; Pennanen et al., 1991; Rettenmeier, 1997).

7.2 Acute and subacute toxicity

Acute toxicity

The results from acute toxicity studies of 2-ethylhexanal following oral administration, dermal application, inhalation and intraperitoneal administration are summarised in Table 1.

In the rat and mouse, acute toxicity of 2-ethylhexanal was found to be low after oral administration with LD_{50} values > 2000 mg/kg body weight (rat: 2630 to 6600 mg/kg body weight, mouse: 3550 and 3200 to 6400 mg/kg body weight, depending on the source of information). Weakness, prostration, ataxia, narcosis, reeling, lying on the abdomen, roughening of the coat, diarrhoea, convulsions and slight tremor have been reported as signs of toxicity (BASF, 1964; Eastman Kodak, 1957, 1960, 1988; Mellon Institute, 1951; Smyth et al., 1951). Necropsy findings in animals which succumbed included lung congestion and haemorrhage, congestion of the liver and kidneys and congestion and opaqueness of the gastrointestinal tract (Eastman Kodak, 1988; Mellon Institute, 1951; Smyth et al., 1951). Necropsy of survivors was without findings with the exception of 2 out of 5 female rats treated with 2500 mg/kg body weight which exhibited hyperkeratosis of the nonglandular gastric mucosa (Eastman Kodak, 1988).

Acute inhalation toxicity of 2-ethylhexanal is also low. Thus, 4-hour whole-body exposure to the maximum concentration of 2-ethylhexanal (97.96% pure) that was technically attainable at 20 °C, approx. 6830 ± 1320 mg/m³, was not lethal to rats in an acute inhalation study conducted in accordance with OECD guideline No. 403. Clinical signs of toxicity seen in the animals included severe nose and eye irritation, reduced respiratory rate and reduced reaction to external stimuli. Necropsy after the 14-day observation period revealed deep-pink to red mottled areas covering the lung surfaces (BIBRA, 1991 a).

Low toxicity following acute inhalation exposure is also suggested by the findings from inhalation hazard tests carried out in the rat, in which no animal died after 8-hour or 42-minute exposure, depending on the study, to atmosphere enriched with or saturated with 2-ethylhexanal at 20 °C or room temperature (theoretical concentration: 30100 mg/m³), and in which only exposure to atmosphere generated at 100 °C (theoretical 2-ethylhexanal concentration: 130000 mg/m³) was lethal to 3 out of 3 animals (BASF, 1964; Eastman Kodak, 1960).

In further studies on the acute inhalation toxicity of 2-ethylhexanal all 6 animals died after exposure to 8000 ppm (approx. 42560 mg/m³) for 4 hours. After 4-hour exposure to 4000 ppm (approx. 21280 mg/m³) only one out of 6 rats succumbed, and 6-hour exposure to 145 ppm (approx. 760 mg/m³) was survived by all animals (Mellon Institute, 1951; Smyth et al., 1951).

Acute dermal toxicity was also very low when investigated in the rabbit, rat and guinea pig, LD_{50} values being clearly > 2000 mg/kg body weight (4143 to > 16400 mg/kg body weight; Eastman Kodak, 1957, 1960, 1988; Smyth et al., 1951; Mellon Institute, 1951; Anonymous, 1988).

When administered intraperitoneally, 2-ethylhexanal was markedly more toxic. For the mouse, LD_{50} values were reported as approx. 247, approx. 329 and 1600 to 3200 mg/kg body weight, while for the rat they were given as 500 and 800 to 1600 mg/kg body weight (BASF, 1964; Eastman Kodak, 1957, 1960; Dave and Lidman, 1978).

Beginning of Table 1

Table 1. Acute toxicity studies with 2-ethylhexanal

Species, strain, sex[1]	Route	Dose (mg/kg body weight or mg/m³)	Purity	Effect	Observation period	Reference
Rat	oral	ca. 2630 (3.2 ml), administered as a 30% aqueous tragacanth gum emulsion	no data	LD_{50}; reeling, lying on the abdomen, diarrhoea, narcosis-like state; necropsy: no findings	14 days	BASF, 1964
Rat	oral	ca. 2877 (3.5 ml), administered as a 30% aqueous tragacanth gum emulsion	no data	LD_{50}; reeling, lying on the abdomen, diarrhoea, narcosis-like state; necropsy: no findings	7 days	BASF, 1964
Rat, Crl:CD(SD)®BR, male	oral	3078	no data	LD_{50}; weakness, death within 24 hours after administration; necropsy of deceased animals: oedema of the glandular gastric mucosa, 1/5 animals with pallor and 1/5 animals with brown discoloration of the glandular gastric mucosa; terminal necropsy: no findings	14 days	Eastman Kodak, 1988
Rat	oral	3200, undiluted	no data	mortality: 0/5, body weight development unaffected, weakness, slight tremor	14 days	Eastman Kodak, 1960
Rat	oral	3200–6400, undiluted	no data	LD_{50}; weakness, ataxia, death within 5 days after administration	14 days	Eastman Kodak, 1957
Rat, Crl:CD(SD)®BR, female	oral	3536	no data	LD_{50}; weakness, death within 24 hours after administration; necropsy of deceased animals: pallor and oedema of the glandular gastric mucosa; terminal necropsy findings: hyperkeratosis of the nonglandular gastric mucosa in 2/5 animals treated with 2500 mg/kg	14 days	Eastman Kodak, 1988
Rat, Sherman, male	oral	3730, administered as a 20% dispersion in 1% Tergitol (surfactants from nonionic ethoxylates of nonylphenol and linear alcohols)	no data	LD_{50}; sluggishness, roughening of the coat, prostration, narcosis; necropsy of deceased animals: lung congestion and haemorrhage, congestion of the liver and kidneys, congestion and opaqueness of the gastrointestinal tract as a result of the chemical's irritant effects	14 days	Mellon Institute, 1951; Smyth et al., 1951
Rat	oral	6600	no data	LD_{50}	no data	Izmerov et al., 1982
Mouse	oral	3200, administered as a 5% solution in corn oil	no data	mortality: 0/5, body weight development unaffected, weakness, roughening of the coat, slight tremor, diarrhoea	14 days	Eastman Kodak, 1960
Mouse	oral	3200–6400, undiluted	no data	LD_{50}; weakness, ataxia, convulsions, unconsciousness, death within 2 days after administration	14 days	Eastman Kodak, 1957

Table 1. Acute toxicity studies with 2-ethylhexanal

Species, strain, sex[1]	Route	Dose (mg/kg body weight or mg/m³)	Purity	Effect	Observation period	Reference
Mouse	oral	3550	no data	LD_{50}	no data	Izmerov et al., 1982
Rat	inhalation	760, calculated (equivalent to 145 ppm according to the investigators), 6-hour exposure	no data	mortality: 0/3; no clinical signs of toxicity, normal body weight development	14 days	Eastman Kodak, 1957
Rat, Fischer 344, female	inhalation	6830 ± 1320 (1279 ± 47 ppm, analysed, maximum vapour concentration technically attainable at 20 °C), 4-hour whole-body exposure	97.96%	mortality: 0/10; severe nose and eye irritation, reduced respiratory rate, reduction in response to noise stimuli, weakness, body weight retardation (all clinical signs reversible within 1 to 3 days); necropsy findings: deep pink to deep red mottled areas covering the surface of all lung lobes, pale kidneys in 2/10 animals, opaque eyes in 1/10 animals	14 days	BIBRA, 1991 a
The test was carried out in accordance with OECD guideline No. 403.						
Rat	inhalation	10700 (calculated, equivalent to 2045 ppm according to the investigators)	no data	mortality: 3/3 within 23 minutes; dyspnoea, convulsions, narcosis	14 days	Eastman Kodak, 1957
Rat, Sherman, female	inhalation	> ca. 12555* (2360 ppm, calculated saturated vapour concentration at 20 °C), 1-hour exposure	no data	mortality: 2/6	14 days	Mellon Institute, 1951
* The saturated vapour concentration was to be attained by passing air through the chemical at room temperature. According to the investigators, the temperature in the washing bottle rose to 50 °C because of polymerisation, resulting in the formation of a fog due to which the intended concentration was possibly exceeded by a considerable amount.						
Rat, Sherman, female	inhalation	ca. 21280 (4000 ppm, analysed), 4-hour exposure	no data	mortality: 1/6	14 days	Mellon Institute, 1951; Smyth et al., 1951
Rat	inhalation	30100 (calculated, equivalent to 5749 ppm according to the investigators), 42-minute exposure to air passed through the chemical at room temperature	no data	mortality: 0/3; prostration; slightly increased blood clotting times at 3 hours after the end of exposure (control: 3.5 minutes, exposed animals: 3.5, 5.5 and 9 minutes)	14 days	Eastman Kodak, 1960
Rat, Sherman, female	inhalation	ca. 42560 (8000 ppm, calculated), 4-hour exposure	no data	mortality: 6/6; necropsy of deceased animals: extreme lung damage with congestion and haemorrhage	14 days	Mellon Institute, 1951

Table 1. Acute toxicity studies with 2-ethylhexanal

Species, strain, sex[1]	Route	Dose (mg/kg body weight or mg/m³)	Purity	Effect	Observation period	Reference
Rat	inhalation	130000 (calculated, equivalent to 24830 ppm according to the investigators), 13-minute exposure to air passed through the chemical at 100 °C	no data	mortality: 3/3; convulsions, vasodilatation; necropsy findings: heart and lungs bright red; blood did not clot	14 days	Eastman Kodak, 1960
Rat	inhalation	atmosphere enriched or saturated at 20 °C, 8-hour exposure	no data	mortality: 0/12; mild mucous membrane irritation, questionable mild narcosis; necropsy: no findings	no data	BASF, 1964
Mouse	inhalation	2 ml were evaporated at room temperature in a 7 l volume of air, 1-hour exposure	> 95%	mortality: 0/3; restlessness	no data	Hoechst, 1951
Rat, Crl:CD(SD)®BR, male, female	dermal	ca. 16440 (20 ml), undiluted, 24-hour occlusive application to the depilated skin	no data	mortality: 0/10; reversible erythema, normal body weight development	14 days	Eastman Kodak, 1988
Rabbit, New Zealand, male	dermal	ca. 4143 (5040 ml), undiluted, 24-hour occlusive application to the depilated skin	no data	LD_{50}; erythema and later desquamation of the skin; necropsy of deceased animals: congested lungs, pale or mottled livers and kidneys, congested intestines	14 days	Mellon Institute, 1951; Smyth et al., 1951
Guinea pig	dermal	ca. 8220 (10 ml), undiluted, 24-hour occlusive exposure	no data	mortality: 0/2; erythema and oedema	14 days	Eastman Kodak, 1957
Guinea pig	dermal	> 16000	no data	LD_{50}	no data	Anonymous, 1988
Guinea pig	dermal	ca. 16440 (20 ml), undiluted, 24-hour application to the depilated skin	no data	mortality: 0/3; erythema and oedema formation, necrosis with scarring and flaky eschar formation, body weight retardation	14 days	Eastman Kodak, 1960
Rat	intraperitoneal	800–1600, undiluted	no data	LD_{50}; weakness, ataxia, death within 3 hours after administration	14 days	Eastman Kodak, 1957
Rat	intraperitoneal	800–1600, undiluted	no data	LD_{50}; weakness, rough coat, ataxia, loss of reflex action, prostration, dyspnoea, cyanosis, death within 2 hours after administration	14 days	Eastman Kodak, 1960
Rat, Sprague-Dawley, male, female	intraperitoneal	500–1000	no data	LD_{50}; mortality was 0/12 at 500 mg/kg body weight and 11/12 at 1000 mg/kg body weight; coma, death within 2 hours after administration; necropsy: no findings	14 days	Dave and Lidman, 1978

Table 1. Acute toxicity studies with 2-ethylhexanal

Species, strain, sex[1]	Route	Dose (mg/kg body weight or mg/m³)	Purity	Effect	Observation period	Reference
Mouse	intraperitoneal	ca. 247 (0.3 ml), administered as an 8% aqueous tragacanth gum emulsion	no data	LD_{50}; reeling, dyspnoea, tonic-clonic convulsions, lying on the abdomen and side, narcosis-like state; delayed deaths; necropsy: no findings	14 days	BASF, 1964
Mouse	intraperitoneal	ca. 329 (0.4 ml), administered as an 8% aqueous tragacanth gum emulsion	no data	LC_{50}; reeling, dyspnoea, tonic-clonic convulsions, lying on the abdomen and side, narcosis-like state; delayed deaths; necropsy: no findings	7 days	BASF, 1964
Mouse	intraperitoneal	< 400	no data	LD_{50}; death within 9 days after administration	14 days	Eastman Kodak, 1957
* Referred to by the investigators as the LD_{50}, but not actually an LD_{50} determination. With administered doses ranging from 400 to 6400 mg/kg body, all animals in the low dose group given 400 mg/kg body weight succumbed, whereas all animals receiving the next higher dose of 800 mg/kg body weight survived (no further details).						
Mouse	intraperitoneal	1600–3200, administered as a 5% solution in corn oil	no data	LD_{50}; weakness, rough coat, ataxia, unconsciousness, prostration, death 2 hours after administration	14 days	Eastman Kodak, 1960
[1] where specified						

End of Table 1

Sensory irritation

2-Ethylhexanal (97.96% pure) was investigated with respect to sensory irritation using the Alarie test. Groups of 4 male Swiss-Webster mice (weighing 25 to 32 g) underwent a single 30-minute (head-only) exposure to nominal concentrations of 0.18, 0.36, 0.67, 1.34, 2.67, 5.34 or 10.68 mg/l. The analytically determined concentration levels were 0.04, 0.14, 0.41, 0.79, 1.27, 3.08 and 2.46 mg/l. Breathing patterns were recorded at intervals by means of a whole-body plethysmograph from 10 minutes before exposure to 10 minutes after exposure. All animals survived the exposure and the 8-day observation period. They showed normal body weight development and were without clinical findings throughout the observation period. On removal from the plethysmographs, all animals exposed to concentrations ≥ 0.14 mg/l exhibited concentration-dependent nasal irritation. Data analysis was hampered considerably in this study due to the fact that all animals displayed irregular breathing patterns both before and after exposure and baseline respiratory rate showed great interindividual variability (150.7 to 340.7 breaths/minute). The percent change in individual respiratory rate was determined by comparing the mean baseline rate observed in the resting animal with the maximum response in respiratory rate depression that sustained for at least one minute. There was concentration-dependent depression of respiratory rate. The investigators evaluated 2-ethylhexanal as a sensory irritant because respiratory rate was depressed due to delayed expiration rather than prolongation of the pauses between individual breaths as in pulmonary irritation. Regression analysis yielded an RD_{50} (concentration causing a reduction in respiratory rate by 50%) value of 1.20 mg/l (equivalent to 1200 mg/m³, or 225 ppm) with a regression coefficient of 13.3. Meaningful 95% confidence intervals could not be calculated according to the investigators due to the wide variation in data (BIBRA, 1991 b). The study was carried out in accordance with the Standard Test Method “American Society for Testing and Materials” designated number E 9/81-84. Classification of 2-ethylhexanal on the basis of the criteria used in analogous studies of 4-chlorobutanoic acid chloride (No. 163; BG Chemie, 2000 b), would require that, in respect of sensory irritation, the chemical be placed in a category even below that of a “mild sensory irritant”.

Subacute toxicity

The toxic effects of 2-ethylhexanal following subacute administration were investigated in male and female Fischer-344 rats (respective mean initial weights 194.6 and 138.4 g) in an inhalation study conducted in accordance with OECD guideline No. 412. Groups of 5 males and 5 females underwent (head-nose) exposure to 2-ethylhexanal (97.3% pure) at nominal concentration levels of 0 (controls), 25, 100 or 250.0 ppm for 6 hours per day over a period of 28 days. The concentration levels as determined by analysis were 0 (control), 25.5, 102.0 and 250.7 ppm (approx. 0 (control), 136, 543, and 1334 mg/m³). The scope of investigation as specified in OECD guideline No. 412 was expanded to include hepatic peroxisome proliferation. As positive controls for this effect, groups of 5 male and female rats inhaled air and received a nominal concentration of 1.2% (analysed as 1.18%) di-(2-ethylhexyl) phthalate in their feed for 28 days. Based on feed consumption, this corresponded to daily di-(2-ethylhexyl) phthalate intakes by males and females of 912 mg and 962 mg, respectively. Clinical signs seen in animals exposed to 2-ethylhexanal were limited to “porphyrine accumulation” in the eyes of 3 out of 10 rats from the top concentration group on a few days during the first week of treatment. There were no deaths apart from the accidental death of one female from the top concentration group. Statistically significantly decreased body weights relative to controls together with temporary body weight loss and generally retarded body weight development were seen in male rats from the top concentration group throughout the treatment period. A similar tendency was observed in female rats of that group, with significantly decreased body weights being seen on study days 17 and 28. In parallel, mean food conversion efficiency values were reduced. Haematology findings in the top concentration group comprised changes in differential blood count in both sexes including a decrease in lymphocytes and an increase in neutrophils, the leftward shift in white blood cell counts reaching the level of statistical significance in female rats only. A tendency was seen towards a decrease in the absolute number of lymphocytes, though this was not statistically significant. Clinical chemistry findings included statistically significantly decreased levels of fasting glucose (blood samples obtained after deprivation of food for 24 hours) on study day 26 in both males and females of the top concentration group. In addition, the males showed a tendency towards increased plasma triglyceride levels and decreased plasma cholesterol levels and the females had signi-

ficantly increased triglyceride and decreased cholesterol levels at study termination. Statistically significant increases in plasma alkaline phosphatase activity, though lacking clear concentration dependence, were noted in all concentration groups except for the 100 ppm group of males. In the absence of macroscopic or histopathological correlates, several changes in organ weights were observed as follows. Relative testes weight increased concentration-independently in the low and high concentration groups. Relative and absolute adrenal weight increased concentration-dependently in all exposed female groups, and an increase in relative adrenal weight was also seen in the males of the high concentration group. Relative kidney weight increased concentration-dependently in the intermediate and high concentration females and concentration-independently in the low and high concentration males. Absolute and relative thymus weight decreased in the high concentration males and females. Absolute heart weight increased concentration-independently in the low and intermediate concentration males, and relative heart weight also increased concentration-independently in low and high concentration males. Relative liver weight increased concentration-independently in males of the low and high concentration groups and in females of the high concentration group. Lastly, relative lung weight increased in both sexes in the high concentration group. No treatment-related macroscopic or histopathological changes were noted in the animals treated with 2-ethylhexanal. Animals treated with di-2-ethylhexyl) phthalate exhibited liver changes in addition to moderate to severe testicular atrophy. The peroxisome proliferation results are presented in Table 2 below.

Beginning of Table 2

Table 2. Results on the peroxisome proliferating activity of 2-ethylhexanal in male and female F344 rats after 4-week inhalation, mean values for 5 rats, as compared with positive controls treated with di-(2-ethylhexyl) phthalate (DEHP; based on BIBRA, 1997)

	Negative control	25 ppm	100 ppm	250 ppm	DEHP (1.2% in feed, positive control)
Findings in males					
Absolute liver weight (g)	6.47	6.64 NS	6.69 NS	6.71 NS	12.34[2]
Relative liver weight (g/kg body weight)	31.2	33.8[1]	31.7 NS	35.4[2]	59.0[2]
Histopathological examination of the liver	no findings	no findings	no findings	no findings	Increase in liver cell size, moderate increase in cytoplasmic eosinophilia, cell necrosis in 1/5 animals

Table 2. Results on the peroxisome proliferating activity of 2-ethylhexanal in male and female F344 rats after 4-week inhalation, mean values for 5 rats, as compared with positive controls treated with di-(2-ethylhexyl) phthalate (DEHP; based on BIBRA, 1997)

	Negative control	25 ppm	100 ppm	250 ppm	DEHP (1.2% in feed, positive control)
Electron microscopic examination of the liver for number and morphology of peroxisomes and for amount of smooth endoplasmic reticulum in centrilobular and portal hepatocytes	no findings	not examined	not examined	no findings	Number and size of peroxisomes markedly increased in portal and centrilobular hepatocytes, amount of smooth endoplasmic reticulum markedly increased in portal hepatocytes and slightly increased in centrilobular hepatocytes
Whole liver homogenate protein content (mg/g liver)	202	200 NS	199 NS	205 NS	220[2]
Microsomal protein content (mg/g liver)	33.4	33.4 NS	36.8[1]	31.5 NS	40.8[2]
Cyanide-insensitive palmitoyl-CoA oxidase activity in whole liver homogenate (nmol/minute/mg protein)	5.26	5.33 NS	5.62 NS	8.29[3]	58.70[3]
Hepatic microsomal lauric acid 11-hydroxylase activity (nmol/minute/mg protein)	0.35	0.39 NS	0.39 NS	0.46[2]	1.62[3]
Hepatic microsomal lauric acid 12-hydroxylase activity (nmol/minute/mg protein)	0.59	0.82[3]	0.83[3]	1.32[3]	6.92[3]
Findings in females					
Absolute liver weight (g)	4.64	4.57 NS	4.55 NS	4.94 NS	7.32[2]
Relative liver weight (g/kg body weight)	31.3	31.6 NS	32.4 NS	36.0[2]	52.0[2]
Histopathological examination of the liver	no findings	no findings	no findings	no findings	Increase in liver cell size, moderate increase in cytoplasmic eosinophilia
Electron microscopic examination of the liver for number and morphology of peroxisomes in centrilobular and portal hepatocytes	no findings	not examined	not examined	no findings	Number and size of peroxisomes markedly increased in portal and centrilobular hepatocytes, amount of smooth endoplasmic reticulum increased in portal and centrilobular hepatocytes
Whole liver homogenate protein content (mg/g liver)	121	217 NS	216 NS	214 NS	228[2]
Microsomal protein content (mg/g liver)	33.7	33.4 NS	33.6 NS	32.8 NS	36.2 NS
Cyanide-insensitive palmitoyl-CoA oxidase activity in whole liver homogenate (nmol/minute/mg protein)	5.63	6.16 NS	6.62[2]	8.39[3]	53.17[3]
Hepatic microsomal lauric acid 11-hydroxylase activity (nmol/minute/mg protein)	0.21	0.23 NS	0.27[1]	0.29[2]	0.64[1]
Hepatic microsomal lauric acid 12-hydroxylase activity (nmol/minute/mg protein)	0.36	0.40 NS	0.46[1]	0.65[1]	2.87[2]

NS statistically nonsignificant, $p > 0.05$
[1] statistically significant, $p \leq 0.05$
[2] statistically significant, $p \leq 0.01$
[3] statistically significant, $p \leq 0.001$

End of Table 2

Subacute exposure to 2-ethylhexanal levels of up to 250 ppm in the 28-day study resulted in only minimal changes in terms of peroxisome proliferation. As expected, the di-(2-ethylhexyl) phthalate-treated positive control showed marked peroxisome proliferation. Apart from a concentration-independent small increase (to 110% of control) in microsomal protein content in the intermediate concentration group of males, treatment with 2-ethylhexanal affected neither whole homogenate nor microsomal protein content in the liver. An increased activity level of cyanide-insensitive palmitoyl-CoA oxidase was noted in whole liver homogenate from males in the top concentration group and females in the intermediate and top concentration groups. Microsomal lauric acid 11-hydroxylase activity was elevated in males from the top concentration group and concentration-dependently increased in females from the intermediate and top concentration groups. Microsomal lauric acid 12-hydroxylase activity was concentration-dependently increased in all three male groups and in the two upper concentration groups of females. However, the increases in activity of these enzymes were considerably smaller in animals treated with 2-ethylhexanal than in positive controls. In addition to the biochemical studies of peroxisome proliferation, livers were examined by electron microscopy with respect to number and morphology of peroxisomes and the amount of smooth endoplasmic reticulum. The ultrastructural examinations were carried out in 2 male and 2 female rats per group from the rats treated with 250 ppm 2-ethylhexanal, the negative controls and the di-2-ethylhexyl) phthalate-treated positive controls. The results for animals treated with 2-ethylhexanal were comparable to those obtained for the negative controls (score: +). In contrast, 1.2% di-(2-ethylhexyl) phthalate induced marked increases in number and size of peroxisomes in centrilobular and portal hepatocytes from both male and female rats (score: ++++). In addition, there was a marked increase in the amount of smooth endoplasmic reticulum in the portal hepatocytes from animals treated with di-(2-ethylhexyl) phthalate, which was not seen in animals treated with 2-ethylhexanal. The results of the ultrastructural examination, according to the investigators, confirmed those of the biochemical analyses, which had shown 2-ethylhexanal to be only a very weak peroxisome proliferator. **In summary**, 2-ethylhexanal proved to be systemically toxic at a concentration level of 250 ppm (approx. 1334 mg/m³) as indicated by reduction in body weight gain and food conversion efficiency, leftward shift in white blood cell count and changes in organ weights of the testes, adrenal glands, kidneys, liver, lungs and thymus, and in males, also

of the heart. Additionally, but only in females, increases were noted in relative adrenal weights at and above the low test concentration of 25 ppm (approx. 136 mg/m³) as well as in relative kidney weights at the intermediate test concentration of 100 ppm (approx. 543 mg/m³). The high concentration group tested at 250 ppm showed changes in carbohydrate metabolism (decreased fasting levels of blood glucose) and lipid metabolism (increased triglycerides and decreased cholesterol). Increases in plasma alkaline phosphatase activity were noted in all concentration groups except for the 100 ppm group of males, whereas the other marker enzymes of hepatotoxicity, alanine aminotransferase and aspartate aminotransferase, remained unchanged. Compared with di-(2-ethylhexyl) phthalate, 2-ethylhexanal induced very little hepatic peroxisome proliferation. The investigators evaluated 2-ethylhexanal as a very weak peroxisome proliferator and determined a *no effect level* (NOEL) of 25 ppm (approx. 136 mg/m³) for this effect (BIBRA, 1997).

A further study, in which male rats were administered 0 (controls) or 2% 2-ethylhexanal (ca. 1333 mg/kg body weight/day, purity not specified) in their feed over a period of 3 weeks, also showed the chemical to have only a moderate peroxisome proliferating effect. Compared with the control, relative liver weight, the hepatic activities of catalase and carnitine acetyltransferase were significantly increased while serum cholesterol and triglyceride levels were significantly reduced. Electron microscopy demonstrated peroxisome proliferation which was evaluated as moderate by the investigators (the ratio between mitochondria and peroxisomes changing from 5 : 1 in the control to 5 : 3). Body weight gain observed in animals treated with 2-ethylhexanal was comparable to that seen in the controls (Moody and Reddy, 1978, 1982).

7.3 Skin and mucous membrane effects

The skin irritation studies of 2-ethylhexanal are summarised in Table 2. Application of 2-ethylhexanal to the skin of rabbits resulted in marked irritation with erythema, oedema and eschar formation. Furthermore, the treated skin was described as hardened, dry, chapped and/or scaly. Where assessed, irritation was reversible after 14 or 19 days. Investigators' evaluation of irritancy in studies conducted in accordance with OECD guideline No. 404 and/or Directive 84/449/EEC (evaluation of irritancy in accordance

with Directive 83/467/EEC) encompasses the range from irritant to severely irritant. Those studies determined irritation indices of 3.88 and 6.08 out of a maximum irritation index of 8 and mean values of 2.0 to 3.0 for erythema and eschar formation and of 0.9 to 3.33 for oedema formation (Hoechst, 1988 a; Hüls, 1986 a; Bagley et al., 1996; ECETOC, 1995). Further skin irritation studies in rabbits led to investigators' skin irritancy evaluation of the chemical as irritant, moderately irritant or falling into grade 5 of a 10-grade rating system (BASF, 1964, 1978, 1987; Union Carbide, 1965; Mellon Institute, 1951; Smyth et al., 1949, 1951). In a guinea pig skin irritation study in which 500 µl undiluted 2-ethylhexanal was applied to the depilated abdominal skin under occlusive cover for 24 hours, the investigators evaluated the chemical as moderately irritant, but not corrosive, to the skin. The animals showed the following signs of skin irritation, which were fully reversible within 14 days: slight to moderate erythema, very slight oedema, slight to moderate necrosis and moderate eschar formation (Eastman Kodak, 1988).

Beginning of Table 3

Table 3. Skin irritancy of 2-ethylhexanal

Species	Guideline and/or dose, route, duration[1]	Findings	Reversibility	Evaluation (by the investigators)	Reference
Rabbit	EC Directive 84/449/EEC and OECD guideline No. 404 (sample purity 99%)	1 to 72 hours p.a.: barely perceptible to moderate erythema and very slight oedema, accompanied by dry, chapped, hardened skin; additionally, the skin of one animal appeared slightly whitish at 1 hour p.a. and the skin of 2 animals showed small areas of light-brown discoloration at 72 hours p.a.; at 7 days p.a.: dry, chapped and cracked skin with small and large scales; 2 animals with now barely perceptible erythema; respective scores (means for 3 animals) for erythema, eschar and oedema formation were 2.1, 2.1 and 0.9	signs of irritation were reversible within 14 days, after which the skin remained dry, chapped and with coarse scales	irritant (according to Directive 83/467/EEC)	Hoechst, 1988 a
Rabbit	OECD guideline No. 404 (sample purity not specified)	1 to 72 hours p.a.: defined to moderate erythema, 1 hour to 6 days p.a.: moderate to severe oedema; additionally, yellow discoloration, hardening and dryness of the application area; 5 or 6 days after application: onset of eschar formation; respective scores (means for 3 animals) for erythema and oedema formation were 3.00 and 3.33	day 16 p.a.: loosening of scab; day 19 p.a.: all animals without findings	severely irritant (irritation index 6.08/8)	Hüls, 1986 a
Rabbit	OECD guideline No. 404 (sample purity not specified)	1 hour to 7 days p.a.: slight to well-defined erythema; up to 72 hours p.a.: very slight to moderate oedema; 7 days p.a.: severe desquamation of the skin; respective scores (means for 4 animals) for erythema and oedema formation were 2.0 and 1.88	day 7 p.a.: very slight erythema and severe desquamation, oedema reversible (no further examination after study day 7)	irritant (irritation index 3.88/8)	Bagley et al., 1996; ECETOC, 1995
Rabbits, 2 females of the White Vienna race	undiluted substance, 4-hour occlusive exposure of the depilated dorsal and lateral skin of the trunk, removal of test substance with a water/Lutrol mixture (1 : 1; sample purity not specified)	at the end of exposure: slight reddening and oedema formation in both animals; after one day: severe reddening (extending beyond the area of exposure in one animal) together with slight oedema formation; after 2 days: slight reddening (extending beyond the area of exposure in one animal) together with slight oedema formation; after 8 days: equivocal reddening together with scale formation; no absorption-related signs of toxicity throughout the duration of the study	tendency towards reversibility at 8 days, no further examination after study day 8	irritant	BASF, 1978, 1987

Table 3. Skin irritancy of 2-ethylhexanal					
Species	Guideline and/or dose, route, duration[1]	Findings	Reversibility	Evaluation (by the investigators)	Reference
Rabbit	undiluted substance, dorsal skin, 1, 5, 15 minutes and 20 hours, and skin of the ear, 20 hours (sample purity not specified)	exposure for 1, 5 or 5 minutes: severe reddening of the area of exposure and beyond after 24 hours; severe desquamation after 8 days; exposure of the dorsal skin for 20 hours: slight necrosis with severe reddening and oedema formation after 24 hours; slight necrosis and severe desquamation after 8 days; exposure of the skin of the ear for 20 hours: severe necrosis after 24 hours and 8 days and severe reddening at 8 days after application	Irritation not reversible within 8 days, no further examinations carried out after day 8	irritant	BASF, 1964, 1987
Rabbit	425 mg, open application (sample purity not specified)	no data	no data	mildly irritant	Union Carbide, 1965
Rabbit	0.01 ml, application of undiluted substance (test conducted similarly to the Draize test, sample purity not specified)	moderate to severe erythema	no data	grade 5 (the maximum grade being 10)	Mellon Institute, 1951; Smyth et al., 1949, 1951
Guinea pig	0.5 ml of undiluted substance, 24-hour occlusive application to the depilated abdominal skin (sample purity not specified)	24 hours after application: slight (3/5) to moderate (2/5) erythema, very slight oedema (5/5), slight (2/5) to moderate (1/5) necrosis and moderate eschar formation (3/5); 7 days after application: slight (1/5) to moderate (2/5) eschar formation	findings were fully reversible within 14 days	moderately irritant, not corrosive	Eastman Kodak, 1988
Guinea pig	5 or 10 ml of undiluted substance, 24-hour occlusive application (sample purity not specified)	dose-dependent slight to severe redness with oedema at the edge of the application area or gross oedema, slight necrosis	no data	moderately irritant	Eastman Kodak, 1957
Guinea pig	5 or 10 ml of undiluted substance, presumably 24-hour occlusive application (sample purity not specified)	dose-dependent slight to severe oedema with necrosis along edges, eschar formation and scarring within 2 weeks	not reversible within 2 weeks, no further examination after week 2	moderately irritant	Eastman Kodak, 1960

[1] where specified
p.a. post administration

End of Table 3

The studies on the mucous membrane irritancy of 2-ethylhexanal are summarised in Table 4. In the rabbit eye, 2-ethylhexanal caused temporary irritation with severe reddening, oedema formation, iritis, ocular discharge and positive fluorescein test results. The two available studies, one conducted in accordance with Directive 84/449/EEC, the other in accordance with OECD guideline No. 405, gave the following respective scores, each representing the mean value for 3 animals: clouding of the cornea 0.0 and 0.56, iritis 0.4 and 0.33, reddening of the conjunctiva 0.6 and 1.78 and conjunctival swelling 0.2 and 0.89. All findings had cleared up completely by 72 hours and by 10 to 13 days after treatment, respectively. The investigators' evaluations of 2-ethylhexanal in these two studies were that the chemical does not require labelling (as per Directive 83/467/EEC) and that it is a slight irritant (irritation index 13.58 out of a maximum score of 110; Hoechst, 1988 b; Hüls, 1986 b). Further studies on the mucous membrane irritancy of 2-ethylhexanal evaluated the chemical as an irritant and as causing grade 2 irritation in a 10-grade rating system (BASF, 1964, 1987; Mellon Institute, 1951; Carpenter and Smyth, 1946; Smyth et al., 1951).

Beginning of Table 4

Table 4. Mucous membrane effects of 2-ethylhexanal					
Species	Guideline and/or dose, route, duration[1]	Findings	Reversibility	Evaluation (by the investigators)	Reference
Rabbit	EC Directive 84/449/EEC and OECD guideline No. 405 (sample purity 99%)	1 and 24 hours p.a.: slight swelling of the conjunctivae and marked hyperaemia to diffuse crimson colouration of the conjunctivae; 24 hours p.a. and 48 hours p.a.: reddening of the iris in all animals and in 1/3 animals, respectively; 24 hours p.a.: the cornea of 2/3 animals showed areas of lighter colour in the fluorescein test which ranged in size from punctiform to max. ¼ of the corneal area; ocular discharge occurred in all animals up to 24 hours p.a.; scores (mean for 3 animals): clouding of the cornea 0.0, iritis 0.4, reddening of the conjunctiva 0.6 and conjunctival swelling 0.2	72 hours p.a.: all signs of irritation were reversible	labelling (as per Directive 83/467/EEC) not required	Hoechst, 1988 b
Rabbit	OECD guideline No. 405 (sample purity not specified)	1 to 24 hours p.a.: all animals showed marked conjunctival hyperaemia to diffuse intense red colouration of the conjunctivae; 48 hours p.a.: 2/3 animals showed only a few still markedly injected conjunctival blood vessels; in 1/3 animals the intense red colouration of the conjunctivae persisted up to 72 hours p.a., at which time the animal additionally displayed a haemorrhagic spot on the mucosa; 6 and 8 days p.a.: 2/3 animals still showed a few markedly injected conjunctival blood vessels; all animals showed definite swelling of the conjunctivae up to 24 hours p.a., 2/3 animals had slightly swollen conjunctivae at both 48 and 72 hours p.a.; ocular discharge was noted up to 48 hours p.a.; the iris was slightly reddened at 24 and 48 hours p.a. in 2/3 and 1/3 animals, respectively; in the fluorescein test, the corneas of 2/3 (24 and 48 hours p.a.) and 1/3 animals (72 hours p.a.) exhibited scattered or diffuse areas of opacity, which affected all of the cornea at times in one animal while it affected max. ¼ of the area of the cornea in the second animal; scores (means for 3 animals): clouding of the cornea 0.56, iritis 0.33, reddening of the conjunctiva 1.78, conjunctival swelling 0.89	all animals were without findings after 10 to 13 days	slightly irritating (irritation index 13.58/110)	Hüls, 1986 b

Table 4. Mucous membrane effects of 2-ethylhexanal					
Species	Guideline and/or dose, route, duration[1]	Findings	Reversibility	Evaluation (by the investigators)	Reference
Rabbit	50 µl undiluted substance, single application (sample purity not specified)	slight reddening and oedema formation seen after one hour, severe reddening after 24 hours	findings were fully reversible within 8 days	irritant	BASF, 1964, 1987
Rabbit (1 animal)	one drop of the undiluted substance (sample purity not specified)	immediately after application: eye closure, conjunctivae and nictitating membrane slightly erythematous, eyelids moderately erythematous; one hour after application: eyelids and conjunctivae slightly erythematous, slight watery discharge; 24 hours after application: conjunctivae slightly erythematous and stained with fluorescein, eyelids moderately erythematous, less than $^1/_8$ of cornea stained with fluorescein	findings were fully reversible within 14 days	No data	Eastman Kodak, 1960
Rabbit	500 ml of the undiluted substance, 24 hours (sample purity not specified)	a total of 15 animals tested showed slight to very severe irritation with a very wide variation in individual response	no data	grade 2 (the maximum grade being 10)	Mellon Institute, 1951; Carpenter and Smyth, 1946; Smyth et al., 1951
[1] where specified p.a. post administration					

End of Table 4

7.4 Sensitisation

No information available.

7.5 Subchronic and chronic toxicity

No information available.

7.6 Genotoxicity

7.6.1 In vitro

When a Salmonella/microsome assay was carried out as a preincubation test using *Salmonella typhimurium* strains TA 97, TA 98, TA 100 and TA 1535, 2-ethylhexanal showed no mutagenic potential, either with or without metabolic activation (S-9 mix from Aroclor 1254-induced rat and hamster liver). The test concentrations, which were selected on the basis of a previously conducted toxicity test, were in the range from 0 to 666 µg/plate (purity not specified; Zeiger et al., 1988).

7.6.2 In vivo

2-Ethylhexanal (97.95%) gave a positive result in a micronucleus assay conducted in accordance with OECD guideline No. 474. Groups of 6 male NMRI mice per dose and time point of investigation were administered a single dose of 2-ethylhexanal in corn oil by oral gavage at levels of 0 (controls), 500, 1000 and 1000 mg/kg body weight. A dose of 2000 mg/kg body weight, the maximum dose to be tested according to the guideline, had proved slightly toxic in a preliminary study. The bone marrow from 5 animals per dose and scheduled time point was isolated at 24 and 48 hours after administration, and 2000 polychromatic erythrocytes were analysed per animal. At 24 hours after administration, the treated groups showed dose-dependent increases in micronucleated polychromatic erythrocytes of 0.110, 0.160 and 0.280% as compared with the vehicle control (0.080%). The increase seen in the top dose group was statistically significant and exceeded the laboratory's highest historical negative control value (0.16%). At 48 hours after administration, the increase in micronucleus frequencies

was only slight and statistically nonsignificant. Cytotoxic effects of 2-ethylhexanal became evident at 48 hours after administration as increased numbers of normochromatic erythrocytes in the bone marrow (1671, 2028 and 2438; control: 1629). Treated orally with cyclophosphamide at 40 mg/kg body weight, the positive control gave the expected results. Thus, 2-ethylhexanal produced a positive response in this test system (RCC, 1999).

7.7 Carcinogenicity

No information available.

7.8 Reproductive toxicity

In a preliminary study to an embryotoxicity/teratogenicity study, groups of 6 pregnant CD rats were administered 2-ethylhexanal (98% pure) by oral gavage at daily dosages of 0 (controls), 100, 400 or 1200 mg/kg body weight in corn oil from days 6 to 19 of gestation (day 0 of gestation was the day of sperm-positive vaginal smear). The animals were observed throughout the study with regard to mortality, clinical signs of toxicity, body weight and food consumption. At study termination on day 20 of gestation, the pregnant females were comprehensively examined in respect of haematology and clinical chemistry and underwent macroscopic examination including determination of liver, kidney and spleen weights. The reproductive tract, complete with ovaries, was dissected out and the gravid uterus weighed; the individual placental weights and placental abnormalities were determined and the numbers of corpora lutea, implantations, resorptions and live and dead foetuses recorded. The foetuses were sexed, weighed and macroscopically examined for any external abnormalities. One female from the group treated with 400 mg/kg body weight was killed in a moribund state on day 19 of gestation. Necropsy revealed blood in the uterus and therefore the investigators considered the animal's condition to be probably treatment-related. Apart from this death, there were no findings in the low and intermediate dose groups that differed significantly from those seen the control group. In the top dose pregnant females, which were treated with 1200 mg/kg body weight, severe clinical signs of toxicity were noted including underactivity, ptosis, salivation, shallow respiration and initial weight

loss and low body weight throughout the study, accompanied by reduced food consumption. Five out of six females were killed in a moribund state between days 8 and 17 of gestation. The top dose female which survived to the end of the study showed increased relative organ weights of the liver and kidneys. The animal had no live foetuses, and of the 15 implantations observed, 14 were early resorptions and one was a late resorption (Huntingdon, 1998).

Designed to complement and expand upon the preliminary study summarised above (Huntington, 1998), a further study was carried out under identical conditions with an additional 2-ethylhexanal dose of 800 mg/kg body weight/day which was tested against a control group. The pregnant females treated with 2-ethylhexanal exhibited salivation and low body weight performance and food consumption. Thromboplastin time, total leukocyte, neutrophil and platelet counts were slightly low, and urea, creatinine, triglycerides and aspartate aminotransferase activity were slightly high, as were absolute and relative liver weights. Foetal and placental weights were slightly reduced. No further significant differences were noted relative to the control (Huntingdon, 1999).

In the subsequent embryotoxicity/teratogenicity study which was conducted in accordance with OECD guideline No. 414, groups of 25 pregnant CD rats were administered 2-ethylhexanal (98% pure, formulated in corn oil) by oral gavage at dose levels of 0 (controls), 100, 300 or 800 mg/kg body weight on days 6 to 19 of gestation. All treated animals survived until terminal examination on day 20 of gestation. Salivation after administration occurred dose-dependently in all treated groups and was considered by the investigators to be related to the palatability of 2-ethylhexanal, rather than representing a sign of toxicity. No further treatment-related findings were noted in the dams of the low and intermediate dose group. As in the preliminary study (see above; Huntingdon, 1999), 2-ethylhexanal caused maternal toxicity at 800 mg/kg body weight/day. Clinical signs seen in the animals included piloerection, underactivity, hunched posture and occasional instances of partly closed eyelids. Following initial weight loss, their body weight gain was markedly reduced and food consumption was reduced. Gravid uterus weight was reduced. There were no gross macroscopic findings at necropsy. No clinical chemistry or haematology studies were carried out. All animals were pregnant and the numbers of corpora lutea, implantations, resorptions and live foetuses were not affected in any of the

treated groups relative to controls. In the 300 mg/kg group, in which the dams were without findings, foetal weights were slightly low and there was an increased incidence of foetuses with incompletely ossified sternebrae and sacrocaudal vertebral arches. The investigators considered the changes to be transient in nature, rather than representing permanent lesions, and did not consider them to be of toxicological relevance during later development. Following administration of the high dose of 800 mg/kg, which produced marked maternal toxicity, foetuses were observed to have a large number of visceral and skeletal abnormalities. These included dilated ventricles of the brain; absent or rudimentary thyroid gland, partly undescended thymus; cardiovascular abnormalities and abnormal umbilical artery; rudimentary or absent renal papillae; subcutaneous oedema; thickened, kinked and/or irregularly ossified ribs; termination of vertebral column associated with tail abnormalities; vertebral configuration abnormalities (including cervical ribs, complete 14th ribs, additional lumbar ribs and thoracolumbar vertebrae, offset pelvic girdle) and thoracic and lumbar vertebral abnormalities, including incomplete ossification and structural changes; incomplete ossification of cranial centres, cervical and sacrocaudal vertebral arches, pelvic bones, metacarpals, metatarsals and sternebrae. The *no observed adverse effect level* (NOAEL) for maternal toxicity and developmental toxicity, as stated by the investigators, was 300 mg/kg body weight/day (Huntingdon, 2002).

7.9 Effects on the immune system

No information available.

7.10 Neurotoxicity

No information available.

7.11 Other effects

Kidney cells from C3H mice were infected with the carcinogenic SV_{40} virus, and the W2K11 cancer cells thus obtained were cultured in vitro and incubated with various aldehydes. The tests were carried out to study the antineoplastic effect of the aldehydes. At 500 µg/ml, 2-ethylhexanal inhibited

cell growth by 89% as compared with the untreated control (no further details; Kochi and Kakei, 1981).

8 Experience in humans

A 48-hour closed-patch test of a 2-percent formulation of 2-ethylhexanal in petrolatum on the backs of 27 subjects produced no skin irritation (no further details; Epstein, 1980).

A Kligman maximisation test in 27 subjects who were treated with 2-ethylhexanal at a maximum concentration of 2% in petrolatum produced no sensitisation reactions. All 27 subjects were without findings. Test concentration selection was based on a reported maximum concentration of the chemical of 0.2% in consumer goods (no further details; Epstein, 1980).

There were no known cases of 2-ethylhexanal-related skin sensitisation in humans during the period from 1989 to May 1996, according to the occupational medicine department of one manufacturer (BASF, 1996).

According to the Informationsverbund Dermatologischer Kliniken (IVDK, Information Network of Departments of Dermatology for the surveillance and scientific evaluation of contact allergies in Germany), there are no hospital or literature reports of skin sensitisation in humans due to 2-ethylhexanal up to 1996 (IVDK, 1996).

9 Classifications and threshold limit values

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (“MAK-Kommission”) has listed 2-ethylhexanal in the “Yellow Pages” of the List of MAK and BAT Values 2004 on the suggestion of BG Chemie in order that a MAK value be established for the chemical (DFG, 2004).

In the former USSR, the maximum permissible concentration of 2-ethylhexanal in the workplace was 20 mg/m³ (Sidorov and Golubovich, 1991).

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