Committee for Risk Assessment

RAC

Annex 1

Background document

to the Opinion proposing harmonised classification and labelling at EU level of

Ethylbenzene

EC number: 202-849-4

CAS number: 100-41-4

ECHA/RAC/CLH-O-0000001542-81-03/A1

Adopted

5 June 2012

PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING

Substance Name: Ethylbenzene

EC Number: 202-849-4

CAS number: 100-41-4

Registration number (s):

Purity: > 99.5 %

Impurities: This information is confidential and then provided in the confidential part of the dossier provided in appendix 1.

Proposed classification based on Directive 67/548/EEC criteria:

F; R11 (Highly flammable)

Xn; R20 (Harmful by inhalation)

Xn; R48/20-65 (Harmful: Danger of serious damage to health by prolonged exposure through inhalation)

Proposed classification based on Regulation (EC) No 1272/2008 criteria:

Flam. Liq. 2; H225 (Highly flammable liquid and vapour)

Acute Tox. 4 *; H332 (Harmful if inhaled)

Asp.Tox. 1; H304 (May be fatal if swallowed and enters airways)

STOT RE 2; (hearing organs) H373 (May cause damage to hearing organs through prolonged or repeated exposure)

Proposed labelling based on Directive 67/548/EEC criteria:

Symbol: F; Xn

Risk phrases: R: 11-48/20-65

Safety phrases: S: (2-)16-24/25-29-62

Proposed labelling based on Regulation (EC) No 1272/2008 criteria:

* Minimum classification

Pictograms: GHS02, GHS07, GHS08

Signal word: Danger

Hazard statement codes: H225

H332

H304

H373

Proposed specific concentration limits (if any):

None

Proposed notes (if any):

Ethylbenzene was a priority substance in the Existing Chemicals program (EEC) 793/93. In the transitional Annex XV Dossier on ethylbenzene it is noted that the discussion on the risk assessment report was not concluded at the Technical Committee for New and Existing Substances (TC NES).

The current classification for ethylbenzene with regard to human health is: Xn, R 20.

In the draft Risk Assessment Report (November 2008) on ethylbenzene it was noted that the substance should be classified and labelled additionally with:

R36/37/38 - Irritating to eyes, respiratory tract and to skin

R48/20 - Harmful: Danger of serious damage to health by prolonged exposure through inhalation

R65 - Harmful: May cause lung damage if swallowed

After re-evaluation of the toxicity of ethylbenzene, classification and labelling as ‘R 36/37/38 Irritating to eyes, respiratory tract and to skin’ is no longer supported.

The classification of ’R48/20 Harmful: Danger of serious damage to health by prolonged exposure through inhalation’ was originally not proposed by the dossier submitter but is supported by RAC. STOT RE.2 (hearing organs)– H373 is also proposed.

JUSTIFICATION

1 IDENTITY OF THE SUBSTANCE AND PHYSICAL AND CHEMICAL PROPERTIES

1.1 Name and other identifiers of the substance

Chemical Name: Ethylbenzene

EC Name: Ethylbenzene

CAS Number: 100-41-4

IUPAC Name: Ethylbenzene

1.2 Composition of the substance

Chemical Name: Ethylbenzene

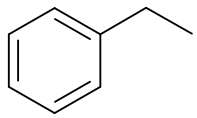
EC Number: 202-849-4

CAS Number: 100-41-4

IUPAC Name: Ethylbenzene

Molecular Formula: C8H10

Structural Formula:



Molecular Weight: 106.165 g/mol

Typical concentration (% w/w): > 99,5 %

Concentration range (% w/w): 99,5 – 100 %

1.3 Physico-chemical properties

Table 1.3-1: Summary of physico- chemical properties

REACH ref Annex, §	Property	IUCLID section	Value	[enter comment/reference or delete column]
VII, 7.1	Physical state at 20°C and 101.3 KPa	3.1	liquid at 25 °C	
VII, 7.2	Melting/freezing point	3.2	- 94.949 °C	Gerhartz (1987)
VII, 7.3	Boiling point	3.3	136.186 °C	Gerhartz (1987)

REACH ref Annex, §	Property	IUCLID section	Value	[enter comment/reference or delete column]
VII, 7.4	Relative density	3.4 density	0.8670 at 20 °C	Lide (1991-1992)
VII, 7.5	Vapour pressure	3.6	p(20 °C) = 9.3 hPa	Auer Technikum (1988)
VII, 7.6	Surface tension	3.10	28.48 mN/m	Gerhartz (1987)
VII, 7.7	Water solubility	3.8	160 mg/L at 25 °C	Lide (1991-1992)
VII, 7.8	Partition coefficient n-octanol/water (log value)	3.7 partition coefficient	3.13 at 25 °C	Tewari et al. (1983)
VII, 7.9	Flash point	3.11	23 °C [1)](recommended value for pure substance)	CHEMSAFE
VII, 7.10	Flammability	3.13	From the structural formula of the substance it can be safely concluded that the substance does not evolve any flammable gases in contact with water or humid air. From the structural formula of the substance it can be concluded that the substance is stable at room temperature on air and is not pyrophoric. *1,0 Vol.% (±10 %)* *7,8 Vol.% (±5%)* [2)]	BAM-II.21: CHEMSAFE
VII, 7.11	Explosive properties	3.14	The substance has no danger of explosion according to the explosive properties of the method EC A. 14.	BAM-II.21:
VII, 7.12	Auto flammability	3.12	430 °C[3)] (recommended value for pure substance)	CHEMSAFE
VII, 7.13	Oxidising properties	3.15	No oxidising properties on the basis of the chemical structure.	BAM-II.21:
VII, 7.14	Granulometry	3.5	Not applicable (liquid)	
XI, 7.15	Stability in organic solvents and identity of relevant degradation products	3.17		
XI, 7.16	Dissociation constant	3.21		

REACH ref Annex, §	Property	IUCLID section	Value	[enter comment/reference or delete column]
XI, 7.17	Viscosity	3.22	0.63 mm^2/s at 40 °C (Kinematic viscosity)	Knothe & Steidley (2005)
	Reactivity towards container material	3.18		
	Thermal stability	3.19		
	Index of refraction (nd)		1.49588 at 20 °C 1.49320 at 25 °C	Gerhartz (1987)

1) Typically impurities may **cause** a **decrease** the flashpoint.

2) Lower Explosive or Flammability Limit (LEL/LFL)/ Upper Explosive or Flammability Limit (UEL/UFL):

   To indicate the value is not prescribed for a liquid substance according REACH, but the Explosive or Flammability Limits are an important safety-related parameter. When mixed with air at room temperature, Ethylbenzene can form a flammable vapour.

3) The amount of impurities has an effect on the auto flammability.

2 MANUFACTURE AND USES

Not relevant for this dossier.

3 CLASSIFICATION AND LABELLING

3.1 Classification and labelling in Annex VI of Regulation (EC) No 1272/2008

Classification based on Regulation (EC) No 1272/2008 criteria (Table 3.1):

Flam. Liq. 2; H225 (Highly flammable liquid and vapour)

Acute Tox. 4 *; H332 (Harmful if inhaled)

Labelling based on Regulation (EC) No 1272/2008 criteria (Table 3.1):

Pictograms: GHS02, GHS07

Signal word: Danger

* Minimum classification

Hazard statement codes: H225

H332

Classification based on Directive 67/548/EEC criteria (Table 3.2):

F; R11 (Highly flammable)

Xn; R20 (Harmful by inhalation)

Labelling based on Directive 67/548/EEC criteria (Table 3.2):

Symbol: F; Xn

Risk phrases: R: 11-20

Safety phrases: S: (2-)16-24/25-29

3.2 Self classification(s)

Not applicable

4 ENVIRONMENTAL FATE PROPERTIES

Not relevant for this dossier.

5 HUMAN HEALTH HAZARD ASSESSMENT

5.1 Toxicokinetics (absorption, metabolism, distribution and elimination)

Toxicokinetics have not been considered as part of this dossier.

5.2 Acute toxicity

Acute toxicity has not been considered as part of this dossier.

5.3 Irritation

Irritation has not been considered as part of this dossier.

5.4 Corrosivity

Corrosivity has not been considered as part of this dossier.

5.5 Sensitisation

Sensitisation has not been considered as part of this dossier.

5.6 Repeated dose toxicity

The proposed classification of ethylbenzene refers to ototoxicity and was observed after inhalation exposure.

Specific human data for ethylbenzene are not available. No clear conclusion can be drawn from human data after exposure to other aromatic solvents or a combination of ethylbenzene with other solvents.

Animal data after oral administration mainly refer to general toxicity; one investigation is available on ototoxicity; data is presented in a tabular form (5.6.1). Data on general toxicity after inhalation exposure is also given in tabular form; data referring to ototoxicity is presented both, in tabular form and in detailed text (5.6.2). Concerning dermal administration, no relevant data is available (5.6.3).

5.6.1 Repeated dose toxicity: oral

Studies on oral repeated dose toxicity are summarised in Table 5.6-1.

Table 5.6-1: Animal studies with repeated oral exposure to ethylbenzene (EB)

Species (strain, animal no.)	Study design/test material (purity)	Compliance to test guidelines	Results	NOAEL (mg/kg bw/d)	LOAEL (mg/kg bw/d)	Reference
Rat (Sprague–Dawley, 6-8 m)	8.47 mmol/kg bw/d or 900 mg/kg bw/d, gavage 5 d/wk for **2 wk** Prep. of cochleae 10 days after last treatment EB (99 %)	Specifically designed for ototoxicity	No effect on clinical signs or body weight gain Nearly complete loss of outer hair cells in all 3 rows, minute loss of inner hair cells EB blood levels: Not reported	-	900	Gagnaire and Langlais (2005)
Rat (Wistar, 5/sex/grp)	75-250-750 mg/kg bw/d, gavage for **4 wk** EB (99.7 %)	Range finding study similar to OECD TG 407	≥ 250 mg/kg bw/d: Increased liver weight with centrolobular hypertrophy (m in high and mid dose, f in high dose). Elevated activity of ALAT, TBil and Chol Increased kidney weight in high and mid dose (males) with histopathological evidence for male rat specific hyaline droplet nephropathy EB blood levels: Not reported	75	250	Mellert et al. (2003; 2007)

Species (strain, animal no.)	Study design/test material (purity)	Compliance to test guidelines	Results	NOAEL (mg/kg bw/d)	LOAEL (mg/kg bw/d)	Reference
Rat (Wistar 10/sex/grp)	75-250-750 mg/kg bw/d, gavage for **3 mo** EB (99.7 %)	OECD TG 408	≥ 250 mg/kg: Changes in haematology indicative of mild regenerative anaemia, elevated activity of ALAT, TBil and Chol, increased liver weight with centrilobular hypertrophy, increased kidney weight (males) Changes in male rat kidney indicative of male specific alpha-2µ-globulin nephropathy EB blood levels: Not reported	75	250	Mellert et al. (2004; 2007)
Rat (Sprague-Dawley, 10-16/sex/grp)	50-250-500 mg/kg bw/d, gavage for **3 mo** EB (99.96 %)	Similar to OECD TG 424; specifically designed for neurotoxicity	≥ 250 mg/kg: Increased liver and kidney weight (m+f) without histopathological correlates; 500 mg/kg: Increased incidence of marginal clinical signs (e.g., excess salivation). No effects in a functional observational battery, motor activity or histopathology of the central and peripheral nervous system EB blood levels: Not reported	500	-	Barnett et al. (2006)/Li et al. (2010)
Rat (Wistar, 10 f/grp)	13.6-136-408-680 mg/kg bw/d, gavage 5 d/wk; 130 applications in **6 mo** EB (> 98 %)	Not given	≥ 408 mg/kg bw/d: Weight↑ in liver and kidneys, slight cloudy swelling of hepatocytes and renal tubular epithelium EB blood levels: Not reported	136	408	Wolf et al., 1956

Ototoxicity was investigated only in one study (Gagnaire and Langlais, 2005) with oral administration of 900 mg/kg bw/d to rats. This high dose caused strong hair cell death in cochleae. By quantitative comparison with other aromatic solvents, ethylbenzene belonged to those with the highest ototoxic potency.

5.6.2 Repeated dose toxicity: inhalation

When using a molecular weight of ethylbenzene of 106.17 g/mol and a molar volume of 24.1 L at 20 °C and 101.3 kPa, a concentration of 1 ppm ethylbenzene is equivalent to 0.0044 mg ethylbenzene/L air.

5.6.2.1 Human data

There are no specific data on neurotoxicity in humans with mono-exposure to ethylbenzene. However, for other aromatic solvents there is evidence for neurotoxicity in humans, e.g. for toluene, xylenes or styrene. Depressive and narcotic effects are described, and there is strong experimental evidence for ototoxicity. Data from toluene-exposed workers that showed hearing loss accompanied with vestibular impairment give concern that ethylbenzene effects on the inner ear may not be limited to the cochlea region (cited from Morata et al., 1994).

Sulkowski et al. (2002) found symptoms of vestibular dysfunction (by electronystagmography) and sensorineural high frequency hearing loss in workers involved in the production of paints and varnishes for 2 to 34 years. In the abstract it was mentioned that the most significant exposure could be attributed to the following mixture constituents: ethylbenzene, xylene and trimethylbenzene isomers. However, exposure data for ethylbenzene were vague. Altogether no conclusion can be drawn concerning ethylbenzene.

5.6.2.2 Animal data - general toxicity

Studies on general toxicity after repeated inhalation exposure are summarised in Table 5.6-2**.**

Table 5.6-2: Animal studies with repeated inhalation exposure to ethylbenzene (EB): General toxicity

Species (strain, animal no.)	Study design/test material	Compliance to test guidelines	Results	NOAEC	LOAEC	Reference
Rat (Sprague-Dawley, 6 m/grp)	2000 ppm or 8.8 mg/L air 6 h/d for **3 d** EB (> 99 %)	Specifically designed for neurotoxic effects	Decrease in nor-adrenaline levels, increase in turnover of nor-adrenaline and dopamine in the forebrain and hypo-thalamus EB blood levels: Not reported	-	2000 ppm (8.8 mg/L air)	Andersson et al. (1981)
Rat (Sprague-Dawley, 4m)	2000 ppm or 8.8 mg/L air 6 h/d for **3 d** Specific study on enzyme activities EB (> 99 %)	Not given	Increase in relative liver and kidney weight; enzyme induction in liver and kidney EB blood levels: Not reported	-	-	Toftgard and Nilsen (1982)
Rat (F344, 5 m/grp)	400-1200-2400 ppm or 1.8-5.3-10.6 mg/L air 6 h/d for **4 d** EB (99.7 %)	Not given	≥ 400 ppm: Increase in liver weight 1200 ppm: Decrease in body weight, increase in kidney weight without histopathological changes ≥ 1200 ppm: Lacrimation, shallow breathing, prostration 2400 ppm: Death of all males before day 4 with red discoloration of lungs, congestion in lungs, nasal mucosa, liver, kidneys EB blood levels: Not reported	400 ppm (1.8 mg/L air)	1200 ppm (5.3 mg/L air)	Biodynamics (1986)

Species (strain, animal no.)	Study design/test material	Compliance to test guide-lines	Results	NOAEC	LOAEC	Reference
Mouse (B6C3F1, 5 m/grp)	400-1200-2400 ppm or 1.8-5.3-10.6 mg/L air 6 h/d for **4 d** EB (99.7 %)		400 ppm: Excess lacrimation 1200 ppm: death of 4/5 males, lacrima-tion, shallow breath-ing, prostation, closed eyes, red dis-coloration of lungs, congestion of lungs, nasal mucosa, liver, kidneys 2400 ppm: Death of all males (symptoms as with dead males at 1200 ppm) EB blood levels: Not reported	400 ppm (1.8 mg/L air)	1200 ppm (5.3 mg/L air)	Biodynamics (1986), ctd.
Rabbit (NZW, 4 m/grp)	400-1200-2400 ppm or 1.8-5.3-10.6 mg/L air 6 h/d for **4 d** EB (99.7 %)		No toxic signs, deaths, treatment related findings EB blood levels: Not reported	2400 ppm (10.6 mg/L air)	-	
Rat (F344, 6-8/sex/grp)	75-750 ppm or 0.3-3.3 mg/L air 6 h/d for **5 d** 750 ppm or 3.3 mg/L air 5 d/w for **4 wk** Investigation of kidneys in rats EB (≥ 99.9 %)	Not a guide-line study	750 ppm: Slight in-crease in kidney weight (m + f), hya-line droplets (after 1 wk only), nephropa-thy, DNA synthesis (males) EB blood levels: Not reported	75 ppm (0.3 mg/L air)	750 ppm (3.3 mg/L air)	Stott et al. (1999; 2003)

Species (strain, animal no.)	Study design/test material	Compliance to test guide-lines	Results	NOAEC	LOAEC	Reference
Mouse (B6C3F1, 6-8/sex/grp)	75-750 ppm or 0.3-3.3 mg/L air 6 h/d for **5 d** 750 ppm or 3.3 mg/L air 5 d/w for **4 wk** Investigation of liver and lung in mice EB (≥ 99.9 %)		Increased liver weight at 750 ppm (m + f) and DNA synthesis (m > f). Increased DNA synthesis in lung (m + f). Some changes in enzymes in liver and lung EB blood levels: Not reported	75 ppm (0.3 mg/L air)	750 ppm (3.3 mg/L air)	Stott et al. (1999; 2003), ctd.
Rabbit (NZ, 8m/grp)	750 ppm or 3.3 mg/L air 12 h/d for **7 d** EB (p.a.)	Specifically designed for neurotoxic effects	Significant depletion of dopamine and increase of homovanillic acid levels in the striatum and tubero-infundibular region of the hypothalamus EB blood levels: Not reported	-	750 ppm (3.3 mg/L air)	Romanelli et al. (1986); Mutti and Franchini (1987); Mutti et al. (1988)
Rat (Wistar 5m/grp)	50-300-600 ppm or 0.2-1.32-2.64 mg/L air 6 h/d, 5 d/wk for **2, 5, 9, 16 wk** EB (99 %)	Not given	≥ 50 ppm: Proliferation of SER in hepatocytes and induction of some liver enzymes, 600 ppm: Induction of some kidney enzymes, kidney/body weight ratio↑ EB blood levels: Not reported	-	-	Elovaara et al. (1985)
Rat (F344)	99-382-782 ppm or 0.4-1.7-3.4 mg/L air 6 h/d, 5 d/wk for **4 wk** (all species) EB (99.7 %)	Similar to OECD 407 (version 1981)	≥ 382 ppm: Sporadic lacrimation, salivation, liver weight↑ without corresponding changes in histopathology and clinical chemistry 782 ppm: Total WBC counts↑ EB blood levels: Not reported	782 ppm (3.4 mg/L air)	-	Cragg et al. (1989)

Species (strain, animal no.)	Study design/test material	Compliance to test guide-lines	Results	NOAEC	LOAEC	Reference
Mouse (B6C3F1) Rabbit (NZW) (5/sex/grp)	99-382-782 ppm or 0.4-1.7-3.4 mg/L air 6 h/d, 5 d/wk for **4 wk** (all spe-cies) EB (99.7 %) 382-782-1610 ppm or 1.7-3.4-7.1 mg/L air 6 h/d, 5 d/wk for **4 wk** (all spe-cies) EB (99.7 %)		782 ppm: Liver weight↑ without corresponding changes in histopa-thology and clinical chemistry EB blood levels: Not reported No adverse effects observed up to the highest dose level EB blood levels: Not reported	782 ppm (3.4 mg/L air) 1610 ppm (7.1 mg/L air)	- -	Cragg et al. (1989), ctd.
Rat (Sprague-Dawley, 10 f/grp)	25-100-500 ppm or 0.11-0.4-2.2 mg/L air 6 h/d for **28 d** EB (99 %)	OPPTS 870.7800	500 ppm: Increased liver and kidney weight No effect on hu-moral immunologi-cal response EB blood levels: Not reported	100 ppm (0.4 mg/L air)	500 ppm (2.2 mg/L air)	Stump (2004)
Rat (Wistar, 18/sex/ grp)	100 ppm or 0.4 mg/L air 6h/d, 5 d/wk for **12 wk** EB (99 %)	Not given	No adverse effect EB blood levels: Not reported	100 ppm (0.4 mg/L air)	--	Clark (1983)
Rat (F344, 10/sex/grp)	100-250-500-750-1000 ppm or 0.4-1.1-2.2-3.3-4.4 mg/L air 6h/d, 5 d/wk for **92-98 d** EB (> 99 %)	Close to B.29	≥ 250 ppm: Liver weight↑ ≥ 500 ppm: Kidney weight↑ ≥ 750 ppm: Histopa-thol. reevaluation of kidneys (Hard, 2002): increased incidence of CPN and hyaline droplets (male rats) EB blood levels: Not reported	1000 ppm (4.4 mg/L air) Males (kidney): 500 ppm (2.2 mg/L air)	-	NTP (1992) Hard (2002)

Species (strain, animal no.)	Study design/test material	Compliance to test guidelines	Results	NOAEC	LOAEC	Reference
Mouse (B6C3F1, 10/sex/grp)	100-250-500-750-1000 ppm or 0.4-1.1-2.2-3.3-4.4 mg/L air 6h/d, 5 d/wk for **92-98 d** EB (> 99 %)		≥ 750 ppm: Liver weight ↑, not relevant 1000 ppm: Kidney weight↑, not relevant EB blood levels: Not reported (both species)	1000 ppm (4.4 mg/L air)	-	NTP (1992) Hard (2002), ctd.
Rat (Wistar, 10-25/sex/grp)	400-600-1250-2200 ppm or 1.8-2.6-5.5-9.68 mg/L air 7-8 h/d, 5 d/wk for **103-138 exposure days** within a **period of 144-214 days** EB (> 98 %)	Not given	≥ 400 ppm: Liver + kidney weight ↑ ≥ 1250 ppm: Growth↓, cloudy swelling of liver cells and renal tubular epithelium EB blood levels: Not reported	-	400 ppm (1.8 mg/L air)	Wolf et al. (1956)
Guinea pig (5-10)	400 – 600 – 1250 ppm or 1.8-2.6-5.5 mg/L air 7-8 h/d, 5 d/wk for **103-138 exposure days** within a **period of 144-214 days** EB (> 98 %)		600 ppm: Liver weight↑ 1250 ppm: Growth↓ EB blood levels: Not reported	400 ppm (1.8 mg/L air)	600 ppm (2.6 mg/L air)	
Rabbit (1-2)	400 – 600 – 1250 ppm or 1.8-2.6-5.5 mg/L air 7-8 h/d, 5 d/wk for **103-138 exposure days** within a **period of 144-214 days** EB (> 98 %)		600 ppm: Degeneration of testicular germinal epithelium EB blood levels: Not reported	400 ppm (1.8 mg/L air)	600 ppm (2.6 mg/L air)	

Species (strain, animal no.)	Study design/test material	Compliance to test guidelines	Results	NOAEC	LOAEC	Reference
Rhesus monkey (1-2f)	400–600 ppm or 1.8-2.6 mg/L air 7-8 h/d, 5 d/wk for **103-138 exposure days** within a **period of 144-214 days** EB (> 98 %)		600 ppm: Liver weight↑, degeneration of testicular germinal epithelium EB blood levels: Not reported	400 ppm (1.8 mg/L air)	600 ppm (2.6 mg/L air)	Wolf et al. (1956), ctd.
Rat (F344, 50/sex/grp)	75-250-750 ppm or 0.3-1.1-3.3 mg/L air 6 h/d, 5 d/wk for **104 wk** (both species) EB (> 99 %,)	NTP carcinogenicity bioassay	Slightly decr. bw in f at all dose levels ≥ 75 ppm: Chronic nephropathy in f (not relevant for humans) ≥ 250 ppm Chronic nephropathy in m (not relevant for humans) 750 ppm: Decr. survival and decr. bw (m) EB blood levels: Not reported	Males: 250 ppm, (1.1 mg/L air) Females: 75 ppm (0.3 mg/L air)	Males: 750 ppm (3.3 mg/L air) Females: 250 ppm, (1.1 mg/L air)	NTP (1999) Hard (2002) Brown (2000)
Mouse (B6C3F1, 50/sex/ grp)	75-250-750 ppm or 0.3-1.1-3.3 mg/L air 6 h/d, 5 d/wk for **104 wk** (both species) EB (> 99 %)		≥ 250ppm: Liver effects in males (syncytial alteration of hepatocytes), pituitary effects in females (hyperplasia pars distalis) 750 ppm: Histopathological effects in male lungs (alveolar epithelial metaplasia), liver effects in females (eosinophilic foci, syncytial alteration, hypertrophy, necrosis), thyroid effects in males and females (thyroid cell hyperplasia) EB blood levels: Not reported	75 ppm (0.3 mg/L air)	250 ppm (1.1 mg/L air)	

5.6.2.3 Animal data – ototoxicity

A number of studies was specifically designed for investigation of ototoxicity after repeated inhalation exposure. These are summarised in Table 5.6-3. More detailed information is given in the text following the table.

Table 5.6-3: Animal studies with repeated inhalation exposure: Ototoxicity

Species (strain, animal no.)	Study design/test material	Results	NOAEC	LOAEC	Reference
Rat (Wag/Rij/Cpb /Hsd, 16 m/grp)	800 ppm or 3.5 mg/L air 8 h/d for **5 d** Reflex modification for audiometry EB (99 %)	Persistently increased auditory thresholds of a noise-evoked startle response; significant loss of outer hair cells of the cochlea EB blood levels: Not reported	-	800 ppm (3.5 mg/L air)	Cappaert et al. (1999)
Rat (Wag/Rij/Cpb /Hsd, 8 /grp)	300-400-550 ppm or 1.3-1.8-2.4 mg/L air 5 h/d for **5 d** EB (99 %)	Increased auditory thresholds, significant loss of outer hair cells of the cochlea EB blood levels: Not reported	300 ppm (1.3 mg/L air)	400 ppm (1.8 mg/L air)	Cappaert et al. (2000)
Rat (Wag/Rij/Cpb /Hsd, 8 /grp)	300-400 ppm or 1.3-1.8 mg/L air 8 h/d for **5 d** EB (99 %)	Significant loss of outer hair cells after exposure to 400 ppm ethylbenzene alone Synergistic effects of noise and ethylbenzene on the loss of outer hair cells of the cochlea, especially of the 3rd row EB blood levels: Not reported	-	EB: 400 ppm (1.8 mg/L air) EB + noise: 300 ppm (1.3 mg/L air)	Cappaert et al. (2001)
Rat (Wag/Rij, 4-8, m+f)	550 ppm or 2.4 mg/L air 8 h/d for **5 d** EB (99 %)	Mid-frequency hearing; significant loss of outer hair cells of the cochlea EB blood levels: Average concentration ca. 23 and 6 µg EB/mL blood on days 1 and 3	-	550 ppm (2.4 mg/L air)	Cappaert et al. (2002)
Guinea pig (4-8 f/grp)	2500 ppm or 11.0 mg/L air 6-8 h/d for **5 d** EB (99 %)	Only little outer hair cell loss. EB blood levels: Average concentration ca. 3 and 1 µg EB/mL blood on days 1 and 3	-	2500 ppm (11.0 mg/L air)	

Species (strain, animal no.)	Study design/test material	Results	NOAEC	LOAEC	Reference
Rats (Long-Evans, 6 m/grp)	Exposure to 400 ppm toluene and 660 ppm (or 2.9 mg/L air) EB 6 h/d, 5 d/wk for **1 or 2 wk** No data on test material purity	No adverse hearing effects (DPOAE amplitude, auditory threshold; loss of outer hair cells) Co-exposure with noise resulted in a potentiation of permanent auditory damage EB blood levels: ca. 0.28 and 0.12 µg/mL at the end of exposure and after a 1 hr recovery period Toluene blood levels: ca. 0.11 µg/mL and < LOQ at the end of exposure and after a 1 hr recovery period	660 ppm (2.9 mg/L air) 2 wk, in co-exposure with 400 ppm toluene	-	Fechter et al. (2007)
Rat (Sprague-Dawley, 14 m/grp)	200-400-600-800 ppm or 0.9-1.8-2.6-3.5 mg/L air 6 h/d, 6 d/wk for **4, 8 and 13 wk** EB (99 %)	Dose-dependent slight to severe ototoxicity Electrophysiological measurements: effect on audiometric thresholds at 400-800 ppm, no recovery within 8 weeks Morphological examination: loss of outer hair cells at all concentrations EB blood levels: Not reported	-	200 ppm (0.9 mg/L air)	Gagnaire et al. (2007)

Cappaert et al., 1999

After exposure to 800 ppm ethylbenzene for 5 days (8 h per day) rats had persistently increased auditory thresholds of a noise-evoked startle response. This was demonstrated by a reflex modification for audiometry testing (behavioural audiometry test, indicating effects on the central and peripheral parts of the auditory pathway without discrimination between affected localisation) at 1 and 4 weeks post-exposure. The RMA thresholds (reflex modification for audiometry) increased significantly about 25 dB in the entire investigated 4-24 kHz region and did not change between 1 and 4 weeks post exposure indicating that neither recovery nor further deterioration of auditory thresholds occurred.

Severe hearing loss was recorded in ethylbenzene-exposed rats at weeks 8 to 11 after the end of exposure. Electrocochleography at the apex of the cochlea (reflecting exclusively effects at the periphery of auditory pathway) demonstrated significantly increased thresholds (shift of stimulus level 10-30 dB) of recorded auditory-evoked responses (compound action potentials) at all frequencies tested (1-24 kHz). Immediately after electrocochleography, cochleas were fixed by a perfusion technique and hair cell counting at 5-6 subsequent and representative sections of the

organ of Corti revealed a significant loss of outer hair cells (required for normal hearing sensitivity, hearing loss of 40-50 dB can occur due to their absence) (52.1 % ± 9.7) in the upper part of the basal turn and in the lower part of the middle turn (65.6 % ± 7.3). These two cochlear turns correspond with the mid-frequency region (11-21 kHz). Inner hair cells were present at 100 % in the exposed and control animals, and spiral ganglion cell appeared normal in both groups. As the threshold shifts were very similar for reflex modification for audiometry testing and compound action potentials, the authors concluded that ethylbenzene primarily exerts its effects on the peripheral part of the auditory system.

Cappaert et al., 2000

In a second study on lower ethylbenzene concentrations, auditory function in rats was tested by measuring compound action potentials in the frequency range of 1-24 kHz and distortion product otoacoustic emissions (DPOAEs, a very sensitive, noninvasive test of cochlear function, detecting impairment of outer hair cells; measurement of emitted sounds produced as stimulus-induced active outer hair cells response) in the frequency range of 4-22.6 kHz. The effects were analysed three to six weeks after the end of exposure. Inhalation exposure to 400 and 550 ppm ethylbenzene for 8 hours/day for 5 consecutive days increased auditory thresholds (significant increase of the threshold for compound action potentials at 8kHz after 550 ppm, at 12 kHz after 400 and 550 ppm and at 16 kHz after 550 ppm), whereas significantly decreased DPOAE amplitude growth curves were observed after 550 ppm dose at 5.6, 8, and 11.3 kHz, but not at other frequencies. Outer hair cell loss was found in two of five examined localisations in the cochlea. At 400 ppm, 25 % outer hair cell loss was found at the 11- and 21-kHz region. The 550 ppm concentration evoked 40 % and 75 % outer hair cell loss at the 11- and 21-kHz regions. No significant effect on measures of hearing function and no statistically significant loss of cochlear hair cells were seen at 300 ppm ethylbenzene, the lowest concentration tested.

Cappaert et al., 2001

Using reduction of hair cells as an indicator of ototoxicity there was a statistically significant synergistic effect between exposure to noise at 105 dB and ethylbenzene exposure at levels of 300 and 400 ppm. No synergistic effect was found by using distortion product otoacoustic emissions (DPOAE) and compound action potential measurements.

The effects of 300 or 400 ppm ethylbenzene and three noise levels (95 or 105 dB mostly in the frequency range of 1.5 and 12.5 kHz or background noise below 65 dB) and all their combinations were investigated for a 5 day-exposure at 8 hrs/day in albino Wag/Rij rats (8 animals/group). Ambient noise was below 50 dB over most of the frequency range. At very low frequencies, where rats were reported to be very insensitive, ambient noise probably produced by the air supply system was highly variable and could reach levels up to 60 dB, but did not exceed 65 dB. Data on hearing function were generated by the measurement of distortion product otoacoustic emissions (DPOAEs) and by the estimation of compound action potentials in electrocochleography. Morphological abnormalities were determined by quantitative estimation of hair cells of the organ of Corti (in representative sections of the mid-frequency sections and in whole cytocochleograms) in perfusion fixed cochleas from both sides. Measurements and cochlea harvesting were conducted between 3 and 7 weeks after exposure. The reason for this time point was that noise-induced hearing loss that still exists 20 to 30 days after the last exposure is considered to be permanent.

DPOAEs and compound action potentials were affected after 105 dB noise alone, and after 105 dB noise in combination with 300 and 400 ppm ethylbenzene. However, the amount of hearing loss with these combinations did not exceed the loss for 105 dB noise alone.

A slight, but not significant outer hair cell loss was found after exposure to 300 ppm ethylbenzene alone; it was located in the third row of outer hair cells. Significant hair cell loss was observed after exposure to 400 ppm ethylbenzene alone, spreading to the second and first outer hair cell rows. Noise alone hardly affected the outer hair cell counts except for a minor loss in the first row of outer hair cells after 105 dB. Noise at 105 dB in combination with ethylbenzene at 300 and 400 ppm, however, showed outer hair cell loss greater than the sum of the losses induced by noise and ethylbenzene alone. The row of inner hair cells was not affected by either agent. The authors located the outer hair cell loss in the mid-frequency region of the cochlea as the target region of ethylbenzene action and found concentration-dependent expansion of findings.

Cappaert et al., 2002

Guinea pigs were less susceptible to the ototoxic effect of ethylbenzene than rats. This can be related to varying blood concentrations of ethylbenzene in guinea pigs and rats.

Eight female guinea pigs (200 g) were exposed to high concentrations of ethylbenzene (2500 ppm, 8 hrs on the first day, thereafter 6 hrs/day, over the following 4 days). Duration of exposure was reduced for guinea pigs after the first day from 8 to 6 hrs because of severe toxicity. A group of eight rats (200 g) was exposed to 550 ppm ethylbenzene for 8 hrs/day on 5 days. Control groups were exposed to ambient air alone. In a supplementary study, blood concentration at 500 ppm ethylbenzene (8 hrs/day, 3 days) were estimated in four animals of each species at the end of day 1 and 3, three air exposed animals/species were used as controls. Hearing function in both species was tested by electrocochleography and histopathology of perfusion-fixed standard sections of the cochleas of all animals was carried out (identical to the methods reported in the above mentioned studies).

Shifts of compound action potential thresholds indicated a mid-frequency hearing loss in rats exposed to 550 ppm ethylbenzene, at 8, 12, 16 and 24 kHz. Mean thresholds were not affected in guinea pigs at 2500 ppm ethylbenzene. Significant loss of outer hair cells was observed in rats in the 11- and 21-kHz regions of the cochlea, the average percentage of remaining outer hair cells was only 25 % in the 21-kHz region. In guinea pigs there was only little outer hair cell loss at any frequency.

Ethylbenzene concentrations in blood showed significant differences between species. On day 1, the level was 8.3 times higher in rats than in guinea pigs and 4.3 times higher in rats than in guinea pigs on day 3. Absolute concentration was lower on day 3 than on day 1 indicating that metabolic transformation rose with increase in treatment duration.

Gagnaire et al. (2007)

Exposure of ethylbenzene to rats for 13 weeks (6h/day) produced moderate to severe ototoxicity without causing important systemic toxicity. The ototoxicity is characterised by increased electrophysiological auditory thresholds and hair cell losses, where hair cell loss was the more sensitive endpoint. The LOAEL for outer hair cell loss was 200 ppm (0.9 mg/L), a NOAEL could not be derived. Calculated theoretical lowest adverse effect levels were around 120 ppm.

Rats were exposed to ethylbenzene concentrations of 200, 400, 600 and 800 ppm (corresponding to 0.9 to 3.5 mg/L). Exposure was for 6 hrs daily, 6 days/week over 13 weeks; 14 male Sprague-Dawley were used per group. The animals were maintained for a recovery period of 8 weeks before they were sacrificed. There was no significant difference in weight gain between controls and groups exposed to ethylbenzene.

Electrophysiological measurements were performed at the end of the 4th, 8th and 13th week of exposure and after a recovery for 8 weeks (at week 21). Electrodes were implanted 3 to 4 weeks before start of exposure. Auditory thresholds were investigated by brainstem auditory-evoked responses with frequencies of 2, 4, 8 and 16 kHz.

At all frequencies analysed the concentration-effect relationship was characterised by increased thresholds after exposure to 400, 600 and 800 ppm. Highest hearing losses were found in the rats exposed to 600 and 800 ppm. Concerning the time-effect relationship, these threshold shifts appeared from the fourth week of exposure onwards; there was no significant increase throughout the exposure period and no recovery 8 weeks after end of exposure.

Morphological examinations were carried out after the recovery period; 8 rats were investigated per concentration. The cochleae were prepared and cytocochleograms (total cell count by histopathology) were constructed from the surface preparation. At all tested concentrations losses of outer hair cells of the organ of Corti were found. Outer cell hair loss was nearly complete in the three rows of the organ of Corti after exposure to 600 and 800 ppm ethylbenzene. Only the basal part of the cochlea (which transcribes the high frequencies) was partly spared. Also after exposure to 400 ppm considerable outer hair cell loss was found in all animals. After exposure to 200 ppm, significant outer hair cell loss in the third row was seen in 4 out of the 8 exposed animals.

Outer hair cell losses were greatest in the third row. After exposure to 200 ppm the average loss in the animals was 4 %, and the EC_{50} was found to be 371 ppm.

Inner hair cell loss was found after exposure to 600 and 800 ppm in the basal part of the organ of Corti. On average, the inner hair cell loss was 32 % at 800 ppm and 14 % at 600 ppm. After exposure to 400 ppm, occasional inner hair cell loss was found in the basal part of the organ of Corti.

In this study the ototoxic effect of ethylbenzene was also tested in combination with two types of mixed xylenes (o-, m-, p-xylene). These co-exposures caused potentiation of the ototoxic effects.

The LOAEC for ototoxic effects was 200 ppm (0.9 mg/L air). However, no NOAEC could be derived. Therefore, the authors calculated theoretical lowest adverse effect levels from the three statistical upper confidence limits of the average losses observed in the controls. All three calculated theoretical lowest adverse effect levels were around 120 ppm (114-130 ppm or 0.5-0.6 mg/L air).

Fechter et al. (2007)

Inhalation exposure of rats to a mixture of ethylbenzene (660 ppm) and toluene (400 ppm) for 5 or 10 days did not have an adverse effect on DPOAE amplitude or auditory threshold. There was no significant loss of outer hair cells. Coexposure to these mixed solvents and noise of 93-95 dB resulted in a potentiation of permanent auditory damage.

In contrast to the other investigations, no adverse hearing effects were found after exposure to high solvent exposures alone (660 ppm ethylbenzene plus 400 ppm toluene)

Groups of 6 male Long-Evans rats were exposed inhalationally to a hydrocarbon mixture of 400 ppm toluene and 660 ppm ethylbenzene for either one or two weeks (5 days/week, 6 hrs/day). The groups of rats were exposed in the presence and absence of an octave band of noise at 93-95 dB. Untreated and noise only-exposed control groups were included. Impairment of auditory function was assessed using distortion product otoacoustic emissions (DPOAE) and compound action potential at 3 days, 1 week and 4 weeks post exposure. The organs of Corti were then dissected to evaluate hair cell loss and a cochleogram was prepared. The uptake and elimination of the solvents

was assessed in additional rats (3-4/group) not used for auditory testing by measuring tissue hydrocarbon (blood, liver, cochlear) levels immediately after exposure and 1 hr after a single 6 hr exposure. Glutathione levels in the liver, brain and lung were measured between 0 and 3 hrs after a 4 hr exposure.

A significant amount of ethylbenzene was present in blood and liver 1 hr post exposure and there was no evidence of glutation depletion.

The combined exposure to toluene and ethylbenzene produced no effects on DPOAE or compound action potentials at any of the post-exposure time points after a 5 or 10 day exposure. The combination with noise over 5 or 10 days produced a deficit in DPOAE amplitude, most pronounced 3 days post-exposure but even 4 weeks post-exposure there remained a deficit. These effects showed statistical significance. There also was a statistically significant loss in pure tone auditory threshold. Noise alone over 5 days produced a deficit of 10-20 dB 3 days post-exposure, however complete recovery was observed by 1 week post-exposure. Rats experiencing noise for 10 days showed some persistent impairment of DPOAE amplitude even at 4 weeks post-exposure but this was less marked than in the rats exposed to mixed solvents and noise. There was no effect of noise alone on auditory threshold.

By histopathology solvent exposure alone did not lead to a significant loss of outer hair cells. Noise alone showed an increase of outer hair cells as compared to controls. This was quite limited but particularly apparent in rows 1 and 2. The outer hair cell loss did not exceed 5 % in any area of the cochlea. The combined treatment with solvent and noise showed after 5 days exposure clear outer hair cell death at 12-24 kHz, greatest in row 1, intermediate row 2 and very limited row 3. Loss of outer hair cells did not exceed 25 % at any locus. A similar pattern of effect was seen after 10 days exposure.

A number of the above studies on ototoxicity following inhalation exposure has also recently been reviewed by Vyskocil et al. (2008), cf. below, section 5.6.5.

5.6.3 Repeated dose toxicity: dermal

Although percutaneous resorption is demonstrated for ethylbenzene, no valid studies with repeated dermal applications are available.

5.6.4 Other relevant information

None relevant

5.6.5 Summary and discussion of repeated dose toxicity:

No relevant human data is available concerning repeated dose toxicity of ethylbenzene. In experimental animals, repeated doses of ethylbenzene specifically affected the nervous system. Ethylbenzene did not induce overt toxicity in any other organ system.

After **oral exposure** to rats for 90 days, a NOAEL of 75 mg/kg bw/d was found, based on indications of a mild regenerative anaemia and liver changes indicative of microsomal enzyme induction. The LOAEL was 250 mg/kg bw/d. The key study for these data is given by Mellert et al. (2004; 2007). Ototoxicity was found after oral administration; however, only one high dose of 900 mg/kg/day was investigated. No classification results are deduced from these data.

No data is available for repeated **dermal administrations**.

After **repeated inhalation exposure** of rats and mice for 3 months, for general toxicity a NOAEC of 1000 ppm (4.4 mg/L) was established (key study: NTP, 1992; Hard, 2002). Observed increases in liver and kidney weight were interpreted to be associated with metabolic enzyme induction.

Irreversible ototoxicity was found in rats after repeated inhalation exposure to ethylbenzene vapour (key study: Gagnaire et al., 2007).

In neurophysiological measurements effects were found on audiometric thresholds after exposure to ethylbenzene concentrations, ranging from 400 to 800 ppm. The threshold shifts appeared from the fourth week of exposure onwards; there was no significant increase throughout the exposure period and no recovery 8 weeks after exposure.

Morphological examinations after 13 weeks of exposure and 8 weeks of recovery demonstrated losses of outer hair cells at all tested concentrations; the LOAEC was 200 ppm (0.9 mg/L air). Outer hair cell loss was nearly complete after exposure to 600 and 800 ppm and still observable in all animals after 600 ppm; after exposure to 200 ppm significant outer hair cell loss in the third row was seen in 4 out of the 8 exposed animals. Outer hair cell losses were greatest in the third row. After exposure to 200 ppm the average loss in the animals was 4 %, and the EC_{50} was found to be 371 ppm (1.6 mg/L air).

These results are in line with those of Cappaert et al. (2000) which showed that the minimum ethylbenzene concentration required to induce significant threshold shifts after exposure for 5 days was 400 ppm, whereas 300 ppm ethylbenzene did not affect the auditory system significantly but caused some minor outer hair cell loss. The fact that hair cell loss is observed at concentrations with only weak or no auditory threshold shifts has already been noted and discussed earlier (e.g., Cappaert et al., 2000). Irreversible hair cell loss may result in a premature onset of signs of normal aging (presbycusis).

At co-exposure to ethylbenzene and high levels of noise, synergistic effects on hearing loss and cell damage of outer hair cells occurred.

Recently, a number of the above studies on ototoxicity following repeated inhalation exposure to ethylbenzene were also reviewed by Vyskocil et al. (2008). The authors considered animal data only when dose levels exceeded current Canadian occupational health thresholds (time-weighted average exposure value, TWAEV) by not more than a factor of 100. They concluded as follows:

> *'[…] Further studies with sufficient data on the ethyl benzene exposure of individual workers are thought necessary to make a definitive conclusion. Given the current evidence from animal studies, we recommend considering ethyl benzene as an ototoxic agent'.*

In the classification criteria (Annex I of CLP-Regulation (EC) No. 1272/2008) category 2 for specific target organ toxicity after repeated exposure is, among others, foreseen when significant toxic effects are observed in a 90 day repeated dose study after inhalation exposure to vapour concentrations ranging from 0.2 to 1.0 mg/L air. The LOAEC for irreversible cell death of outer hair cells of the cochleae was 0.9 mg/L air. Therefore, it is proposed to classify(/label) ethylbenzene as:

STOT RE 2 (hearing organs); H373 (May cause damage to organs through prolonged or repeated exposure)

The guidance value according to Directive 67/548/EEC for R48/20 is $\leq$ 0.25 mg/L air/6 h/d, which is the below the LOAEC for irreversible cell death of outer hair cells of the cochlea (0.9 mg/L). Nevertheless, ethylbenzene leads to irreversible damage in outer hair cells of the hearing organ with major functional changes in hearing assessed by appropriate methods (electrophysiology). In the

criteria for classification and labelling it is stated that serious damage to health is to be considered to include death, clear functional disturbance or morphological changes which are toxicologically significant. It is particularly important when these changes are irreversible. Evidence indicating that R48 should be applied when major functional changes in the central or peripheral nervous systems, including sight, hearing and the sense of smell, assessed by clinical observations or other appropriate methods (e.g. electrophysiology) occurred.

Regarding to the ototoxicty of toluene, a related compound; impaired hearing function has been caused by exposure concentration levels of 1000-1400 ppm (3800-5320 mg/m^3) for 2-8 weeks in rats. In one study an exposure level of 700 ppm (2660 mg/m^3) was determined as a no-effect concentration for auditory toxicity. Further, transient auditory system impairment has been revealed at a much lower toluene concentration when using distortion product otoacoustic emission to evaluate auditory function (McWilliams, 2000). Toluene was classified as Xn: R 48/20. Remarkably, the LOAEC of ethylbenzene was 200 ppm, which was quite lower than the LOAEC of toluene. This gives rise to concern for a possible harmful effect of hearing loss, Hence, it cannot be excluded that functional damage (hearing loss) can occur during normal handling and use in occupational settings concerning substances with a high saturated vapour concentration. The dossier submitter did not originally propose classification for repeated dose toxicity under the DSD. However, RAC concludes that the following classification for ethylbenzene is appropriate.

R48/20 Harmful: Danger of serious damage to health by prolonged exposure through inhalation

5.7 Mutagenicity

Mutagenicity has not been considered as part of this dossier.

5.8 Carcinogenicity

Carcinogenicity has not been considered as part of this dossier.

5.9 Toxicity for reproduction

Toxicity for reproduction has not been considered as part of this dossier.

5.10 Other effects

5.10.1 Aspiration hazard

Ethylbenzene has a very low kinematic viscosity of 0.63 mm^2/s as determined at 40 °C following the standard method ASTM D445 (Knothe and Steidley, 2005). This method which - according to http://www.astm.org/Standards/D445.htm (as of 2010-10-11) - corresponds to method ISO 3104 directly assesses kinematic viscosity of liquids in the range of 0.2-300000 mm^2/s..

In the classification criteria for aspiration hazard (Regulation (EC) No. 1272/2008) it is argued that a substance needs to be classified in category 1, if it is a hydrocarbon and has a kinematic viscosity of 20.5 mm^2/s or less, measured at 40 °C.

The aspiration hazard of ethylbenzene is supported by experimental data (Gerarde and Linden, 1963). Three male Wistar rats, weighing from 250 to 350 g, were anaesthetised to the point of a-pnoea. The mouth was held open and the tongue pulled forward. With the animals' heads elevated, 0.2 mL (or 0.25 mL, contradictory data) of commercial ethylbenzene were delivered into the mouth. As breathing resumed and became regular, the nostrils were closed with the fingers at the end of the expiration phase of the breathing cycle. This was repeated until the liquid had been aspirated or the animal showed signs of regaining consciousness. All three animals died instantly.

With respect to aspiration toxicity it is therefore proposed to classify(/Label) ethylbenzene:

- according to Annex I of CLP-Regulation (EC) No. 1272/2008 as:

  Asp. Tox. 1; H304 (May be fatal if swallowed and enters airways)

- according to the criteria of Directive 67/548/EEC as:

  Xn; R65 (Harmful: May cause lung damage if swallowed)

5.11 Derivation of DNEL(s) or other quantitative or qualitative measure for dose response

Not applicable for this dossier.

6 HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

Not relevant for this dossier. It is however noted that according to Annex VI of Regulation (EC) No. 1272/2008 ethylbenzene is classified as a Flammable Liquid, Cat. 2.

7 ENVIRONMENTAL HAZARD ASSESSMENT

Not relevant for this dossier.

JUSTIFICATION THAT ACTION IS REQUIRED ON A COMMUNITY-WIDE BASIS

Ethylbenzene was a priority substance in the existing chemicals program (EEC) 793/93. A classification proposal was not yet discussed at the TC C&L level.

The observed toxicity following repeated administration of ethylbenzene (ototoxicity) could potentially be considered severe enough to fulfil the criteria of Article 57 f of the REACH Regulation. If the proposed C & L is adopted, the need might thus be identified to propose ethylbenzene as a candidate substance for Annex XIV.

For CMR substances, section 3.1.2 of ECHA's 'Guidance for the preparation of an Annex XV dossier on the identification of substances of very high concern' states that:

> *'[…]Nonetheless, it is recommended to propose and achieve an entry for a harmonised classification in Annex I to Directive 67/548/EEC before a CMR substance is proposed to be identified for inclusion in the candidate list for authorisation. […]'*

It appears reasonable to follow this recommendation also for other endpoints justifying inclusion into Annex XIV, which by definition (as per Article 57 f of the REACH) are considered to pose an equivalent level of concern to CMR or PBT substances.

Also under procedural aspects it appears appropriate to first establish agreement on C & L at the European Level before starting a complex and work-intensive procedure such as the one for including substances into Annex XIV of REACH.

REFERENCES

Andersson, K., Fuxe, K., Nilsen, O.G., Toftgard, R., Eneroth, P., Gustafsson, J.-A. (1981): Production of discrete changes in dopamine and noradrenaline levels and turnover in various parts of the rat brain following exposure to xylene, ortho-, meta-, and para-xylene, and ethylbenzene. Toxicol. Appl. Pharmacol. 60, 535-548

Barnett, J. F. Jr. (2006). Oral (Gavage) subchronic neurotoxicity study of ethylbenzene in rats with recovery group. Laboratory Project ID MHV00001. Charles River DDS Argus Division Laboratory, Horsham, Pennsylvania. Sponsored by the Ethylbenzene Panel, American Chemistry Council, Arlington, VA. Reported in: Li et al. (2010)

Biodynamics (1986): A four day inhalation toxicity study of ethylbenzene in the rat, mouse and rabbit, Project No. 85-7852, EPS-OTS 86-8700000423

Brown, WR(2000): Toxicology and Carcinogenesis Study of Ethylbenzene in B6C3F1 Mice (CAS 100-41-4) NTP Report Number 466. Histopathology of Liver and Lung. Report prepared for the American Chemistry Council Ethylbenzene Panel

Cappaert, N.L.M., Klis, S.F.L., Baretta, A.N., Muijser, H., Smorrenburg, G.F. (2000): Ethylbenzene-induced ototoxicity in rats: A dose-dependent mid-frequency hearing loss. JARO 01, 292-299

Cappaert, N.L.M., Klis, S.F.L., Muijser, H., de Groot, J.C.M.J., Kulig, B.M., Smoorenburg, G.F. (1999): The ototoxic effects of ethylbenzene in rats. Hearing Research 137, 91-102

Cappaert, N.L.M., Klis, S.F.L., Muijser, H., Kulig, B.M., Ravensberg, L.C., Smorrenburg, G.F. (2002): Differential susceptibility of rats and guinea pigs to the ototoxic effects of ethylbenzene. Neurotoxicology and Teratology 24, 1-8

Cappaert, N.L.M., Klis, S.F.L., Muijser, H., Kulig, B.M., Smorrenburg, G.F. (2001): Simultaneous exposure to ethylbenzene and noise: synergistic effects on outer hair cells. Hearing Research 162, 67-69

Carpenter, C. P.; Smyth, H. F. (1946). Chemical burns of the rabbit cornea. Am. J. Ophthalmol. 29:1363-1372.

Clark, D.G. (1983): Ethylbenzene hydroperoxide (EBHP) and ethylbenzene: 12 week inhalation study in rats. Group Research Report SBGR.81.300 [EPA OTS Public Files, Shell Oil Co., Doc. No. 86870001629 Fiche No. 0516206 and TSCATS: OTS 0516206, DOC. I.D.: 86-870001625, Jan. 01, 1983], Shell Chemical Company

Cragg, S. T. ; Clarke E.A. ; Daly, I.W.; Miller, R.R.; Terrill, J.B.; Ouellette, R.E. (1989). Subchronic inhalation toxicity of ethylbenzene in mice, rats and rabbits. Fundam. Appl. Toxicol. 13:399-408.

De Ceaurriz, J. C.; Micillino, J. ; Bonnet, P. ; Guenier, J. (1981). Sensory irritation caused by various industrial airborne chemicals. Toxicol. Lett. 9:137-144.

Elovaara, E., Engström, K., Aito, N.A., Vainiuo, H. (1985): Biochemical and morphological effects of long-term inhalation exposure of rats to ethylbenzene. Xenobiotica 15, 299-308

Fechter, L.D., Gearhart, C., Fulton, S., Campbell, J., Fisher, J., Na, K., Cocker, D., Nelson-Miller, A., Moon, P. and Pouyatos, B. (2007): Promotion of noise-induced cochlear injury by toluene and ethylbenzene in the rat. Tox. Sci. 98, 542-551

Gagnaire, F., Langlais, C. (2005): Relative ototoxicity of 21 aromatic solvents. Arch. Tox. 79, 346-354

Gagnaire, F., Langlais, C., Grossmann, S. and Wild, P. (2007): Ototoxicity in rats exposed to ethylbenzene and to two technical xylene vapours for 13 weeks. Arch. Tox. 81:127-143Gerade, H.W.; Linden, NJ (1963): Toxicological studies on hydrocarbons. IX. The aspiration hazard and toxicity of hydrocarbons and hydrocarbon mixtures. Archives on Environmental Health 6: 35-47

Gerade, H.W.; Linden, NJ (1963): Toxicological studies on hydrocarbons. IX. The aspiration hazard and toxicity of hydrocarbons and hydrocarbon mixtures. Archives on Environmental Health 6: 35-47

Hard, G.C., (2002): Significance of the renal effects of ethylbenzene in rodents for assessing human carcinogenic risk. Tox. Sci. 69, 30-41

Knothe, G; Steidley, KR (2005): Kinematic viscosity of biodiesel fuel components and related compounds. Influence of compound structure and comparison to petrodiesel fuel components. Fuel 84: 1059–1065

Li, A.A., Maurissen, J.P.J., Barnett Jr., J.F., Foss, J., Freshwater, L., Garman, R.H., Preachee, V.L., Hong, S.J., Stump, D.G., Bus, J.S. (2010). Oral gavage subchronic neurotoxicity and inhalation subchronic immunotoxicity studies of ethylbenzene in the rat. Neurotoxicology 31, 247-258.

McWilliams, M L; Chen, G-D; Fechter L D (2000). Low level toluene disrupts auditory function in guinea pigs. Submitted to Toxicology and Applied Pharmacology.

Mellert, W. et al. (2003): Ethybenzene - Range-finding study in Wistar rats. Administration by gavage for 4 weeks. Experimental Toxicology and Ecology, BASF, Ludwigshafen, Germany. Laboratory Project Identification Project No. 50C0153/99152. Sponsored by the Styrenics Steering Committee, CEFIC, Brussels, Belgium

Mellert, W. et al. (2004): Subchronic toxicity study in Wistar rats. Oral Administration by gavage for 3 months. Experimental Toxicology and Ecology, BASF, Ludwigshafen, Germany. Laboratory Project Identification Project No. 50C0153/99153. Sponsored by the Styrenics Steering Committee, CEFIC, Brussels, Belgium.

Mellert, W., Deckardt, K., Kaufmann, W., van Ravenzwaay, B. (2007): Ethylbenzene: 4- and 13-week rat oral toxicity. Arch. Tox. 81, 361-370

Morata, T.C., Dunn, D.E., Sieber, W.K. (1994): Occupational exposure to noise and ototoxic organic solvents. Arch. Environmen. Health 49, 359-365

Mutti, A., Falzoi, M., Romanelli, A., Bocchi, M.C., Ferroni, C., Franchini, I. (1988): Brain dopamine as a target for solvent toxicity: Effects of some monocyclic aromatic hydrocarbons. Toxicology 49, 77-82

Mutti, A.; Franchini, I. (1987): Toxicity of metabolites to dopaminergic systems and the behavioural effects of organic solvents. Br. J. Ind. Med. 44, 721-723

Nielsen, G. D.; Alarie, Y. (1982). Sensory irritation, pulmonary irritation, and respiratory stimulation by airborne benzene and alkylbenzenes: Prediction of safe industrial exposure levels and correlation with their thermodynamic properties. Tox. Appl. Pharm. 65:459-477.

NTP (1992): NTP Report on the toxicity studies of ethylbenzene in F334/N rats and B6C3F1 mice (Inhalation studies). NIH Publication No. 92-3129, U.S. Department of Health and Human Services, PB93-149722

NTP (1999): NTP Technical Report on the Toxicology and Carcinogenesis Studies of Ethylbenzene (CAS No. 100-41-4) in F344/N Rats and B6C3F1 Mice (Inhalation Studies). NTP TR466. NIH Publication 96-3956. US Department of Health and Human Services, Research Triangle Park, NC.

Romanelli, A., Falzoi, M., Mutti, A., Bergamaschi, E., Franchini, I. (1986): Effects of some monocyclic aromatic solvents and their metabolites on brain dopamine in rabbits. J. Appl. Toxicol. 6, 431-435

Smyth, H. F., Jr.; Carpenter, C. P.; Weil, C. S.; Pozzani, U. C.; Striegel, J. A. (1962). Range finding toxicity data: List VI. Am. Ind. Hyg. Assoc. J. 23:95-107.

Stott, T.W., Johnson, K.A., Bahnemann, R., Day, S.J., McGuirk, R.J. (2003): Evaluation of potential modes of inhaled ethylbnzene in rats and mice. Tox. Sci. 71, 53-66

Stott, W.T., Johnson, K.A., Day, S.J., McGuirk, R.J. (1999): Ethylbenzene: Mechanism of tumorigenicity in Fischer 344 rats and B6C3F1 mice. Dow Chemical Co. Health & Environmmental Research Laboratories Study ID 981138. Sponsor Styrene Steering Committee Cefic.

Stump, D.G. (2004): A 28 day inhalation splenic antibody formation study of ethylbenzene in rats. WIL Research Laboratories Inc. Study number WIL-186029 Sponsored by the American Chemistry Council, Ethylbenzene Panel.

Sulkowski, W.J., Kowalska, S., Matyja, W., Guzek,W., Wesolowski, W., Szymczak, W., Kostrzewski, P. (2002): Effects of occupational exposure to a mixture of solvents to the inner ear: a field study. Int. J. Occup. Med. Environm. Health 15, 247-256

Toftgard, R., Nilsen, O.G. (1982): Effects of xylene and xylene isomers on cytochrome P450 and in vitro enzymatic activities in rat liver, kidney and lung. Toxicology 23, 197-212

van Thriel, C.; Haumann, K.; Kiesswetter, E,; Blaszkawicz, M.; Seeber, A. (2002). Time courses of sensory irritations due to 2-butanone and ethylbenzene exposure: Influences of self-reported multiple chemical sensitivity (sMCS). Int. J. Hyg. Environ. Health. 204:367-369.

Vyskocil, A., Leroux, T., Truchon, G., Lemay, F., Gendron, M, Gagnon, F., El Majidi, N., Viau, C. (2008): Ethyl benzene should be considered ototoxic at occupationally relevant exposure concentrations. Toxicology and Indistrial Health 24, 241-246

Wolf, M.A., Rowe, V.K., McCollister, D.D., Hollingsworth, R.L., Oyen, F. (1956): Toxicological studies of certain alkylated benzenes and benzene. Experiments on laboratory animals. A.M.A: Archives of Industrial Health 14, 387-398

Yant, W. P.; Schrenk, H.H.; Waite, C.P.; Patty, F.A. (1930). Acute response of guinea pigs to vapours of some new commercial organic compounds II Ethylbenzene. Publ. Health Res. 45:1241-1250.