Committee for Risk Assessment

RAC

Annex 1

Background document

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

Chlorobenzene

EC Number: 203-628-5
CAS Number: 108-90-7

CLH-O-0000004060-90-03/D

The background document is a compilation of information considered relevant by the dossier submitter or by RAC for the proposed classification. It includes the proposal of the dossier submitter and the conclusion of RAC. It is based on the official CLH report submitted to public consultation. RAC has not changed the text of this CLH report but inserted text which is specifically marked as 'RAC evaluation'. Only the RAC text reflects the view of RAC.

Adopted

14 March 2014

ANNEX 1 - BACKGROUND DOCUMENT TO RAC OPINION ON CHLOROBENZENE

CLH report

Proposal for Harmonised Classification and Labelling

Based on Regulation (EC) No 1272/2008 (CLP Regulation),
Annex VI, Part 2

Substance Name: Chlorobenzene

EC Number: **203-628-5**

CAS Number: **108-90-7**

Index Number: **602-033-00-1**

Contact details for dossier submitter: biuro@chemikalia.gov.pl

Bureau for Chemical Substances

30/34 Dowborczykow Street

90-019 Lodz, Poland

Version number: 2 **Date: 30.07.2013**

CONTENTS

Part A.

Part A.

1 PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING

1.1 Substance

Table 1: Substance identity

Substance name:	***Chlorobenzene***
EC number:	***203-628-5***
CAS number:	***108-90-7***
Annex VI Index number:	***602-033-00-1***
Degree of purity:	**≥ *99 % w/w***
Impurities:	No (Eco)toxicological relevant impurities are present

1.2 Harmonised classification and labelling proposal

Table 2: The current Annex VI entry and the proposed harmonised classification

	CLP Regulation	**Directive 67/548/EEC (Dangerous Substances Directive; DSD)**
Current entry in Annex VI, CLP Regulation	Flam. Liq. 3; H226 Acute Tox. 4 (*); H332 Aquatic Chronic 2; H411	R10 Xn; R20 N; R51-53 SCL: Xn; R20: C ≥ 5.0 %

Current proposal for consideration by RAC	Skin. Irrit. 2; H315 Removal of (*) from Acute Tox. 4	Xi; R38
Resulting harmonised classification (future entry in Annex VI, CLP Regulation)	Flam. Liq. 3; H226 Acute Tox. 4; H332 Skin. Irrit. 2; H315 Aquatic Chronic 2; H411	R10 Xn; R20 Xi; R38 N; R51-53 SCL: Xn; R20: C ≥ 5.0 %

1.3 Proposed harmonised classification and labelling based on CLP Regulation and/or DSD criteria

Table 3: Proposed classification according to the CLP Regulation

CLP Annex I ref	Hazard class	Proposed classification	Proposed SCLs and/or M-factors	Current classification [1)]	Reason for no classification [2)]
2.1.	Explosives	None		None	Not evaluated
2.2.	Flammable gases	None		None	Not evaluated
2.3.	Flammable aerosols	None		None	Not evaluated
2.4.	Oxidising gases	None		None	Not evaluated
2.5.	Gases under pressure	None		None	Not evaluated
2.6.	Flammable liquids	Flam. Liq. 3; H226[#]		Flam. Liq. 3; H226[#]	
2.7.	Flammable solids	None		None	Not evaluated
2.8.	Self-reactive substances and mixtures	None		None	Not evaluated
2.9.	Pyrophoric liquids	None		None	Not evaluated
2.10.	Pyrophoric solids	None		None	Not evaluated
2.11.	Self-heating substances and mixtures	None		None	Not evaluated
2.12.	Substances and mixtures which in contact with water emit flammable gases	None		None	Not evaluated
2.13.	Oxidising liquids	None		None	Not evaluated
2.14.	Oxidising solids	None		None	Not evaluated
2.15.	Organic peroxides	None		None	Not evaluated
2.16.	Substance and mixtures corrosive to metals	None		None	Not evaluated
3.1.	Acute toxicity - oral	None		None	Not evaluated
	Acute toxicity - dermal	None		None	Not evaluated
	Acute toxicity - inhalation	Acute Tox. 4; H332		Acute Tox. 4(*); H332	
3.2.	Skin corrosion / irritation	Skin. Irrit. 2; H315		None	
3.3.	Serious eye damage / eye irritation	None		None	Not evaluated
3.4.	Respiratory sensitisation	None		None	Not evaluated
3.4.	Skin sensitisation	None		None	Not evaluated
3.5.	Germ cell mutagenicity	None		None	Not evaluated
3.6.	Carcinogenicity	None		None	Not evaluated
3.7.	Reproductive toxicity	None		None	Not evaluated
3.8.	Specific target organ toxicity – single exposure	None		None	Not evaluated
3.9.	Specific target organ toxicity – repeated exposure	None		None	Not evaluated
3.10.	Aspiration hazard	None		None	Not evaluated
4.1.	Hazardous to the aquatic environment	Aquatic Chronic 2; H411[#]		Aquatic Chronic 2; H411[#]	
5.1.	Hazardous to the ozone layer	None		None	Not evaluated

[1)] Including specific concentration limits (SCLs) and M-factors

[2)] Data lacking, inconclusive, or conclusive but not sufficient for classification
This dossier does not propose a change in the classification of this hazard propoerty

Labelling:

Pictogram: GHS02
GHS07
GHS09
Signal word: Warning
Hazard statements: H226: Flammable liquid and vapour
H332: Harmful if inhaled
H315: Causes skin irritation
H411: Toxic to aquatic life with long lasting effects
Precautionary statements: No precautionary statements are proposed since precautionary statements are not included in Annex VI of Regulation EC no. 1272/2008.

Proposed notes assigned to an entry: None

Table 4: Proposed classification according to DSD

Hazardous property	Proposed classification	Proposed SCLs	Current classification [1)]	Reason for no classification [2)]
Explosiveness	None		None	Not evaluated
Oxidising properties	None		None	Not evaluated
Flammability	R10#		R10#	
Other physico-chemical properties	None		None	Not evaluated
Thermal stability	None		None	Not evaluated
Acute toxicity	Xn; R20# Xn; R20: C ≥ 5.0 %		Xn; R20# Xn; R20: C ≥ 5.0 %	
Acute toxicity – irreversible damage after single exposure	None		None	Not evaluated
Repeated dose toxicity	None		None	Not evaluated
Irritation / Corrosion	Xi; R38		None	
Sensitisation	None		None	Not evaluated
Carcinogenicity	None		None	Not evaluated
Mutagenicity – Genetic toxicity	None		None	Not evaluated
Toxicity to reproduction – fertility	None		None	Not evaluated
Toxicity to reproduction – development	None		None	Not evaluated
Toxicity to reproduction – breastfed babies. Effects on or via lactation	None		None	Not evaluated
Environment	N; R51-53#		N; R51-53#	

[1)] Including SCLs
[2)] Data lacking, inconclusive, or conclusive but not sufficient for classification
This dossier does not propose a change in the classification of this hazard propoerty

Labelling: Indication of danger: Xn; N

R-phrases: R10: Flammable
R20: Harmful by inhalation
R38: Irritating to skin
R51-53: Toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment

S-phrases: (2-): Keep out of the reach of children
24/25: Avoid contact with skin and eye
37: Wear suitable gloves
61: Avoid release to the environment. Refer to special instructions/safety data sheets

2 BACKGROUND TO THE CLH PROPOSAL

2.1 History of the previous classification and labelling

Chlorobenzene (Index No. 602-033-00-1) was classified as R10 (Flammable.); Xn; R20 (Harmful by inhalation); in Annex to Commission Directive 93/72/EEC of 1 September 1993 adapting to technical progress for the nineteenth time Council Directive 67/548/EEC on the approximation of the laws, regulations and administrative provisions relating to classification, packaging and labelling of dangerous substances. This classification was amended in Commission Directive 2004/73/EC of 29 April 2004 adapting to technical progress for the 29th time Council Directive 67/548/EEC on the approximation of the laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances. The Risk Phrase R51/53 (Toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment) and the indication of danger N were inserted to this entry.

2.2 Short summary of the scientific justification for the CLH proposal

One joint REACH registration dossier and two individual registration dossiers were available for chlorobenzene when these CLH proposal was prepared. The information from REACH registration dossiers (from the joint registration dossier and from the other two registration dossiers) were considered during preparation CLH proposal for chlorobenzene.

The available data on chlorobenzene indicate that the current harmonised classification for human health should also included classification for skin irritation.
Additionally based on the review of the available data for acute inhalation toxicity for chlorobenzene, the reference indicating minimum classification (*) is no longer necessary.

2.3 Current harmonised classification and labelling

2.3.1 Current classification and labelling in Annex VI, Table 3.1 in the CLP Regulation

Classification: Flam. Liq. 3; H226
Acute Tox. 4*; H332
Aquatic Chronic 2; H411

Labelling: GHS02
GHS07
GHS09
Wng
H226
H332
H411

Table 5: Notified classification and labelling according to CLP criteria

Source: http://echa.europa.eu/information-on-chemicals/cl-inventory-database

Classification		Labelling			Specific Concentration	Notes	Number of Notifiers	Joint Entries
Hazard Class and	Hazard	Hazard	Supplementary	Pictograms,				

Category Code(s)	**Statement Code(s)**	**Statement Code(s)**	**Hazard Statement Code(s)**	**Signal Word Code(s)**	**limits,** **M-Factors**			
Flam. Liq. 3	H226		-	GHS07 GHS02 GHS09 Wng	-	-	498	-
Acute Tox. 4	H332							
Aquatic Chronic 2	H411							
Flam. Liq. 3	H226	H226	-	GHS07 GHS02 GHS06 GHS09 GHS05 Dgr	-	-	305	-
Acute Tox. 4	H312	H312						
Eye Dam. 1	H318	H318						
Acute Tox.2	H330	H330						
Aquatic Chronic 2	H411	H411						
Flam. Liq. 3	H226	H226	-	GHS01 Wng	-	-	47	-
Acute Tox. 4	H332	H332						
Aquatic Chronic 2	H411	H411						
Flam. Liq. 3	H226	H226	-	GHS07 GHS02 GHS09 Wng	-	-	43	-
Skin Irrit. 2	H315	H315						
Acute Tox. 4	H332	H332						
Aquatic Chronic 2	H411	H411						
Flam. Liq. 3	H226	H226	-	GHS07 GHS02 GHS09 Wng	-	-	4	-
Acute Tox. 4	H302	H302						
Acute Tox. 4	H332	H332						
Aquatic Chronic 2	H411	H411						
Flam. Liq. 3	H226	H226	-	GHS07 GHS02 GHS09 Wng	M=1	-	2	OK
Acute Tox. 4	H332	H332						
Aquatic Chronic 2	H411	H411						
Flam. Liq. 3	H226	H226	-	GHS07 GHS02 GHS09 Wng	M=1	-	2	OK
Skin Irrit. 2	H315	H315						
Acute Tox. 4	H332	H332						
Aquatic Chronic 2	H411	H411						
Flam. Liq. 3	H226	H226	-	GHS07 GHS02 GHS09 Wng	M(Chronic)=1	-	2	-
Skin Irrit. 2	H315	H315						
Eye Irrit. 2	H319	H319						

Acute Tox. 4	H332	H332						
Aquatic Chronic 2	H411	H411						
Flam. Liq. 3	H226	H226	-	GHS07 GHS02 GHS09 Wng	M(Chronic)=1 M=1	-	2	-
Acute Tox. 4	H332	H332						
Aquatic Chronic 2	H411	H411						
Flam. Liq. 3	H226	H226	-	Wng	-	-	1	-
Acute Tox. 4	H332	H332						
Aquatic Chronic 2	H411	H411						
Not classified							1	

2.3.2 Current classification and labelling in Annex VI, Table 3.2 in the CLP Regulation

Classification: R10;
Xn; R20;
N; R51-53;
Labelling: Xn; N;
R: 10-20-51/53
S: (2)24/25-61

SCL: Xn; R20: C ≥ 5.0%

2.4 Current self-classification and labelling

2.4.1 Current self-classification and labelling based on the CLP Regulation criteria

Self-classification notifications for chlorobenzene by industry are available in the C&L Inventory (http://echa.europa.eu/information-on-chemicals/cl-inventory-database).
According to the information from the registration dossiers and information found in C&L Inventory data base a lot of entrepreneurs classified chlorobenzene as:

Classification: Flam. Liq. 3; H226
Acute Tox. 4*; H332
Skin Irrit. 2; H315
Aquatic Chronic 2; H411

Labelling: GHS02
GHS07
GHS09
Wng
H226
H315
H332
H411

2.4.2 Current self-classification and labelling based on DSD criteria

Classification:	R10; Xn; R20; Xi; R38; N; R51-53;
Labelling:	Xn; N; R: 10-20-38-51/53 S: (2)24/25-61
SCL:	Xn; R20: C ≥ 5.0%

3 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

According to article 36 (3) CLP Regulation where a substance fulfils the criteria for other hazard classes or differentiations than those of CMR, respiratory sensitisation (Cat. 1) and the substance is not an active substance under Plnat Protection Product Directive (PPPD) and Biocidal Product Directive (BPD), a harmonised classification and labelling proposal can be submitted on a case-by-case basis if the dossier submitter (DS) provides justification demonstrating the need for such action at Community level.

A review of the available toxicity data for chlorobenzene (submitted during registration) has revealed that the classification listed in Annex VI of Regulation EC No.1272/2008 is not in line with the classification provided in joint submission dossier, registration dossiers submitted individually and with the classification provided by notifiers in the C&L Inventory. The toxicological data provided in registration dossier by lead registrant (joint REACH registration dossier) indicates that chlorobenzene should be also classified as skin irritant. Modification of existing harmonized entry of chlorobenzene is based on new evaluation of existing skin corrosion/irritation data.

The current Annex VI entry for chlorobenzene includes also acute toxicity category 4 with hazard statement H332 (Harmful if inhaled) as a minimum classification as indicated by the reference * in the column “Classification” in Table 3.1. Based on the review of the available experimental data for acute inhalation toxicity for chlorobenzene, the dossier submitter come to conclusion that, the reference indicating minimum classification (*) is no longer necessary.

This proposal seeks to amend the current human health classification and labeling of chlorobenzene.

Part B.

SCIENTIFIC EVALUATION OF THE DATA

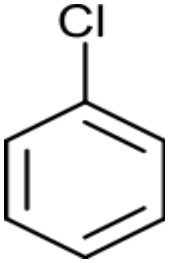
1 IDENTITY OF THE SUBSTANCE

1.1 Name and other identifiers of the substance

Table 6: Substance identity

EC number:	203-628-5
EC name:	Chlorobenzene
CAS number (EC inventory):	108-90-7
CAS number:	108-90-7
CAS name:	Benzene, chloro-
IUPAC name:	Chlorobenzene
CLP Annex VI Index number:	602-033-00-1
Molecular formula:	C_6H_5Cl
Molecular weight range:	112.56 g/mol

Structural formula:



1.2 Composition of the substance

Table 7: Constituents (non-confidential information)

Constituent	Typical concentration	Concentration range	Remarks
Chlorobenzene	99.0 % (w/w)		

Current Annex VI entry: chlorobenzene

Table 8: Impurities (non-confidential information)

Impurity	Typical concentration	Concentration range	Remarks
			No (Eco)toxicological relevant impurities are present

Current Annex VI entry: None specified

Table 9: Additives (non-confidential information)

Additive	Function	Typical concentration	Concentration range	Remarks

Current Annex VI entry: None specified

1.2.1 Composition of test material

1.3 Physico-chemical properties

Table 10: Summary of physico - chemical properties

Property	Value	Reference	Comment (e.g. measured or estimated)
State of the substance at 20°C and 101.3 kPa	colourless liquid with faint but not unpleasant odour	O'Neil MJ (ed) (2006) Test material (EC name): chlorobenzene CAS No: 108-90-7 purity unknown	-
Melting/freezing point	-45.2 °C	Lide DR (2007) Test material (EC name): chlorobenzene CAS No: 108-90-7 purity unknown	measured
Boiling point	131 – 132 °C at 1013.25 hPa	The Merck Index (2006) Test material (EC name): chlorobenzene CAS No: 108-90-7 purity unknown	measured
Relative density	1.107 g/cm³ at 20 °C	The Merck Index (2006) Test material (EC name): chlorobenzene CAS No: 108-90-7 purity unknown	measured
Vapour pressure	11.73 hPa at 20 °C (1) 15.81 hPa at 25 °C (2)	Neumüller O-A, (1979) Mackay D and Shiu WY (1981) Test material (EC name): chlorobenzene CAS No: 108-90-7 purity unknown	measured
Surface tension	33.86 mN/m at 15 °C 33.28 mN/m at 20 °C 32.11 mN/m at 30 °C	Rathjen H (1975) Test material (EC name): chlorobenzene CAS No: 108-90-7 purity unknown	measured
Water solubility	0.499 ± 0.07 g/L at 25 °C	Wasik SP et al (1983)	measured

		Test material (EC name): chlorobenzene CAS No: 108-90-7 purity unknown	

Partition coefficient n-octanol/water	2.98 ± 0.04 at 25°C	Wasik SP et al (1983) Test material (EC name): chlorobenzene CAS No: 108-90-7 purity unknown	RP-HPLC method (measured)
Flash point	28 °C	The Merck Index (2006) Test material (EC name): chlorobenzene CAS No: 108-90-7 purity unknown	measured
Flammability	not investigated		In accordance with section 1 of REACH Annex XI, the flammability study does not need to be conducted as the flammability is deduced from flash point and boiling point.
Explosive properties	non explosive		There are no chemical groups associated with explosive properties present in the molecule. The exothermic decomposition energy determined by a Differential Scanning Calorimetry is less than 500J/g.
Self-ignition temperature	590°C autoflammability	Beck U (1986) Test material (EC name): chlorobenzene CAS No: 108-90-7 purity unknown	measured
Oxidising properties	no oxidising properties		The Substance is incapable of reacting exothermically with combustible materials on the basis of the chemical structure.
Granulometry	not investigated		The study does not need to be conducted because the substance is marketed or used in a non solid granular form.
Stability in organic solvents and identity of relevant degradation products	not investigated		In accordance with Annex IX of the Regulation EC 1907/2006 testing is not necessary because the stability of the substance is considered not to be critical.
Dissociation constant	not investigated		The substance does not contain any ionic structure.
Viscosity	0.756 mPa s at 20°C	Kirk-Othmer (2001)	Dynamic viscosity (20°C)

		Test material (EC name): chlorobenzene CAS No: 108-90-7 purity unknown	
Explosion limits in air:	1.4 - 7.1 Vol.%	BASF AG (1979)	measured

2 MANUFACTURE AND USES

2.1 Manufacture

A mixture of mono-, di- and trichlorobenzenes is manufactured from benzene and chlorine in the presence of a catalyst in a reactor at 60-100°C. Incidental hydrochloride escapes as gas and is reprocessed to hydrochloric acid (30%) in another part of the plant.

The mixture is distilled, whereas the low-boiling component benzene is lead back to the manufacturing process. In the next step, chlorobenzene pure is separated as low-boiling component. A mixture of di- and trichlorobenzene as high-boiling components remains.

Out of this mixture, para-dichlorobenzene raw is separated in the next distilling step as low-boiling component. Ortho-dichlorobenzene raw together with trichlorobenzene remains as high-boiling components. Afterwards, this mixture of high-boiling components is distilled, where ortho-dichlorobenzene arises as low-boiling component. The final product is stored at ambient temperature. It is filled into tank container, rail tank car, ships or it is drummed.
The whole manufacturing step will be conducted in a closed system. In certain cases the transfer of bottled container can be located open-air. No contaminated wastewater arises within manufacturing process. Exhaust air from the reaction and from separation of low-boiling- and high-boiling components are incinerated in the in-house thermal exhaust gas treatment.

2.2 Identified uses

Following its production phase, chlorobenzene is used as an intermediate and solvent in several industrial processes as well as in analytical laboratories in non-industrial uses.

3 CLASSIFICATION FOR PHYSICO-CHEMICAL PROPERTIES

No changes in the classification for the physico-chemical endpoints are proposed in this dossier. Classification for flammability of the chlorobenzene is inserted in Annex VI of Regulation (EC) No 1272/2008.

4 HUMAN HEALTH HAZARD ASSESSMENT

4.1 Toxicokinetics (absorption, metabolism, distribution and elimination)

The results of experimental data on toxicokinetics are summarised in Table 11.

4.1.1 Non-human information

Table 11: Overview of experimental data on basic toxicokinetics

Method	Results	Remarks	Reference
Rat, Sprague-Dawley, male/female Inhalation (vapour) Doses: 469, 1871 and 3275 mg/m^3 Similar to OECD 417	Distribution: Dose-dependent increases in especially adipose tissue and some in liver and other organs. Excretion: Mainly in the urine and slightly in the faeces. Unmetabolized chlorobenzene in the exhaled air. Metabolism of chlorobenzene is saturated at repeated and high doses.	2 (reliable with restrictions) Key study Experimental result Test material (EC name): chlorobenzene CAS-No. 108-90-7 purity unknown	Sullivan, T.M. et al. (1983)
Rabbit, Dutch, female Oral (gavage) Conc.: 0.5 g/twice/day (4 days) Similar to OECD 417	Absorption: Mainly through the gastrointestinal tract. Metabolism: Metabolite by the cytochrome P-450 system. Excretion: Chlorobenzene metabolites in the urine and the faeces. Unmetabolized chlorobenzene is detected in the expired air.	2 (reliable with restrictions) Supporting study Experimental result Test material (EC name): chlorobenzene CAS-No. 108-90-7 purity unknown	Smith, J.R.L. et al. (1972)

4.1.2 Human information

Not evaluated in this dossier.

4.1.3 Summary and discussion on toxicokinetics

Chlorobenzene can be absorbed via the lung or the gastrointestinal tract. Suitable studies for evaluating the percutaneous uptake are not available.

As the compound is a lipophilic substance, its distribution in the organism is essentially dependent on the fat content of individual organs.

As a metabolite by the cytochrome P-450 system, the following metabolites of chlorobenzene were detected (% radioactivity ratio): 3,4-dihydro-3,4-dihydroxy chlorobenzenes (0.6); monophenols (2.8); diphenols (4.17); mercapturic acids (23.8); sulfoconjugates (33.9); glucuronoconjugates (33.6).

Chlorobenzene is eliminated in the form of metabolites, principally in the urine and to a smaller extent in the faeces as well. Unmetabolized chlorobenzene is mainly exhaled via the lungs.

Moreover, it could be demonstrated, that the metabolism of chlorobenzene is saturated at repeated and high doses.

4.2 Acute toxicity

4.2.1 Acute toxicity: oral.

Not evaluated in this dossier.

4.2.2 Acute toxicity: dermal.

Not evaluated in this dossier.

4.2.3 Acute toxicity: inhalation

4.2.3.1 Non-human information.

The results of relevant inhalation acute toxicity studies are summarized in Table 12.

Table 12: Overview of experimental data on acute inhalation toxicity.

Method	Results	Remarks	Reference
Test animals: rat, male/female Inhalation Hazard Test GLP: no data OECD Guideline 403 (Acute Inhalation Toxicity) Deviations: yes For each exposure time only 3 animals of each sex were used instead of 5 for each sex. Analytical purity not reported. Housing condition of the animals was not reported.	LC_{50} = 66 mg/l/ × (1.8h/4h) = 29.7 mg/L	2 (reliable with restrictions) Key study Experimental result Test material (EC name): chlorobenzene CAS-No. 108-90-7	Klimisch, H.J. (1988)
Test animals: rats Strain: Sprague-Dawley Sex: male Route of administration: inhalation: vapour Well documented study, comparable to guideline study (OECD Guideline 403 Acute Inhalation Toxicity) Non- GLP study Rats were exposed to concentrations ranging from 2000 to 3500 ppm (9.17 - 13.6 mg/l) over 6 hours. Vapour was generated at 24°C, 50 % relative humidity. Rats were observed for 14 days.	LC_{50} (male): 13.6 mg/l (2965 ppm)	2 (reliable with restrictions) Key study Experimental result Test material (EC name): chlorobenzene CAS-No. 108-90-7 purity unknown	Bonnet, P. et al. (1982)
Test animals: rats	LC_{50} (approximately): 14.1 mg/l	3 (not reliable)	De Jongh J et al.

Sex: no data Route of administration: inhalation: vapour GLP: no data Guidline: no guideline followed Exposure duration: 6 hours	(3000 ppm)	Key study Experimental result Test material (EC name): chlorobenzene CAS-No. 108-90-7 purity unknown	(1998)

4.2.3.2 Acute toxicity: Human information
No data available.

4.2.4 Acute toxicity: other routes
Not evaluated in this dossier.

4.2.5 Summary and discussion of acute toxicity

The experimental studies which was used by dossier submitter in order to evaluate acute inhalation toxicity of chlorobezene are mentioned in Table 12. Ideally, classification should be achieved using data generated from studies conducted in accordance with officially adopted OECD test guidelines. According to the Regulation (EC) No 440/2008 laying down test methods pursuant to Regulation (EC) No 1907/2006 of the European Parliament and of the Council on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), the acute inhalation toxicity should be performed according to the B.2 method. For all studies mentioned in Table 12 there are some deviations from B.2 method. The study performed by Klimisch (1988) was performed in accordance with OECD Guideline 403 but for each exposure time only 3 animals of each sex were used instead of 5 for each sex. The study performed by Bonnet (1982) is comparable to OECD Guideline study. The exposure time in each study mentioned in Table 12 was different than exposure time required in B.2 method (4 hours). The LC_{50} value mentioned in Table 12 were calculated for 1.8 hours exposure (Klimisch; 1988) and for 6 hours exposure (Bonnet; 1982 and De Jongh, 1988).

In principle, the classification criteria for acute inhalation toxicity relate to a 4-hour experimental exposure period. If data for a 4-hour period are not available then extrapolation of the results to 4 hours are often achieved using Haber's Law ($C \cdot t = k$). However, there are limits to the validity of such extrapolations, and it is recommended that the Haber's Law approach should not be applied to experimental exposure durations of less than 30 minutes or greater than 8 hours in order to determine the 4-hour LC_{50} for C&L purposes (ECHA: Guidance on information requirements and chemical safety assessment. Chapter R.7a: Endpoint specific Guidance).
Nowadays a modification of Haber's Law is used ($C^n \cdot t = k$) as for many substances it has been shown that n is not equal to 1 (Haber's Law). In case extrapolation of exposure duration is required, the *n* value should be considered. If this n value is not available from literature, a default value may be used. It is recommended to set n = 3 for extrapolation to shorter duration than the duration for which the LC_{50} or EC_{50} was observed and to set n = 1 for extrapolation to longer duration), also taking the range of approximately 30 minutes to 8 hours into account.
The LC_{50} (for a 4-hour periof of exposure) was calculated, by dossier submitter, according to the modified Haber's rule. The following value of LC_{50}, for 4 hours exposure, was obtained:
LC_{50} = 29,6 mg/l (for study performed by Klimisch),
LC_{50} = 15,5 mg/l (for study performed by Bonnet),
LC_{50} = 16,1 mg/l (for study performed by De Jongh J.).

It should be noted that two of the above mentioned values of LC_{50} are appriotiate for classification.

4.2.6 Comparison with criteria

The lowest LC_{50} values for chlorobenzene are 15,5 mg/l (Bonnet's study) and 16,1 mg/l (study performed by De Jongh J.).

According to the CLP chlorobenzene should be classified as Acute Tox Cat. 4 because the LC_{50} is within the limits, $10,0 < ATE \leq 20,0$ (vapours, mg/l). Therefore the minimum classification Acute Tox. Cat 4*, is considered no longer necessary.

The current classification according to 67/548/EEC remains unchanged. According to 67/548/EEC chlorobenze should be classified as Xn; R20 because the LC_{50} inhalation, rats, for gases, vapours, is within the limits, $2,0 < LC_{50} \leq 20,0$ mg/l/4h.

4.2.7 Conclusions on classification and labelling for acute toxicity

According to CLP regulation requirements chlorobenzene should be classified as Acute Tox. Cat. 4 with hazard statement H332 (Harmful if inhaled).

According to DSD requirements chlorobenzene should be classified as harmful with risk phrase R20 (Harmful by inhalation).

RAC evaluation of acute toxicity
Summary of the Dossier submitter's proposal The dossier submitter (DS) provided an overview of the toxicokinetic data and summarised the results from available acute inhalation studies. For acute inhalation toxicity in rats, the dossier submitter concluded that the lowest LC_{50} values for chlorobenzene are 15,5 mg/l (Bonnet *et al*, 1982) and 16,1 mg/l (De Jongh, 1998). According to the CLP Regulation, chlorobenzene should be classified as Acute Tox Cat. 4 because the LC_{50} is within the range $10,0 < ATE \leqslant 20,0$ (vapours, mg/l). Therefore the minimum classification Acute Tox. Cat. 4*, is considered no longer necessary. **Comments received during public consultation** Five member states supported the proposed classifications as specified in the dossier. One member state stated that the CLH report would had benefitted from more details on the method and observed effects and indicated that in one study the reported LC_{50} of 16,1 mg/l was based on a PB-PK model using LC_{50} values retrieved from literature (De Jongh, 1998). **Additional key elements** Additional information on the mouse was found in a hazard assessment report from the Chemicals Evaluation and Research Institute (CERI), Japan (2007). The LC_{50} value for this species was 8.8 mg/l (1889 ppm) after a 6 hour exposure time. The corresponding 4h-LC_{50} value using the Haber's Law extrapolation was 10.07 mg/l. No further information was given in this report. The same information was found in a report from the GDCh BUA (1990) with the study of Bonnet *et al*. (1982) identified as the source. **Assessment and comparison with the classification criteria**

RAC in general agrees with the dossier submitter's conclusion on the classification on acute inhalation toxicity.

The CLH report summarises results from three acute inhalation studies that were identified by the dossier submitter as key studies. Two of these studies were assessed by the DS as being compliant with OECD TG 403. In fact, none of the studies was in full agreement with the guideline test design. Information on the purity of the test substance was lacking in all studies. Exposure durations were shorter or longer than the 4 h standard exposure time and all LC_{50} values were extrapolated to a 4h LC_{50} value. The test groups in one study included 3 (instead of 5) animals/sex. In the end, the calculated LC_{50} values of all studies were in the same size range (15.5 mg/l, 16.1 mg/l, 29.7 mg/l).

The small differences in LC_{50} values between the two guideline-compliant studies provide evidence that these values may be relied on for the purpose of classification. However, the information on the LC_{50} from the Klimisch (1988) study is very scarce. The only information on observed effects that is given in this publication is that an LT_{50} value (the time of exposure after which 50% of the animals died) was 1.8 hours at a nominal concentration of 66 mg/l chlorobenzene (corresponding to an extrapolated 4h value of 29.7 mg/l). As no information is given on whether other vapour concentrations were tested and how many animals died after 1.8 h, it can not be excluded that the LC_{50} value could actually be lower.

The lowest LC_{50} value of 15.5 mg/l (from Bonnet *et al*., 1982) is used for the categorisation. This LC_{50} value is within the range of $10.0 < ATE \leq 20.0$ (vapours, mg/ml), corresponding to Acute Tox. 4.
The published LC_{50} value for mice is also consistent with the Acute Tox. 4 category criteria.

RAC agrees with the proposal to remove the reference indicating minimum classification for Acute Tox. 4 for the inhalation route. According to the CLP regulation, chlorobenzene should be classified as Acute Tox. 4, H332 (Harmful if inhaled).

4.3 Specific target organ toxicity – single exposure (STOT SE)

Not evaluated in this dossier.

4.4 Irritation

4.4.1 Skin

4.4.1.1 Non-human information

The primary irritant/corrosive effect of pure chlorobenzene, has been tested on rabbit skin according to OECD Guideline for Testing of Chemicals No. 404 referenced as Method B4 ("Acute toxicity: Dermal Irritation/Corrosion") in Commission Regulation (EC) No 440/2008 without deviations (Suberg, H. (1983a)).

Table 13: Overview of experimental data on skin irritation.

Method	Results	Remarks	Reference
Test animals: Species: Rabbits Strain: New Zeland White OECD Guideline for Testing of Chemicals No. 404" without deviations Environmental conditions Temperature: 19 – 25°C Humidity: 40 – 60% Photo period: 12 hrs dark / 12 hrs light	irritant The primary irritant/corrosive effect of pure chlorobenzene, has been tested on rabbit skin according to "OECD Guideline for Testing of Chemicals No. 404" without deviations. 3 New Zealand White rabbits have been tested with 0.5 mL of pure chlorobenzene for 4 hour-exposure followed by a post expsoure period of 14 days. The evaluation was performed according to Draize.	1 (reliable without restrictions) Key study Experimental result Test material (EC name): chlorobenzene CAS-No. 108-90-7 purity unknown	Suberg, H. (1983a)
Test animals: Species: Rabbits Strain: no data GLP – no (was not mandatory as of time when study was performed) Comparable to guideline study (OECD Guideline for Testing of Chemicals No. 404) but with acceptable restrictions (no data on purity of the substance, no GLP) Before OECD Guideline 404 was established, skin irritation was tested using an internal BASF method.	irritant (according to registrants) The BASF scoring system was converted to the scoring system by Draize. Scoring of skin changes was performed as following: day of application, then after 24h, 48h, 72h, 6d, 8d, 10d, 13d, 15d, 17d, and 20d.	2 (reliable with restrictions) Key study Experimental result Test material (EC name): chlorobenzene CAS-No. 108-90-7 purity unknown	Company data (BASF AG) (1960)
Test animals: Species: no data Strain: no data Type of method: no data Test guideline: no guideline followed	Slight reddening of the skin was observed from application of chlorobenzene either on the uncovered or covered skin. Continous contact for a week may result in moderate erythema and slight superficial necrosis.	4 (not assignable) Only secondary literature Experimental result Test material (EC name): chlorobenzene CAS-No. 108-90-7 purity unknown	Irish, D.D. (1962)

In a primary dermal irritation study, three New Zealand White rabbits have been tested with 0.5 ml of pure chlorobenzene to an area of approximately 2.5 cm x 2.5 cm for 4 hour-exposure followed by a post exposure period of 14 days (Suberg, H. (1983a)). The evaluation was performed using the scale included in B.4 Method “Grading of skin reaction” based on the scale of Draize.

All three animals showed marked erythema and oedema on the application sites. The intensity of the skin reaction pertained the margins of the application sites. Until three days after the treatment

skin desquamation was observed. No significant differences in skin reaction appeared among each animals.

The skin findings were reversible in all animals within 6 days after removal of the patches.

The results of the skin findings are summarized in Table 14.

Table 14: Skin irritation scores following 4-h dermal exposure.

Readings	Animal no	Erythema	Oedema
24 h	64	3	1
24 h	95	3	1
24 h	100	2	1
48 h	64	3	1
48 h	95	3	1
48 h	100	2	1
72 h	64	3	1
72 h	95	3	1
72h	100	2	1
Mean 24 -72h	64	3	1
Mean 24 -72h	95	3	1
Mean 24 -72h	100	2	1
Total mean		**2.7**	**1**

Mean scores over 24, 48, and 72 hours for each animal were 2.7 of max 4 for erythema and 1 of max 4 for edema.

In the dossiers submitted by individual registrants there are also information on other skin corrosion/irritation test (Company data (BASF AG); year of performence of test: 1960). The test is comparable to guideline for this kind of study (B.3 or OECD) but with acceptable restrictions (no data on purity of the substance, no GLP). Hovewer it should be underlined that GLP criteria were developed in 90s Based on the results of the test (the oryginal BASF scoring system was converted to the Draize scoring system used in the test guidance):

Irritation parameter: erythema score
Time point 24 and 48h
animal #1: Score 2
animal #2: Score 1.7
Max. score 4
Reversibility: fully reversible

Irritation parameter: edema score
Time point 24 and 48h

animal #1: Score 0
animal #2: Score 1
Max. score 4
Reversibility: fully reversible

the registrants classify chlorobenzene as skin irritant.

4.4.1.2 Human information

The skin irritation properties of chlororbenzene were tested in 1 h dermal exposure experiment on volunteers (Oettel, H. (1936)). Dermal exposure of 5 volunteers to chlorobenzene for 1 h resulted in burning pain, hyperemia, whealing, and erythema formation at the application site. 12 hours postexposure a minimal local vesiculation was seen. After a 5 hours exposure this effect was slightly increased.

4.4.1.3 Summary and discussion of skin irritation

According to the results of the rabbit skin irritation study (Suberg, H. (1983a), chlorobenzene is irritant to the intact shaved rabbit skin.
The study presented by individual dossier submitter (Company data (BASF AG); 1960) - there is no enough information to conclude that based on that study chlorobenzene should be classified as skin irritant.

4.4.1.4 Comparison with criteria

According to DSD requirements the substance is classified as skin irritant if:

- in the case where the B.4 test has been completed using three animals, either erythema and eschar formation or oedema formation equivalent to a mean value of 2 or more calculated for each animal separately has been observed in two or more animals.

According to CLP requirements the substance is classified as skin irritation category 2 if:
- mean value of ≥ 2.3 - ≤ 4.0 for erythema/ eschar or for oedema in at least 2 of 3 tested animals from gradings at 24, 48 and 72 hours after patch removal or, if reactions are delayed, from grades on 3 consecutive days after the onset of skin reactions.

4.4.1.5 Conclusions on classification and labelling

The decision on classification of chlorobenzene as skin irritant was based on test performed by Suberg, H. (1983a). The test was performed according to OECD Guideline for Testing of Chemicals No. 404. Mean scores over 24, 48, and 72 hours for each animal, obtained in above mentioned test, were 2.7 of max 4 for erythema and 1 of max 4 for edema and the results meets the criteria of classification of substances as skin irritant found in DSD and CLP.

According to DSD requirements chlorobenzene should be classified as skin irritant with risk phrase R38 (Irritating to skin).

According to CLP regulation requirements chlorobenzene should be classified as skin irritation Cat. 2 with hazard statement H315 (Causes skin irritation).

RAC evaluation of skin corrosion/irritation

Summary of the Dossier submitter's proposal

The dossier submitter gave an overview on the experimental studies on skin irritation. Two studies were identified as key studies (Suberg, 1983a; BASF AG, 1960), but only the Suberg study was compliant with OECD TG 404. Limitations were also reported for the BASF study (no GLP, use of internal scoring system, only two animals). A third study (Irish, 1962) was identified as not suitable for assessment (Klimish score of 4).

The dossier submitter concluded that the decision on classification of chlorobenzene as skin irritant was based on the test performed by Suberg (1983a). The test was performed according to OECD TG 404. The shaved skin of three rabbits were tested with 0.5 ml of pure chlorobenzene for 4 h-exposure followed by a post-exposure period of 14 days. Mean scores over 24, 48, and 72 hours for each animal, obtained in the above mentioned test, were 2.7 of max 4 for erythema and 1 of max 4 for oedema and the results meets the criteria for classification of the substance as skin irritant in the CLP Regulation.

The CLH report also documented skin irritation properties of chlororbenzene in 5 volunteers (Oettel, 1936). Dermal exposure for 1 h resulted in burning pain, hyperaemia, whealing, and erythema formation at the application site. At 12 hours post-exposure, minimal local vesiculation was seen. After 5 hours exposure this vesiculation was slightly increased.

Comments received during public consultation

Four member states supported the proposed classifications as specified in the dossier. One member state did not comment on skin irritation.

Assessment and comparison with the classification criteria

Based on the results from the study of Suberg (1983a), mean scores over 24, 48, and 72 hours from all 3 animals were 2.7 for erythema, and 2 out of 3 animals had erythema scores of 3 at 24, 48, and 72 hours. All skin findings were reversible within 6 days after the end of treatment. According to CLP classification criteria, a substance fulfills the criteria for classification for skin irritation in category 2 (H315, Causes skin irritation) if mean values of ≥2.3 - ≤4 for erythema/eschar or for oedema are observed in at least 2 of 3 tested animals from gradings at 24, 48 and 72 h after patch removal.

RAC agrees with the dossier submitter's assessment that classification of chlorobenzene as Skin Irrit. 2 according to the CLP Regulation is warranted.

4.4.1 Eye

Not evaluated in this dossier

4.5 Corrosivity

See section 4.4.

4.6 Sensitisation

Not evaluated in this dossier.

4.7 Repeated dose toxicity

Not evaluated in this dossier.

4.8 Specific target organ toxicity (CLP Regulation) – repeated exposure (STOT RE)

Not evaluated in this dossier.

4.9 Germ cell mutagenicity (Mutagenicity)

Not evaluated in this dossier.

4.10 Carcinogenicity

Not evaluated in this dossier.

4.11 Toxicity for reproduction

Not evaluated in this dossier.

4.12 Other effects

Not evaluated in this dossier.

5 ENVIRONMENTAL HAZARD ASSESSMENT

Not evaluated in this dossier.

6 OTHER INFORMATION

One joint REACH registration dossier and two individual registration dossiers were available for chlorobenzene when these CLH proposal was prepared. The information from REACH registration dossiers were considered during preparation CLH proposal for chlorobenzene.

7 REFERENCES

BASF AG (1979). Raport no SIK-Nr. 78/1100 BASF, Department of Safty Engineering. BASF SE, D-67056 Ludwigshafen.

BASF AG (1960). Abt. Toxikologie, Unveroeffentlichte Untersuchung, (X/44).

Beck U (1986). Chlorinated Hydrocarbons. In: Ullmann´s Encyclopedia of industrial chemistry, fifth, completely revised edition, Band A6, VHC Verlagsgesellschaft mbH Weinheim, 328-340. Cited in: www.apps.echa.europa.eu.

Bonnet, P., Morele, Y., Raoult, G., Zissu, D. and Gradiski, D. (1982). Determination of the median lethal concentration of the main aromatic hydrocarbons in rats. Arch. Mal. Prof. Trav. Secur. Soc. 43, 261-265.
Irish, D.D. (1962). Halogenated hydrocarbons: II. Cyclic In: Patty, F.A. (ed.): Industrial Hygiene and Toxicology, Vol. II, John Wiley & Sons, New York, 1333 – 1335.

De Jongh J et al., (1998). Role of kinetics in acute lethality of nonreactive volatile organic compounds (VOCs). Toxicological sciences, 45, 26-32.

ECHA: Guidance on information requirements and chemical safety assessment. Chapter R.7a: Endpoint specific Guidance, Version 2.0, November 2012.
(http://echa.europa.eu/documents/10162/13632/information_requirements_r7a_en.pdf)

Kirk-Othmer (2001). Encyclopedia of chemical technology. Chlorobenzenes. John Wiley & Sons Vol 6, p 214. Cited in: www.apps.echa.europa.eu.

Klimisch, H.J. (1988). The inhalation hazard test; principle and method. Arch. Toxicol. 61, 411-416

Lide DR (2007). CRC Handbook of Chemistry and Physics 88TH Edition 2007-2008. CRC Press, Taylor & Francis, Boca Raton, FL, p. 3-92. Cited in: Hazardous Substances Data Bank (HSDB), a database of the National Library of Medicine's TOXNET system (http://toxnet.nlm.nih.gov).

Mackay D and Shiu WY (1981). A critical review of Henry´law constants for chemicals of environmental interest. J. Phys. Chem Ref. Data 10, 1175-1193. Cited in: www.apps.echa.europa.eu.

Neumüller O-A (1979). Römpps Chemie-Lexicon. 8. Aufl., Bd 1, Frank´sche Verlagsbuchhandlung, Stuttgart, p 715.

Oettel, H. (1936): Naunyn-Schmiedebergs Arch. Exp. Pathol. Pharmakol. 183, 641 – 662.

O'Neil MJ (ed) (2006). The Merck Index - An Encyclopedia of Chemicals, Drugs and Biologicals, Whitehouse Station, New Jersey: Merck and Co., Inc., p. 351. Cited in: Hazardous Substances Data Bank (HSDB), a database of the National Library of Medicine's TOXNET system (http://toxnet.nlm.nih.gov).

Rathjen H (1975). Chlorkohlenwasserstoffe, aromatische, kernchlorierte. Ullmans Encyklopädie der technichen Chemie, 4. Auflage, Band), Verlag Chemie Weinheim/Bergstr., 499 -509. Cited in: www.apps.echa.europa.eu.

Smith, J.R.L. et al. (1972). Mechanisms of mammalian hydroxylation: Some novel metabolites of chlorobenzene. Xenobiotica 2 (3), 215-226.

Suberg, H. (1983a). Chlorbenzol rein - Prüfung auf primär reizende/ätzende Wirkung an der Kaninchenhaut. Lanxess Company Study No. T2015574, 1983-05-10.

Sullivan, T.M. et al. (1983). The pharmacokinetics of inhaled chlorobenzene in the rat. Toxicol. Appl. Pharmacol. 71, 194-203.

The Merck Index (2006). Merck & Co., Inc., Whitehouse Station, New Jersey, USA. Cited in: www.apps.echa.europa.eu.

Wasik SP et al (1983). Determination of the vapor pressure, aqueous solubility, and octanol/water partition coefficient of hydrophobic substances by coupled geneator column/liquid chromatographic methods. Residue Reviews 85:29-42. Cited in: www.apps.echa.europa.eu.