European Chemicals Bureau

Institute for Health and Consumer Protection

European Chemicals Bureau

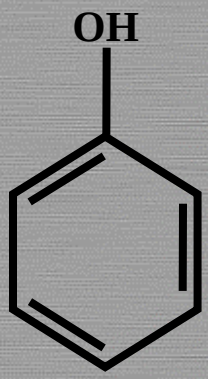
Existing Substances

European Union Risk Assessment Report

CAS: 108-95-2

EINECS: 203-632-7

phenol



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The mission of the IHCP is to provide scientific support to the development and implementation of EU polices related to health and consumer protection. The IHCP carries out research to improve the understanding of potential health risks posed by chemical, physical and biological agents from various sources to which consumers are exposed.

The Toxicology and Chemical Substances Unit (TCS), commonly known as the European Chemicals Bureau (ECB), provides scientific and technical input and know-how to the conception, development, implementation and monitoring of EU policies on dangerous chemicals including the co-ordination of EU Risk Assessments. The aim of the legislative activity of the ECB is to ensure a high level of protection for workers, consumers and the environment against dangerous chemicals and to ensure the efficient functioning of the internal market on chemicals under the current Community legislation. It plays a major role in the implementation of REACH through development of technical guidance for industry and new chemicals agency and tools for chemical dossier registration (IUCLID5). The TCS Unit ensures the development of methodologies and software tools to support a systematic and harmonised assessment of chemicals addressed in a number of European directives and regulation on chemicals. The research and support activities of the TCS are executed in close co-operation with the relevant authorities of the EU MS, Commission services (such as DG Environment and DG Enterprise), the chemical industry, the OECD and other international organisations.

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European Union Risk Assessment Report

PHENOL

Revised Edition

CAS No: 108-95-2

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RISK ASSESSMENT

EXPLANATORY NOTE

This report is the revised edition of the European Risk Assessment Report (RAR) on phenol that has been prepared by Germany in the context of Council Regulation (EEC) No. 793/93 on the evaluation and control of existing substances and published in 2006 on the European Chemicals Bureau website (European Risk Assessment Report Vol. 64, EUR 22229 EN)[1].

Afterwards, the Rapporteur has brought up some changes, mainly on the consumer aspects of the Human health part of the Risk assessment.

The present version incorporates those changes in a consolidated text.

With respect to the previous version of the RAR the changes are the following:

- The wording of the **conclusion (iii)** for dermally exposed consumers was extended (under Section 0 and 5).
- Section 4.1.1.3 has been modified taking into account the more precise wording for the disinfectant scenario. For example, the term “cleaner” was replaced by “disinfectant”.
- The same has been done for Section 4.1.3.3 introductory §.
- Section 4.1.3.3.3 - Irritation/Corrosivity and Section 4.1.3.3.5 - Repeated dose toxicity are now focusing on the dermal route,
- A reference to the Cosmetics Directive Amendment of November 2005 regarding phenol has been included.
- For Section 4.1.3.5 - Combined exposure, a typing error has been removed, conclusion ii has been corrected into **conclusion (iii)**
- Editorial change: the date of the 29th ATP has been amended (April instead of August)

[1] European Chemicals Bureau – Existing Chemicals – http://ecb.jrc.it

PHENOL

Revised Edition

CAS No: 108-95-2

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RISK ASSESSMENT

Final Report, November 2006

Germany

The risk assessment of phenol has been prepared by Germany on behalf of the European Union.

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Date of Last Literature Search:	**1997 (Environment)** **2003 (Human Health)**
Review of report by MS Technical Experts finalised:	**2005**
Final report:	**November, 2006**

Foreword

We are pleased to present this Risk Assessment Report which is the result of in-depth work carried out by experts in one Member State, working in co-operation with their counterparts in the other Member States, the Commission Services, Industry and public interest groups.
The Risk Assessment was carried out in accordance with Council Regulation (EEC) 793/93[1] on the evaluation and control of the risks of "existing" substances. "Existing" substances are chemical substances in use within the European Community before September 1981 and listed in the European Inventory of Existing Commercial Chemical Substances. Regulation 793/93 provides a systematic framework for the evaluation of the risks to human health and the environment of these substances if they are produced or imported into the Community in volumes above 10 tonnes per year.
There are four overall stages in the Regulation for reducing the risks: data collection, priority setting, risk assessment and risk reduction. Data provided by Industry are used by Member States and the Commission services to determine the priority of the substances which need to be assessed. For each substance on a priority list, a Member State volunteers to act as "Rapporteur", undertaking the in-depth Risk Assessment and recommending a strategy to limit the risks of exposure to the substance, if necessary.
The methods for carrying out an in-depth Risk Assessment at Community level are laid down in Commission Regulation (EC) 1488/94[2], which is supported by a technical guidance document[3]. Normally, the "Rapporteur" and individual companies producing, importing and/or using the chemicals work closely together to develop a draft Risk Assessment Report, which is then presented at a meeting of Member State technical experts for endorsement. The Risk Assessment Report is then peer-reviewed by the Scientific Committee on Health and Environmental Risks (SCHER) which gives its opinion to the European Commission on the quality of the risk assessment.
If a Risk Assessment Report concludes that measures to reduce the risks of exposure to the substances are needed, beyond any measures which may already be in place, the next step in the process is for the "Rapporteur" to develop a proposal for a strategy to limit those risks.
The Risk Assessment Report is also presented to the Organisation for Economic Co-operation and Development as a contribution to the Chapter 19, Agenda 21 goals for evaluating chemicals, agreed at the United Nations Conference on Environment and Development, held in Rio de Janeiro in 1992 and confirmed in the Johannesburg Declaration on Sustainable Development at the World Summit on Sustainable Development, held in Johannesburg, South Africa in 2002.
This Risk Assessment improves our knowledge about the risks to human health and the environment from exposure to chemicals. We hope you will agree that the results of this in-depth study and intensive co-operation will make a worthwhile contribution to the Community objective of reducing the overall risks from exposure to chemicals.

Roland Schenkel
Director General
DG Joint Research Centre

Mogens Peter Carl
Director General
DG Environment

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[1] O.J. No L 084, 05/04/199 p.0001 – 0075

[2] O.J. No L 161, 29/06/1994 p. 0003 – 0011

[3] Technical Guidance Document, Part I – V, ISBN 92-827-801 [1234]

0 OVERALL RESULTS OF THE RISK ASSESSMENT

CAS No:	108-95-2
EINECS No:	203-632-7
IUPAC Name:	Phenol
Synonyms:	Carbolic acid, Monohydroxybenzene, Phenylalcohol

Environment

Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

This conclusion applies to the industrial WWTPs at 8 out of 32 sites. For all these sites the $Clocal_{eff}$ is based on default values and could possibly be lowerd by site-specific and traceable exposure data. However, it is not expected to obtain exposure data for all these sites with reasonlable efforts and time expenditure. In additon, the concern cannot be removed by testing due to the result from an available respiration inhibition test with industrial activated sludge.

Conclusion (i) There is need for further information and/or testing.

This conclusion applies to unintentional releases of phenol to:

- the aquatic compartment as a product of human metabolism. Water concentrations of 22.57 µg/l result for direct discharges of municipal waste water into a receiving stream. With regars to Europe it is assumed that approximately 30% of the population release their waste water direct into a receiving stream.Taking into consideration a PNECaqua of 7.7 µg/l, a PEC/PEC ratio > 1 results for the direct discharges of phenol as a product of human metabolism without purification of the municipal waste water in a biological treatment plant. This emission pathway is not the subject of this risk assessment, but further investigations, i.e. measurement of the phenol content in the influent of municipal WWTPs or in untreated municipal waste water and/or monitoring of the phenol content in streams of direct discharges should be considered by the responsible authorities.
- to the aquatic environment from cooking, gasification and liquefaction of coal, refineries and pulp manufacture, as it was not possible to estimate the exposure from these areas (see Section 3.1.3.4).
- to the terrestrial compartment as a result of the spreading of liquid manure from livestock farming. For the spread of liquid manure derived from livestock farming over agricultural areas it is not possible to estimate a total release to soil (see Section 3.1.4.2).
- to the aquatic and terrestrial compartment from landfills without landfill leachate collecting system. It is not possible to estimate the exposure from this area (see Section 3.1.3.4).

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

This conclusion applies to the production and industrial use of phenol and all environmental compartments i.e.

Aquatic compartment
Atmosphere

Terrestrial compartment
Secondary poisoning

Human Health

Human health (toxicity)

Workers

Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

For phenol risk assessment, three occupational exposure scenarios are defined: production and further processing (Scenario 1), formulation of phenolic resins (Scenario 2) and use of phenolic resins, the latter being divided in a subscenario without (Scenario 3a) and with spraying techniques (Scenario 3b).

For all dermal exposure scenarios corrosivity following skin contact and contact to the eyes gives reason for concern. It is known, that sensation of pain due to local exposure to phenol may be diminished possibly leading to less awareness and thus higher degrees of local damage. Special emphasis should be given by risk managers to all dermal exposure scenarios (Scenario 1, 2 and 3) when deciding on the possible need for further risk reduction measures.

For all scenarios concern is expressed with respect to systemic toxicity following repeated inhalation. No concern is reached for respiratory tract irritation. In addition, for Scenarios 2 and 3b, concern is expressed for systemic toxicity following repeated dermal exposure. With respect to acute toxicity, concern is indicated for Scenario 2 (only for inhalation) and for Scenario 3b (only for dermal contact).

Consumers

Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

Dermal exposure of consumers via disinfectants leads to **Conclusion (iii)** because of systemic repeated dose toxicity and possible skin irritation.

In addition application of floor waxes leads to concern with respect to systemic repeated dose toxicity by inhalation.

Humans exposed via the environment

Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

There is concern for local indirect exposure via plant shoot.

Human health (risk from physico-chemical properties)

There are no significant risks from physico-chemical properties

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

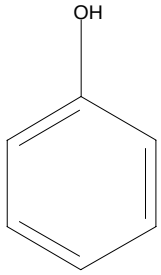
CONTENTS

TABLES

1 GENERAL SUBSTANCE INFORMATION

1.1 IDENTIFICATION OF THE SUBSTANCE

CAS No: 108-95-2
EINECS No: 203-632-7
IUPAC Name: Phenol
Synonyms Carbolic acid, Monohydroxybenzene, Phenylalcohol
Molecular weight: 94.11 g/mol
Empirical formula: C_6H_6O
Structural formula:



1.2 PURITY/IMPURITIES, ADDITIVES

Commercial phenol obtained using the cumene method has a purity of > 99.8% and a water content of maximum 0.05% (Phenolchemie GmbH, 1991). Phenol resulting from the cumene method may typically contain the following impurities in the ppm range: mesityloxide, 2-methylbenzofuran, cumene, acetophenone, dimethylphenylcarbinol, acetone, alpha-methylstyrene, cyclohexanol, hydroxyacetone, sec-butanol, isopropanol, 2-phenylbutene(2) (IARC, 1989).

1.3 PHYSICO-CHEMICAL PROPERTIES

Table 1.1 Physico-chemical properties

Parameter	Value	Reference
Physical state	Phenol is a weak acid. Pure phenol is colourless to light pink crystalline solid. Pure phenol absorbs easily water from air and liquefies.	
Melting point	40.9°C	CRC (1991/92) Ullmann (1991) Kirk-Othmer (1982)
Boiling point	181.8°C at 1,013 hPa	Kirk-Othmer (1982) CRC (1991/92)
Relative density	1.132 g/cm^3 at 25°C 1.05 g/cm^3 at 50°C	Kirk-Othmer (1982) Ullmann (1991)
Vapour pressure	0.2 hPa at 20°C	Ullmann (1991)
Surface tension	71.3 mN/m at 20°C (0.118% solution in water)	CRC (1991/92)

Table 1.1 continued overleaf

Table 1.1 continued Physico-chemical properties

Parameter	Value	Reference
Water solubility	84 g/l at 20°C (above 68.4°C completely miscible with water)	Ullmann (1991) Sörensen and Arlt (1979)
Partition coefficient	logPow 1.47 HPLC method	Butte et al.(1981)
Flash point	82°C	CHEMSAFE
Auto flammability	595°C	CHEMSAFE
Flammability	Not highly flammable	Test A.10 not conducted [1)] Test A.12 not conducted because of structural reasons
Explosive properties	Not explosive	No test because of structural reasons
Oxidising properties	No oxidising properties	No test because of structural reasons
Dissociation constant	pKa = 9.89 at 20°C	Lide (1994)

1) It is possible to predict the probable behaviour of phenol in such a test on the basis of knowledge of the melting point and the low flash point. Phenol will melt and only be ignitable as a result of a prolonged effect of the flame. After the ignition source has been removed, the flame will go out after a short time. Therefore phenol should be excluded from the possibility of being "highly flammable".

Odour and taste threshold in water

Phenol and especially most of its reaction products with chlorine (2- and 4-chlorophenol, 2,4- and 2,6-dichlorophenol, 2,4,6-trichlorophenol) have an unpleasant taste and odour. The occurrence of phenol in drinking water is unacceptable, if the substance or one of the reaction products after drinking water chlorination can be detected by taste and odour.

For phenol a threshold for odour perception in air of 184 µg/m^3 and a threshold for taste and odour in water of 150 µg/l has been reported (Verschueren 1996).

Chlorophenols generally have very low organoleptic thresholds. The taste threshold in water for 2-chlorophenol, 2,4-dochlorophenol and 2,4,6,-trichlorophenol are 0.1, 0.3 and 2 µg/l (WHO, 1996).

From these values it can be concluded that phenol in drinking water will normally not give rise to taste and odour problems. However, drinking water containing only a few µg/l of phenol may be unacceptable after chlorination due to the low threshold values for chlorophenols. Therefore, the Federal Environmental Agency of Germany recommends an aesthetic guide value (*ästhetischer Leitwert*) of 1 µg phenol per litre of drinking water in order to guarantee the option to chlorinate water if necessary without deteriorating its aesthetic quality with respect to taste and odour.

1.4 CLASSIFICATION

In Germany Phenol is classified as belonging to water-hazard class 2 (water-polluting). In the general administrative provisions to the Federal Immission Control Act - Technical Instructions on Air Quality Control (TA-Luft of 27.06.1986) - phenol is listed in Annex E and classified according to class I.

Classification according to Annex I:

Classification and labelling according to the 29th ATP of Directive 67/548/EEC[5]:

R 23/24/25	Toxic by inhalation, in contact with skin and if swallowed
R 34	Corrosive: Causes burns
R 48/20/21/22	Harmful: danger of serious damage to health by prolonged exposure through inhalation, in contact with skin and if swallowed
Muta. Cat. 3, R 68	Possible risks of irreversible effects

Specific concentration limits:

$c \geq 10\%$	T	R23/24/25-48/20/21/22-34-68
$3 \leq c < 10\%$	C; Xn	R20/21/22-34-68
$1 \leq c < 3\%$	Xn	R36/38-68

Annex I of Directive 67/548/EEC does not currently contain any environmentally relevant classifications for phenol.

[5] The classification of the substance is established by 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 (OJ L 152, 30.04.2004, p.1).

2 GENERAL INFORMATION ON EXPOSURE

2.1 PRODUCTION

According to available data there are 32 production and/or processing sites of phenol within the EU. The sources of the data are essentially the IUCLID data sets provided by the individual companies and further announcements.

Taking into account the quantities provided in the IUCLID data sets and actual statements of some companies, the resultant quantity of phenol produced in the EU amounts to 1,819,100 tonnes/annum (12 companies). Most of the companies, where phenol is only processed on site, bought phenol from production companies in the EU. In addition, a quantity of 113,400 tonnes/annum is annually imported. 290,000 tonnes/annum phenol are exported to non-EU member states. The quantity used in the EU therefore amounts to approximately 1,642,500 tonnes/annum.

Phenol is mainly produced synthetically, the most important method being the Hock method on the basis of cumene. The method for the production of phenol, which takes toluene as the starting point, is also of industrial significance. In 1989 the cumene method accounted for about 93% of the production capacity for phenol in Western Europe and the toluene method for about 7%. Phenol can also be obtained by processing coal-tar fractions (Jordan et al., 1991). Within the EU approximately 15,000 tonnes/annum of phenol are obtained by processing coal-tar fractions (Wiessermel, Arpe 1994).

2.2 USES

Phenol is mainly used as an intermediate in organic synthesis. In this, phenol essentially serves as a raw material for the production of bisphenol A, phenol resins, alkylphenols, caprolactam, salicylic acid, nitrophenols, diphenyl ethers, halogen phenols and other chemicals.

A small non-quantifiable part serves as a component in cosmetics and medical preparations. In Germany, phenol is no longer used as a disinfection component in laundry, cleaning, scouring and care agents (Industrieverband, 1996).

In the Danish product register 2002 the quantity of used phenol is given as 1,378 tonnes/annum. The following product types are described: intermediate, adhesive, binder, impregnating agent, paints, lacquers and varnishes and solvents.

Phenol is also listed in the Swedish product register. In 1993, approximately 15,500 tonnes of the substance were registered as intermediates, binders, in paints and lacquers, flooring, hardeners, insulating materials, adhesives and other products. The Swedish product register 2000 gives the information that there are 5 consumer products that contain phenol. Three products have a phenol content of maximum 0.1%, 2 products (hardeners for adhesives) have a phenol content of 1-5%.

The Norwegian product register for 1994 cites the use of 3,785 tonnes of phenol in approximately 100 products. The substance is essentially used as a raw material and additive, binder and adsorbing agent in the manufacture of chemical products and woodworking. More recent data from the Norwegian product register (2002) give the information that phenol is contained in 208 products, containing a total quantity of 2,272 tonnes/annum.

It is not clear from the product registers which quantity of the substance is used as an intermediate in the manufacture of products such as phenol resins and binders and how much remain unchanged in the final product.

The product data base of BgVV is listing some phenol-containing products used by consumers: primers (content < 1.0%) and two-component adhesives (content < 2.5%). The exact number of paints/primers being on the market and containing phenol is not known (see Section 4.1.1.3).

The following table shows the main, industrial and use categories and the mass balance of phenol for the European market.

Table 2.1 Use categories of phenol according to the Technical Guidance Document

Main category (MC)	Industrial category (IC)	Use category (UC)	Mass balance [in %]
Non-dispersive use (1 b and 3)	Chemical industry (3)	Intermediate (33)	About 100
Wide dispersive use (4)	Personal/domestic (5)	Cosmetics (15) Pharmaceuticals (41) Biocides, non-agricultural (39) Adhesives (2) Impregnation agents (31)	Small Non-quantifiable part

2.3 LEGISLATION CONCERNING PHENOL

In Germany phenol is classified into the emissions class I according to the Technical Guideline for Clean Air (TA-Luft from 27.02.1986). At a mass steam of ≥ 0.1 kg/hour, its emission must be limited at 20 mg phenol/m^3.

According to the "German Framework Administrative Guideline for Minimum Requirements on the Discharge of Waste Water into Water Bodies" (Rahmen-AbwasserVwV of 1.6.2000) a phenol index value of ≤ 0.15 mg/l is set for waste water before mixture with other waste water for the production of hydrocarbons (Appendix 36) and oil processing (Appendix 45). The emission of phenol to surface water is limited for the production of fibre boards (Appendix 13), iron and steel foundry (Appendix 24) and hard coal coking (Appendix 46) as follows:

Table 2.2 Limitation of the phenol index in waste water according to Rahmen-AbwasserVwV

Industrial source	Appendix	Limit of phenol index based on the product
Production of fibre boards	13	0.3 g/t
Iron and steel foundry	24	2.5 g/t
Hard coal coking	46	0.15 g/t

In the UK there is a non-statutory environmental quality standard for surface water of 30 µg/l annual average concentrations and 300 µg/l maximum allowable concentrations.

In Denmark release of phenol to ambient air from industrial plants is regulated with an emission value of 0.02 mg/m^3, an emission limit value of 5 mg/m^3 and a mass-flow limit of 100 g/hour (Danish EPA 2002 a,b).

In Denmark a health based limit value for phenol, cresols and xylenols in soil has been set at 70 mg phenols/kg soil (Danish EPA 1995).

In Denmark a limit value for drinking water of 0,5 µg/l of phenol and other phenols has been set. The value has set to protect against taste from chlorinated phenols generated by chlorination of the water (Danish EPA 2001).

3 ENVIRONMENT

3.1 ENVIRONMENTAL EXPOSURE

3.1.1 General discussion

Phenol is released from a number of human-made sources. The primary sources of environmental phenol are automobile exhaust (direct emission and photochemical degradation of benzene), human and animal metabolism and different combustion processes. From industrial sources, it enters the environment from production and processing operations. Releases also occur due to the waste water from cooking plants and low-temperature carbonisation plants using hard coal and brown coal, from refineries, from pulp manufacture and landfill leachate.

The purpose of this report is to describe quantitatively the exposure situation in the EU that results from industrial sources of phenol production and processing. The diffuse emissions by automobile exhaust, human and animal metabolism and different combustion processes are higher than the industrial emissions (see Section 3.1.6). An attempt was made to quantify these sources as best as possible, in order to provide an overall picture of all possible phenol emissions in the EU.

3.1.2 Environmental releases

Site specific information from phenol production and/or processing sites was gathered. For environmental exposure assessment site specific data are preferred. TGD default values were used where such data were unavailable. In the following table these values are summarised.

Table 3.1 Default emission factors

	Waste water		Air	
	Production	**Processing**	**Production**	**Processing**
Emission factors [t/t]	0.003	0.007	0.00001/0.0001	0.0/0.001
Main category	---	---	1b/1c	1b/3
Source in TGD	ESD IC - 3	ESD IC - 3	A-table 1.2	A-table 3.3
Vapour pressure [Pa]	---	---	10-100	10-100

The following exposure calculation is based on the assumption that every company involved in the production and/or processing of phenol discharges its wastewater to a WWTP.

3.1.2.1.1 Degradation

Biodegradation

The biodegradability of phenol in water has been shown in a number of investigations under the most varied conditions. Only two standardised tests for ready biodegradability are available. In these MITI-I-tests, levels of degradation amounting to between 60 and 70% (after 4 days) and to 85% (after 14 days) were determined (Urano and Kato 1986, MITI 1992). With these results

phenol can be classified as readily biodegradable. The results from the other available tests also points toward ready biodegradability. However, on account of the ubiquitous occurrence of phenol, adaptation is to be assumed in the case of all of the inocula. Since this also applies to WWTPs, a degradation rate constant of $k = 1\ h^{-1}$ can be used for them.

Several investigations exist for the estimation of the biodegradability of phenol in surface waters. The most relevant studies are described below.

Hwang et al. (1986) determined the rates of microbial degradation of ^{14}C-labelled phenol in estuarine water samples using phenol concentrations of 25 µg/l. Investigations were conducted in summer (24°C) and in winter (10°C). Half-lives for the mineralisation of phenol were 7 days ($k = 0.095\ d^{-1}$) in summer and 73 days ($k = 0.01\ d^{-1}$) in winter. As the experiments were conducted in sun light the rate constants are both due to biodegradation and photolysis. The authors could show however, that biodegradation was the primary removal process for phenol in both winter and summer.

Calculating the arithmetic mean of the rate constants of $0.095\ d^{-1}$ and $0.01\ d^{-1}$ result in an average rate constant of $0.05\ d^{-1}$.

Rheinheimer et al. (1992) examined the mineralisation of phenol in freshwater, estuarine water and seawater using phenol concentrations of 1 µg/l. Mineralisation was determined by measuring the formation of $^{14}CO_2$ from the ^{14}C-labelled test substance. The samples were incubated in the dark at 10°C and 20°C. In the freshwater sample the mineralisation after 24 hours was 31.4%. After 200 hours mineralisation was about 50% and remained constant until the end of the experiment (50 days). In the estuarine water sample mineralisation after 40 hours was only 2%, but reached about 80% after 200 hours. In different seawater samples mineralisation between 60% after 21 days and 93.5% after 50 days was found.

The biodegradability of phenol in ground water, river water and harbour water was examined by Vaishnav and Babeu (1987). Phenol concentrations of 0.8, 1.6 and 3.2 mg/l were employed. Biodegradation was measured as BOD related to TOD. Biodegradation of about 60% (river water) and 45% (ground water) after 20 days and 88% (harbour water) after 15 days related to BOD was found. For ground water, river water and harbour water rate constants of $0.035\ d^{-1}$, $0.065\ d^{-1}$ and $0.247\ d^{-1}$ respectively were found and half-lives of 20, 11 and 3 days could be calculated.

The above cited test results show that phenol can be mineralised in both freshwater and seawater. A rate constant of $k_{\mathbf{surface\ water}} = 0.05\ d^{-1}$ can be determined from the paper of Hwang et al. (1986). This value is in good agreement with the rate constant of $0.047\ d^{-1}$ proposed in the TGD for readily biodegradable substances.

Haider et al. (1981) examined the biodegradation of ^{14}C-labelled phenol in soil. 2 mg of the labelled substance were mixed with 100 g of a parabrownish soil and the formation of $^{14}CO_2$ was measured for up to 10 weeks. After 3 days, 1, 2, 5 and 10 weeks mineralisation of 45.5%, 48%, 52%, 60% and 65% respectively was measured.

Incomplete mineralisation in soils was found in other experiments. Scow et al. (1986) measured less than 50% mineralisation of phenol ($^{14}CO_2$ formation) in soil. The authors concluded that this may be a result of adsorption of the test substance. Thornton-Manning et al. (1987) found 20-43% mineralisation (measured as $^{14}CO_2$) of phenol under optimal nutrient and temperature conditions in slurries of different soils and attributed this fact to the incorporation of phenol or its metabolites into polysaccharides, polypeptides or humic acid polymers. This theory is supported

by the fact that the most extensive mineralisation was observed in the soil with the lowest content of organic matter.

A rate constant for biodegradation of phenol in soils of k_{soil} = 0.1 d^{-1}can be derived from the available investigation of Haider et al. (1981).

Biodegradation of phenol under anaerobic conditions was shown by several authors (e.g. ECETOC 1988, Horowitz et al., 1982, Shelton/Tiedje 1984). However, a longer adaptation phase than under aerobic conditions and therefore a slower degradation of phenol was found.

Biodegradation rate constant for phenol are summarised in the **Table 3.2**.

Table 3.2 Biodegradation rat constants for phenol

Compartment	Rate constant
WWTP	k bio_{WWTP} = 1h^{-1}
Aquatic environments, Determined experimentally	k bio_{water} = 0.05 d^{-1}
Sediment, (for the calculation see Appendix A)	k bio_{sed} = 0.01 d^{-1}
Soil, determined experimentally	k bio_{soil} = 0.1 d^{-1}

Photodegradation

In the atmosphere phenol reacts with photochemicaly formed hydroxyl radicals. A value of $k_{OH} = 28.3 \cdot 10^{-12}$ $cm^3 \cdot molecule^{-1} \cdot s^{-1}$ was determined for the rate constant of the reaction of phenol with OH radicals at room temperature (Atkinson, 1987). A half-life of 14 hours ($kdeg_{OH} = 0.051$ h^{-1}) was calculated for the photochemical degradation in the atmosphere on the basis of an atmospheric concentration of the OH radicals amounting to $5 \cdot 10^5$ molecules/cm^3. Products of this degradation are catechol and ring cleavage products (Canton et al., 1986).

In addition to the photochemical degradation due to hydroxyl radicals, the degradation through NO_3 radicals may also play an important role in the atmosphere. In experiments conducted in smoke chambers, the rate constant of this reaction was determined as $(2.0 \pm 0.4) \cdot 10^{-12}$ $cm^3 \cdot molecule^{-1} \cdot s^{-1}$ (Carter et al., 1981). Products of the degradation through NO_3 radicals are 2- and 4-nitrophenol (Atkinson et al., 1984). The atmospheric concentration of NO_3 radicals in a relatively uncontaminated atmosphere at night is given as $2.4 \cdot 10^8$ molecules/cm^3 by Sabljic and Güsten (1990). On account of their absorption of light with a wavelength above 600 nm, the NO_3 radicals are, however, relatively quickly photolysed in daylight. If therefore a concentration of NO_3 radicals of $2.4 \cdot 10^8$ molecules/cm^3 is assumed at night and of approximately $2.4 \cdot 10^7$ molecules/cm^3 during the day (10% of the concentration at night), a mean NO_3 radical concentration of $1.32 \cdot 10^8$ molecules/cm^3 results. A half-life of approximately 44 minutes ($kdeg_{NO3} = 0.95$ h^{-1}) can be calculated for phenol from the experimentally determined rate constant and the derived mean NO_3 radical concentration.

Compared to the reaction of phenol with hydroxyl and NO_3 radicals, the reaction with ozone as well as direct photolysis play a subordinate role with regard to the degradation of phenol in the atmosphere (Canton et al., 1986).

A half-life of 42 minutes is calculated for the degradation of phenol in the atmosphere ($k_{deg\text{-}air} = 1.0\ h^{-1}$) in consideration of the cited degradation constants for the photochemical degradation with OH- and NO_3 radicals.

Rate constants for the reaction of phenol with various radical species in water at a temperature of 15-25°C have been measured and are shown in the **Table 3.3** (Anbar and Neta 1967).

Table 3.3 Degradation rate constants for phenol

Radical species	pH	Second order rate constant
Hydrated electrons	11	$< 4 \cdot 10^6$ l/ mol · s
Hydrogen atoms	7	$4 \cdot 10^9$ l/ mol · s
Hydroxyl radicals	7	$0.42 - 1.06 \cdot 10^{10}$ l/ mol · s
	9	$5.1 \cdot 10^9$ l/ mol · s

Typical concentrations of hydroxyl radicals in surface water are in the range $5 \cdot 10^{-19}$ molecules/l to $2 \cdot 10^{-17}$ mol /l (Howard et al., 1991). Using these concentrations and the reaction rate constants, the half-life of phenol in water due to reaction with hydroxyl radicals can be calculated to be between 38 days and 10.4 years. No information was found on the typical concentrations of other radical species in surface water.

Compared to the reaction of phenol with hydroxyl radicals the biodegradation is the important elimination process of phenol in the hydrosphere. The reaction with hydroxyl radicals plays a subordinate role in the hydrosphere.

Hydrolysis

No investigations are available in connection with the hydrolytic degradation of phenol. However, no hydrolytic degradation is to be expected due to the chemical structure of the substance.

3.1.2.1.2 Distribution

A Henry constant of 0.022 Pa m^3/mol at 20°C is calculated from the data given in Section 1.3 relating to the vapour pressure and the water solubility of phenol. Consequently, the substance is only slightly volatile from an aqueous solution (for the calculation see Appendix A). The soil sorption coefficients (K_{oc} values) for phenol which are described in the literature are located within the range 14.0 l/kg (UBA, 1993) to 91 l/kg (Scott et al., 1983). On the basis of the $logP_{ow}$ value (measured $logP_{ow}$ value for phenol 1.47), in accordance with the TGD, the K_{oc} value is calculated as 82.8 l/kg (for the calculation see Appendix A). The calculated K_{oc} value is located within the range of the experimentally determined values and is taken into account in the further considerations.

The partition coefficients in the individual environmental compartments can be calculated according to the organic carbon content as follows:

Table 3.4 Partition coefficients for phenol

Compartment	Partition coefficient
Soil-water	Kp_{-soil} = 1.656 l/kg
Sediment-water	Kp_{-sed} = 8.278 l/kg
Suspended matter-water	Kp_{-susp}= 8.278 l/kg
Sewage sludge-water, calculated	$Kp_{-sludge}$= 30.627 l/kg

(For the calculation see Appendix A)

The following theoretical distribution in the environment results for phenol using the distribution model according to Mackay (level 1):

Table 3.5 Distribution of phenol

Compartment	Percentage
Air	0.8
Water	98.8
Soil	0.2
Sediment	0.2

The hydrosphere is therefore the target compartment for phenol in the environment.

Elimination in waste-water treatment plants (WWTPs)

Based on the physico-chemical properties of phenol and the rate constant for biodegradation of 1 h^{-1} the elimination in WWTPs can be determined with the help of the SIMPLETREAT model as follows:

Table 3.6 Behaviour of phenol in WWTP's

Evaporation to air (%)	0
Release (dissolved) to water (%)	12.6
Adsorption to sewage sludge (%)	0.3
Degradation (%)	87.1
Total elimination from water (%)	**87.4**

According to currently available investigations on the elimination of phenol in industrial waste-water treatment plants belonging to 3 companies involved in the production and/or further processing of the substance in Germany, elimination rates of 96 to 99% result for the phenol index (Leuna, 1995, Emschergenossenschaft, 1995,) and > 95 to 99% for phenol (Bayer, 1992).

For seven municipal wastewater treatment plants in Ontario (Canada) the concentration of phenol in raw sewage and in final effluents are available. Based on the average concentration, the percent efficiency removal of phenol for the 7 MWWTPs is estimated to be 82%. (Government of Canada 1998). This result is in good agreement with the SIMPLETREAT model calculation.

In the following exposure estimates, an 87.4% elimination of phenol from the waste water is assumed in WWTPs if no site specific information is available.

3.1.2.1.3 Accumulation

Bioaccumulation

The bioaccumulation of phenol was studied by Butte et al. (1985) using *Brachydanio rerio* as test organism. The test was conducted according to OECD guideline 305 E; the BCF was calculated from the kinetic of the accumulation and clearance phase.

Fish were exposed in a flow-through system to a phenol concentration of 2 mg/l. Accumulation and clearance was measured over 5 and 10 hours. After 3 hours of accumulation the phenol concentration in fish remained constant.

With a rate constant for the accumulation phase of 14.6 h^{-1} and for the depuration of 0.838 h^{-1} a BCF of 17.5 could be calculated. The maximum concentration of phenol in fish was 35 mg/kg.

Freitag et al. (1985) measured the bioaccumulation of ^{14}C-labelled phenol in *Leuciscus idus*. The fish were exposed to a phenol concentration of 50 µg/l over 3 days. A BCF of 20 related to ^{14}C was found. No information is given whether steady-state was reached.

Kobayashi and Akitake (1975) investigated adsorption and excretion of phenol by goldfish (*Carassius auratus*). Fish were exposed to phenol concentrations ranging from 5 to 100 mg/l in a semi-static system over 5 days.

Phenol accumulation was very rapid. After 1 hour a phenol concentration of 24 mg/kg was measured in fish exposed to 20 mg/l phenol but the subsequent increase was slower. Concentration factors of 1.2 to 2.3 were found. Phenol excretion by fish exposed to 20 mg/l phenol for 24 hours and then transferred to phenol-free water was also examined. After 1 hour the phenol concentration in fish fell to approximately one-fourth of the initial concentration. Subsequent decrease was slower. Most of the phenol excreted by goldfish within 1 hour was free-form, but the ratio of bound- to free-phenol gradually increased with time.

Uptake, elimination and metabolism of phenol by *Pimephales promelas* was investigated by Call et al. (1980). Fish were exposed in flow-through systems for 28 days to ^{14}C-labelled phenol in concentrations of 2.5 and 32.7 µg/l. Subsequently fish were transferred to clean water for depuration studies. Depuration was also followed over 28 days.

Uptake of phenol was very rapid with a rate of 0.7 $\mu g \cdot g^{-1} \cdot h^{-1}$ (phenol concentration 2.5 µg/l) and of 5.6 $\mu g \cdot g^{-1} \cdot h^{-1}$ (phenol concentration 32.7 µg/l). Concentration factors related to ^{14}C of 14,500 and 17,000 were found.

Depuration of ^{14}C was slow. Half-lives of 385 and 497 hours were calculated.

Phenol was rapidly metabolised by *Pimephales promelas*. Aceton-unextractable ^{14}C comprised 78.5% and 89.1% of total radioactivity at the ends of uptake and depuration phase respectively. At the ends of uptake and depuration phenol comprised 8.8% and 1.5% respectively of the total ^{14}C, equivalent to a phenol concentration in fish of 141 mg/kg and 11 mg/kg.

These results indicated a high retention of certain phenolic metabolites or conjugation products. Also metabolism of phenol and subsequent incorporation of the radiolabel into endogenous substances is possible.

From the phenol concentration in fish at the end of uptake and in water a BCF of 4,300 can be calculated. However, this value is in contradiction to all other values found for phenol. Call et al. (1980) have also examined the bioaccumulation of 4-nitrophenol and 2,4,5-trichlorophenol with

the same test design. As the BCFs found for these two substances are in good agreement with values reported by other authors the BCF for phenol of 4,300 should be used with care and is not considered for the risk assessment.

The cited studies show that uptake and metabolism of phenol in fish take place very fast. Binding of polar conjugates and metabolites to plasma proteins is possible. This fact may explain why in studies using ^{14}C-measurement only a slow depuration is observed.

As a conclusion from the available test results it can be stated that phenol has only a low bioaccumulation potential. This is also supported by the log Pow of 1.47. According to the equation of Veith et al. (1979) given in the TGD a BCF_{fish} of 3.5 can be calculated from this value.

For the further assessment the BCF of 17.5 found by Butte et al. (1985) is used.

Geoaccumulation

The soil sorption coefficient (K_{oc}) of 82.8 l/kg does not provide any indication that a significant geoaccumulation potential is to be expected in the case of phenol. Consequently, the substance can be washed out of the soil into the ground water by rain water depending on the elimination in soil by degradation and distribution.

3.1.3 Aquatic compartment

3.1.3.1 Release during production and processing of phenol

The current production and/or processing volumes provided by the companies are considered for the determination of the $Clocal_{water}$. If no specific data are available, the maximum production and/or processing quantity is assumed for the derivation of the $Clocal_{water}$ for production and processing.

Releases into the waste water occur during production and further processing. Since comprehensible exposure data relating to production and further processing were not submitted by all companies, a release into the waste water of 0.3% of the production quantity and of 0.7% of the processing quantity is assumed in accordance to the TGD.

The data gap for the exposure estimation results from the fact that for some of the companies (producer and/or importer) it is not known whether phenol is processed at the same site or sold to other processors.

If no data are available in this regard, it is assumed for the further estimation of exposure that the total production or used quantity is processed further at the same site.

For all production sites in the EU site specific data are available for the calculation of the $Clocal_{water}$. 96% of the used quantity of phenol in the EU (approximately 1,572,310 of 1,642,500 tonnes/annum, see **Table 3.8**) are covered by site specific calculations of the $Clocal_{water}$. The default emission value from the TGD (0.7%) is used for the remaining tonnage.

Further searches after processing sites for the remaining 4% phenol are not necessary, since with the available data for 20 sites all large processing sites are covered. The remaining quantity of phenol is processed at smaller sites (as for example at the locations, Pc5, Pc16, Pc18, Pc21-Pc24).

3.1.3.2 Determination of the $Clocal_{water}$ for production and processing

A $Clocal_{water}$ can be calculated for all individual sites (32 sites) using the currently available data for the individual production and/or processing companies. For the calculation of the $Clocal_{water}$, site-specific data and exposure information from the individual companies were considered. However, no site-specific data (e.g. volumetric flow rate for the WWTP, volumetric flow rate for the receiving stream) are available for some of the companies. In part, no exposure information (e.g. release into the waste water or the receiving stream, WWTP discharge concentration) was given either. Consequently, the $Clocal_{water}$ calculation was performed using the "default values" from the TGD.

From the calculation described in **Table 3.8**, local concentrations from 0.0 to 11.49 µg/l are calculated for all 32 sites of production and processing of phenol in the EU. The 90th percentile of the local concentrations is 2.83 µg/l.

Table 3.7 Data used to calculate the local concentrations

Input data	Value/unit	Source
Emission Scenario	IC3/UC33	TGD: ESD Intermediates
Production volume	Site specific otherwise IUCLID maximum value [tonnes/annum]	provided by producer or by IUCLID
Emission factor: f_{water} production and/or processing at one site	Site specific otherwise default: f = 0.003 (production) f = 0.007 (processing)	provided by the companies or TDG default
fraction of emission directed to water by STP: $F_{STPwater}$	Site specific otherwise default: 0.126 (12.6%)	provided by the companies or calculated by SimpleTreat
Emission duration: $T_{emission}$	Site specific otherwise default: 300 days	provided by the companies or TGD default
STP water flow rate	Site specific otherwise default: 2,000 m^3/day	provided by the companies or TGD default
Receiving water flow rate	Site specific otherwise default: 60 m^3/s	provided by the companies or TGD default
Dilution for the emission to the sea	site specific otherwise default: 10	provided by the companies or TGD default
Factor (1+Kp · SUSPwater)	1	TGD
Output data		
Emission per day to WWTP	kg/day	
Emission per year to receiving water	tonnes/annum	
$Clocal_{effl.}$	µg/l	
$Clocal_{water}$	µg/l	

Table 3.8 Site specific calculations of local receiving water concentrations

Site	Production (kt/a)	Processed (kt/a)	Release fraction to WWTP (t/t)	Release to WWTP (kg/d)	Release to surface water (t/a)	Clocal $_{effl.}$ (µg/l)	Clocal$_{water}$ (µg/l)	PEClocal$_{water}$ (µg/l)
Production								
P1	529	0	8.58E-05	124.35	5.72	11.33	0.17	2.58
P2	391.636	0	2.17E-06	2.33	0.11	320.00	0.03	2.44
P3	100	0	4.76E-06	1.59	0.06	7.66	0.77	3.18
P4	96.2	0	8.32E-06	2.67	0.10	168.00	0.06	2.47
P5	5	0	1.19E-03	19.83	0.75	1,000.00	0.48	2.89
sum:	1,121.836	0	/	150.76	6.74	/	/	/
Production and Processing								
PP1	52.764	49.694	1.62E-04	26.92	1.02	529.26	0.52	2.93
PP2	110	110	7.22E-05	26.46	1.00	114.9	11.49	13.9
PP3	263	263	7.54E-05	66.14	2.50	69.44	1.57	3.98
PP4	5	5	8.4E-06	0.14	0.01	40	0.01	2.42
PP5	5	5	0.01[4)]	166.67	6.30	10,500.00	4.05	6.46
PP6	151.5	151.5	3.14E-04	158.72	6.00	13,300.00	0.23	2.64
PP7	110	110	2.31E-06	0.85	0.03	9.50	0.95	3.36
sum:	697.264	694.194	/	445.76	16.86	/	/	/
Processing								
Pc1	0	118	6.19E-05	20.00	0.07	10.00	0.0022	2.41
Pc2	0	12	0.00945	310.68	1.13	69.97	0.03	2.44
Pc3 [1)]	0	0						/
Pc4	0	116.631	8.85E-07	0.28	0.01	0.38	0.0014	2.41

Table 3.8 continued overleaf

Table 3.8 continued Site specific calculations of local receiving water concentrations

Site	Production (kt/a)	Processed (kt/a)	Release fraction to WWTP (t/t)	Release to WWTP (kg/d)	Release to surface water (t/a)	Clocal effl. (µg/l)	Clocalwater (µg/l)	PEClocalwater (µg/l)
Pc5	0	9	0.007[4)]	210.00	7.94	57.15	0.41	2.82
Pc6	0	6	0.007[4)]	140.00	5.29	8,820.00	3.40	5.81
Pc7	0	23	1.45E-05	0.95	0.04	50.00	0.08	2.49
Pc8	0	40	0.00045	60.7	0.034	250	0.11	2.52
Pc9	0	8.089	6.10E-04	20.57	0.62	500.00	0.50	2.91
Pc10	0	5	0.007[4)]	116.67	4.41	7,350.00	2.83	5.24
Pc11	0	130	1.84E-03	654.63	0.48	123.93	0.15	2.56
Pc12	0	200	1.00E-04	66.67	2.52	97.22	2.43	4.84
Pc13	0	38	3.02E-06	0.38	0.01	24.07	0.0093	2.42
Pc14 [1)]	0	0	/	/	/	/	/	/
Pc15	0	120	5.6E-06	2.32	00.9	100	0.02	2.43
Pc16	0	5	0.007[4)]	116.67	4.41	7,350.00	2.83	5.24
Pc17 [1)]	0	0	/	/	/	/	/	/
Pc18	0	5	0.007[4)]	116.67	4.41	7,350.00	2.83	5.24
Pc19 [2)]	0	24	0.00	0.00	0.00	0.00	0.00	2.41
Pc20	0	3.4	0.007[4)]	79.33	3.00	5,000.00	1.93	4.34
Pc21 [2)]	0	5	0	0	0	0	0	2.41
Pc22	0	5	0.007[4)]	116.67	4.41	7,350.00	2.83	5.24
Pc23 [1)]	0	0	/	/	/	/	/	/
Pc24 [2)]	0	5	0	0	0	0	0	2.41
Pc25 [1)]	0	0	/	/	/	/	/	/

Table 3.8 continued overleaf

Table 3.8 continued Site specific calculations of local receiving water concentrations

Site	Production (kt/a)	Processed (kt/a)	Release fraction to WWTP (t/t)	Release to WWTP (kg/d)	Release to surface water (t/a)	Clocal effl. (µg/l)	Clocalwater (µg/l)	PEClocalwater (µg/l)
sum:	0	878.12	/	2,032.49	39.67	/	/	
Total	1,819.10	1,572.31	/	2,629.13	63.27	/	/	

1) No phenol is processed; the company is only a trader.
2) No emission of waste water at this site.
3) PEClocal = $Clocal_{water}$ + $PECregional_{water}$ (see Section 3.1.6.2).
4) Based on TGD default values (see Table 3.1)

From the calculations described in **Table 3.8**, a release of approximately 63.27 tonnes/annum phenol into the hydrosphere (859.85 tonnes/annum release to industrial WWTPs) results for production and further processing at known sites in Europe. For the quantity of 70,190 tonnes/annum phenol processed at unknown sites the default values from the TGD were used to estimate the emission to water. The emission to waste water is 1.64 tonnes/day (491.33 tonnes/annum releases to industrial WWTPs) and the emission to surface water is 61.9 tonnes/annum.

3.1.3.3 Release through the use of products containing phenol

A non-quantifiable part of phenol is used as a constituent of disinfectants and medical preparations (e.g. in skin-peeling preparations). In the case of such use of the substance, release of the total utilised quantity into the municipal waste water can be assumed. It is not possible to undertake an estimation of the $Clocal_{water}$ for these areas of use since no use quantities are known.

In Nordic product registers the presence of phenol in different products is described. For most products only very small amounts of phenol are given. Only for two product types a significant amount of unreacted phenol is indicated. The Danish product registers give the information that an amount of 127 tonnes/annum of phenol is contained in adhesives and binding agents in Denmark. Although it is unclear whether this tonnage really addresses unreacted phenol, a generic exposure scenario is estimated for the releases of unreacted phenol from these products to estimate very roughly whether a possible concern for the local aquatic environment is resulting. If the use in DK is proportional to the consumption in the EU, the EU tonnage would be 10,160 tonnes/annum.

If it can be assumed that the adhesives and binding agents are phenolic resins, the production of these products is already considered with the scenario for the processing of intermediates.

The releases of phenol from processing of the binds could be estimated with the A/B tables of the TGD using IC 11, polymer industry (Table A 3.11). Applying the 10%-rule gives an amount of unreacted phenol in resins in a region of 1,016 tonnes/annum. The highest release factor into the waste water in Table A 3.11 is 0.001, giving a release of phenol of 1.016 tonnes/annum. From a content of phenol in binders of maximum 20% (product register information) a volume of binders of 5,080 tonnes/annum being processed can be derived. From the Table B 3.9 a fraction of main source of 0.1 and a processing duration of 300 days/annum can be derived. Therefore, 338.7 g/day are emitted in a sewage treatment plant of 2,000 m³/day, giving a concentration of 170 µg/l. With an elimination of 87.4% the effluent concentration is 21.41 µg/l. A dilution 1:10 gives a Clocal of 2.1 µg/l. With a PECregional of 2.41 µg/l the PEClocal is 4.51 µg/l.

Releases of phenol during the service life of the binders can only very roughly be estimated. As a realistic worst-case, it is assumed that 10% of the unreacted phenol in the binders is releases into the environment per year by diffusion. With the 10%-rule this gives an amount of 102 tonnes/annum being released. For modelling purposes a fraction of main source of 0.002 (personal/domestic) and a number of days of 365 days is used. 560 g/day are thus emitted into a WWTP with 2,000 m³/day giving an influent concentration of 279 µg/l. With an elimination of 87.4% and a dilution factor of 10 a Clocal of 3.5 µg/l and a PEClocal of 5.91 µg/l is resulting.

These estimations are based on limited data and rough assumptions and the results are not considered reliable enough to feed them into the calculation of the regional and continental

background concentration. Besides, the resulting change of the PECregional would be insignificant. On a local scale, however, the estimates are considered for risk characterisation to indicate whether a risk may arise from the processing and use of phenol-containing binders.

In addition, the Danish product register gives the information that an amount of 500 tonnes/annum of phenol is used as solvent. If the use in DK is proportional to the consumption in the EU, the EU tonnage would be 40,000 tonnes/annum. No further information on the type and application area of the indicated solvents could be obtained from the Nordic product registers. The European producers of phenol organised in the Phenol Producers Association tried to trace the use of phenol in solvents (Meeting of the Phenol Sector Group 16./17.05.2002 in Bordeaux and Phenol Toxicology Task Force 23./24.05.2002 in Helsinki). They confirmed that to their knowledge phenol is not used in solvents in significant amounts and that an estimate of 40,000 tonnes/annum in Europe would be totally unrealistic (Ineosphenol, 2002). Therefore, the data basis is judged to be too scarce to quantify the amounts and environmental releases of phenol from the use in solvents.

3.1.3.4 Release from other areas

Release via the waste water from cooking plants and low-temperature carbonisation plants

The pollutant load of the waste water which occurs in the case of the cooking, gasification and liquefaction of coal depends on the feed coal and process conditions. Phenol concentrations (for two sites) ranging from 68 to 720 mg/l were determined in the waste water from cooking plants (Klein et al., 1990). As a rule, the waste water is dephenolised by means of extraction as well as biologically purified in WWTPs before release into the receiving stream. It is not possible to estimate a $Clocal_{water}$ for this area due to insufficient data on the phenol content in the waste water and on the treatment of the waste water.

Release via refinery waste water

Phenols (mixture of phenol and alkyl phenols) are typical components of refinery waste water. Occurring during thermal and catalytic conversion processes, they are, however, also contained in petroleum itself. Total phenol determinations in the waste water were carried out in three petroleum and two lubricant oil refineries during the period 1989/1990. Investigations carried out in the influent of the biological waste-water purification plants produced total phenol contents (calculated as phenol) from 0.1 to 48 mg/l. In the effluent of the waste-water purification plants the total phenol concentration amounted to between < 0.01 mg/l and 0.2 mg/l (Huber et al., 1991).

As a rule, the waste water is dephenolised by means of extraction as well as biologically purified in WWTPs before release into the receiving stream. It is not possible to estimate a $Clocal_{water}$ for this area due to insufficient data on the phenol content in the waste water and on the treatment of the waste water.

The average concentrations of phenol in final effluents of seven refineries in Ontario (Canada) were monitored for a 12 month period in 1989-90. The concentrations ranged from 0.24 to 9.56 µg/l. (Government of Canada 1998)

Release via the waste water from pulp manufacture

Phenol in concentrations up to 50 µg/l were detected in the waste water from pulp manufacture (Christmann et al., 1985) within the framework of investigations into the situation regarding waste water in the pulp industry in Germany (1982-1984). It is not absolutely clear from the documents relating to the investigations whether the measurements were performed in the waste water before or after waste-water treatment.

It is not possible to estimate a $Clocal_{water}$ for this area due to insufficient data on the phenol content in the waste water and on the treatment of the waste water.

In 1996, the highest monthly average concentration of phenol in final effluent of 26 mills (from pulp, paper and wood products sector) in Ontario (Canada) ranged from not detectable (< 2.4 µg/l) to 404.6 µg/l. (Government of Canada 1998)

Release via landfill leachate

Phenols (phenol in a mixture with substituted phenols) were detected in 175 samples at a level of 49.2 mg/l (mean value) or 370 mg/l (maximum value) in landfill leachate in Germany (Gajewski and Korherr, 1993). No information is given by the authors about the source of phenol.

Direct release into the geosphere and hydrosphere results in the case of landfills without landfill leachate collection systems, whereas collected leachate is, in the main, subjected to purification, e.g. in WWTPs. It is not possible to estimate a $Clocal_{water}$ for this area due to insufficient data on the phenol content in the leachate and on the fate of the leachate.

Release via municipal waste water

Phenol is eliminated by humans as a product of metabolism in the urine and faeces. A number of investigations into phenol in the urine (in free, unbound form) are available. The data on the phenol content of the urine vary within the range: 5 to 55 mg/l (Sitting, 1980), 40 mg/l (Hoschek and Fritz, 1978), 4 to 8 mg/l (Balikova and Kohlicek, 1989). With the assumption that humans excrete about 1 to 1.5 l urine per day, phenol release rates into the municipal waste water of 4 to 80 mg per day and person result. The release of phenol in bound form in both the urine and the faeces is not considered here.

Furthermore, phenol occurs in human sweat. Concentrations between 20 and 80 mg/l phenol were determined in the sweat (Dugan, 1972). The phenol eliminated via sweat essentially enters the waste water via the washing of the body or the laundry. A precise estimation of this release into the hydrosphere is not possible.

For the purpose of calculating a $Clocal_{water}$ it is assumed on the basis of the investigations on the phenol content in the urine (in free, unbound form) that a person eliminates about 40 mg phenol per day via the urine. If the population of the EU (370 million) is considered, an annual quantity of approximately 5,400 tonnes/annum results for the release of phenol into the waste water. In the case of 70% of the population being connected to municipal WWTPs, 1,620 tonnes/annum are released directly into the hydrosphere and 3,780 tonnes/annum are discharged into municipal WWTPs. Taking into account a level of elimination amounting to 87.4%, approximately 476 tonnes/annum enter the hydrosphere from WWTPs.

Assuming that a person consumes approximately 200 litres of water per day, a waste-water concentration of 0.2 mg/l phenol results. A dilution of 1:10 is assumed for direct discharge of the waste water into the receiving stream and a $Clocal_{water}$ (water concentration) of 20 µg/l is to be

expected. If the waste water is purified in a municipal WWTP, an elimination of approximately 87.4% is to be considered and a $Clocal_{water}$ of 2.52 µg/l results.

Emission per inhabitant to waste water	40 mg/day
Consumption of water per inhabitant	200 l/day
Number of inhabitant released to STP	10 000
Elimination in WWTP	87.4%
No. of days	365 days/annum
Dilution in receiving water	10
Factor $(1+K_p \cdot SUSP_{water})$	1

$$Clocal_{eff} = \frac{40\ mg/l \cdot 10{,}000 \cdot 365\ d/a \cdot (1 - 0.874)}{200\ l/d \cdot 10{,}000 \cdot 365\ d/a} = 25.2\ \ \mu g / l$$

$$Clocal_{water} = \frac{25.2\ \mu g/l}{1 \cdot 10} = 2.52\ \ \mu g / l$$

In this estimation of exposure, no account is taken of the release of phenol in bound form in the urine and faeces or of the use of phenol as a disinfectant and medical.

In 1987, raw sewage concentrations of phenol in 28 municipal wastewater treatment plants in Ontario (Canada) ranged from 15.7 to 276.2 µg/l (24 hours composites; detected in 55% of 221 samples). The highest measured final effluent concentrations of phenol for 7 of those 28 plants ranged from 4.1 to 17.3 µg/l (detected in 22% of 55 samples). In 1997, in two municipal wastewater treatment plants in Ontario (based on 9 samples) phenol was not detected in the final effluent (detection limit 1.7 µg/l). (Government of Canada 1998)

As a result of the release of phenol into municipal WWTPs, accumulation of the substance in sewage sludge is also possible. In consideration of the above-mentioned assumptions, a sewage sludge concentration of 1.69 mg/kg (dry weight) can be calculated for a model WWTP (10,000 inhabitants, 2,000 m^3/day).

Emission to STP	0.4 kg/day
Fraction of emission directed to sludge	0.003 (0.3%)
Sludgerate of STP	710 kg/day

$$C_{sludge} = \frac{0.4\ kg/d \cdot 0.003}{710\ kg/d} = 1.69\ \ mg / kg$$

Investigations of the sewage sludge of 204 municipal WWTPs in the US state of Michigan in 1980 revealed positive detections of phenol in 179 of the 229 samples investigated in total. The mean concentration amounted to 9.2 mg/kg (dry weight); the concentration range was between 0.016 and 288 mg/kg phenol (Jacobs and Zabik, 1983). Phenol concentrations between < 0.002 and 300 mg phenol/kg (dry weight) are given for sewage sludges in Germany by Drescher-Kaden et al. (1989). The mean amounts to 2 mg/kg and are in good agreement with the calculated concentration in sewage sludges.

Release via products of animal metabolism

Animals eliminate phenol as a product of metabolism together with the urine and the faeces. Between 0.5 and 45 mg/l phenol were detected in the liquid manure (12 hours after excretion) produced by pigs (Yasuhara and Fuwa, 1983).

In the main, the liquid manure derived from livestock farming is spread over agricultural areas for the purpose of fertilisation or discharged into WWTPs. Release into the hydrosphere is to be expected. It is, however, not possible to estimate a $Clocal_{water}$ for this area due to insufficient data.

3.1.3.5 Data on occurrence in the hydrosphere

Only very few investigations are available with regard to the occurrence of phenol itself in the hydrosphere. They mostly contain only data on the quantity of steam-volatile phenols or on the Phenol Index (as summary parameters of all phenol compounds without substituted p-position).The Phenol Index based on the DIN 38409 include all substances which can be coupled oxidative like aromatic amines, so this results should be used with care.

The individual results of the investigations are summarised in the following table:

Table 3.9 Concentration of phenol in the aquatic environment

Location	Analysed substance	Period	Source	Concentration in µg/l
Saale	Σ st. vol. phenols	1989 - 1991	UBA 1991	6-52
Weiße Elster	Σ st. vol. phenols	1989 - 1991	UBA 1991	13-50
Mulde	Σ st. vol. phenols	1989 - 1991	UBA 1991	28-450
Mulde near to Bad Düben	Σ st. vol. phenols	1988	Matthes et al. 1992	2-120
Mulde near to Bad Düben	Σ st. vol. phenols	1989	Matthes et al. 1992	5-110
Mulde near to Bad Düben	Σ st. vol. phenols	1990	Matthes et al. 1992	1-80
Mulde near to Bad Düben	Σ st. vol. phenols	1991	Matthes et al. 1992	5-50
Elbe	Σ st. vol. phenols	1989 - 1991	UBA 1991	6-66
town well Berlin	Phenol Index	1986	Krüger und Beyer 1988	< 10-30
Müggelsee	Σ st. vol. phenols	1988 - 1989	Rummel 1991	11-42
rain water Germany	phenol	1989 - 1990	Levsen et al. 1990	0.68-59.7
Emscher WWTP influent	Phenol Index	1994	Emscherg. 1995	50-1,220
Emscher WWTP influent	Phenol Index	1997 – 8/2000	Emscherg. 2000	< 10-650
Emscher WWTP effluent	Phenol Index	1994	Emscherg. 1995	< 10-21
Emscher WWTP effluent	Phenol Index	1997 – 8/2000	Emscherg. 2000	< 10-30
Rhein near to Lobith	Σ st. vol. phenols	1983 - 1984	IAWR 1983-85	< 0.1-0.3
Rhein near to Lobith	Σ st. vol. phenols	1985 - 1986	IAWR 1986/87	< 0.1-2.0
Rhein near to Lobith	Phenol Index	1. - 4. Quartal 1983	Canton et al. 1986	5.8-9.2

Table 3.9 continued overleaf

Table 3.9 continued Concentration of phenol in the aquatic environment

Location	Analysed substance	Period	Source	Concentration in µg/l
Maas near to Eysden	Phenol Index	1. - 4. Quartal 1983	Canton et al. 1986	5.7-15.7
Ijsselmeer	phenol	1983	Canton et al. 1986	0.3-7
port of Rotterdam / Amsterdam	phenol	1983	Canton et al. 1986	up to 260
North sea	phenol	1986	Hurford et al. 1989	< 0.1-0.88
Schelde	phenol	1980	Goethals 1991	5
Schelde	phenol	1984	Goethals 1991	4.5
Schelde	phenol	1988	Goethals 1991	2
Saar, different sites n = 290	phenol	1990-1997	UBA 2000	< 10-20
Mosel, different sites n = 140	phenol	1990-1992	UBA 2000	< 10-20
Rhein Setz n = 207	phenol	1980-1992	UBA 2000	< 10-20

Σ st. vol. phenols = sum of the steam-volatile phenols

The available monitoring data are, in part, relatively old and cannot be assigned to the individual emission sources or the measured values. They only provide an indication of the orders of magnitude which are to be expected (if there are only data on the phenol index or Σst. vol. phenols). As a product of human and animal metabolism phenol is a natural occurring substance. It is disputable, however, if elevated concentrations in densely populated areas due to human metabolism can be regarded as the "natural" background concentration in term of environmental risk assessment. From the available monitoring data a quantitative breakdown of the phenol from anthropogenic sources, human metabolism, animal keeping and wildlife is not possible. In addition, most values are related to the phenol index or Σst. vol. phenols and not to phenol itself. Therefore, risk characterisation cannot be performed on the basis of the monitoring data.

3.1.3.6 Sediment

A local water concentration ($Clocal_{water}$) of approximately 2.83 µg/l is calculated from the estimation of exposure for a typical company (90^{th} percentile of the local concentrations from **Table 3.8**). In accordance with the TGD, the sediment concentration can be estimated from this water concentration. A sediment concentration of approximately 0.0073 mg/kg sediment was calculated for phenol.

Concentration in surface water	2.83 µg/l
Partition coefficient suspended matter-water	2.97 m^3/m^3
Bulk density of suspended matter	1 150 kg/m^3

$$PEClocal_{sed} = \frac{2.83\ \mu g/l \cdot 2.97\ m^3/m^3 \cdot 1{,}000}{1{,}150\ kg/m^3} = 7.3\ \mu g/kg$$

In 1996 phenol was analysed in sediment of the river Oder (East Germany). The occurrence of phenol in the sediment at different sites is in the range of 0.015 to 45.5 µg/kg (UBA 2000).

A few results of investigations conducted in 1989 within the framework of hazardous waste site studies involving tar-contaminated sediment of the Warnow are available. They revealed phenol concentrations (as phenol index) of 400 mg/kg (Hübner et al., 1991). Up to 0.6 mg/kg phenol were detected in the sludge of a residual hole at an opencast brown coal mine near Wolfen which was used as a landfill and settling basin by a chemical company (Barkowski, 1992).

3.1.4 Atmosphere

3.1.4.1 Release during production and processing

Direct releases into the atmosphere occur during production and processing. Release of phenol from industrial or municipal WWTPs as a result of volatilisation into the air is not to be expected since the substance, with a Henry constant of 0.022 Pa m^3/mol, can be classified as only slightly volatile from an aqueous solution. In accordance with the SIMPLETREAT model, there is no release into the atmosphere from WWTPs. The $PEClocal_{air}$ can be calculated for the individual sites by using the currently available emission data of individual production and/or processing companies. Where no site-specific data were available, the $PEClocal_{air}$ calculation was performed using the "default values" of the TGD in the Gaussian Plume Model (OPS Model) as described by van Jaarsveld.

The regional concentration is used as background concentration and, therefore, is added to the local concentration.

For all production sites in the EU site specific data are available for the calculation of the $PEClocal_{air\text{-}annual}$. 96% of the used quantity of phenol in the EU (approximately 1,572,310 of 1,642,500 tonnes/annum, see **Table 3.11**) are covered by site specific calculations of the $PEClocal_{air\text{-}annual}$. The default emission value from the TGD (0.1%) is used for the remaining tonnage.

Further searches after processing sites of the remaining 4% phenol are not necessary, since with the available data for 20 sites all large processing sites are covered. The remaining quantity of phenol is processed at smaller sites (as for example at the locations, Pc5, Pc16, Pc18, Pc21-Pc24).

Site specific calculation

Site specific calculations of the $PEClocal_{air\text{-}annual}$ could be performed for all phenol production and most of the processing sites in the EU.

Table 3.10 Data used in OPS model for $PEClocal_{air}$ calculation

Input data	Value/unit	Source
Local direct emission rate to air during emission episode: $Elocal_{air}$	kg/day	Provided by production and/or processing companies or calculated with default values of TGD (see Table 3.1)
Local direct emission rate to STP during emission episode: $Elocal_{water}$	kg/day	Taken from Section 3.1.2.1.2
Fraction of emission to air from STP: $Fstp_{air}$	0.0%	Calculated by SimpleTreat Model
Emission duration:	D	Provided by production and/or processing companies or calculated with default values of TGD
Main category (prod./proc.)	1b or 1c / 1b or 3	TGD (see Table 3.1)
Fraction main source	1	TGD
Regional concentration ($PECreg._{air}$)	0.026 µg/m³	Section 3.1.6
Fraction of chemical bound to aerosol: $Fass_{aer}$	$2.5\ 10^{-6}$	Junge equation, TGD
Aerosol-bound deposition flux: $DEPstd_{aer}$	0.01 mg/m² d	TGD
Gaseous deposition flux as a function of Henry's Law coefficient: $DEPstd_{gas}$	$4 \cdot 10^{-4}$ mg/m² d	TGD
Output data		
Annual local air concentration 100 m away from point source: PEClocalair-annual	µg/m³	
Annual total deposition flux to soil within 1000 m² around point source: $DEPtotal_{annual}$	µg/m² d	

The following table shows the site specific input data for the calculation of $PEClocal_{air}$.

Table 3.11 Site specific emission to air

Site	Production (kt/a)	Processed (kt/a)	Release fraction to air direct	Release to air direct (kg/d)	Release to air direct (t/a)
Production					
P1	529	0	4.35E-08	0.06	0.02
P2	391.636	0	2.55E-07	0.27	0.10
P3	100	0	0.0001[2)]	33.33	10.00
P4	96.2	0	0.0001[2)]	32.07	9.62
P5	5	0	0.0001[2)]	1.67	0.50
Sum:	1,121.836	0	/	67.40	20.24
Production and Processing					
PP1	52.764	49.694	0.00001[2)]	1.76	0.53
PP2	110	110	2.09E-05	7.66	2.30
PP3	263	263	1.57E-05	13.80	4.14

Table 3.11 continued overleaf

Table 3.11 continued Site specific emission to air

Site	Production (kt/a)	Processed (kt/a)	Release fraction to air direct	Release to air direct (kg/d)	Release to air direct (t/a)
PP4	5	5	0.00001[2)]	0.17	0.05
PP5	5	5	0.00001[2)]	0.17	0.05
PP6	151.5	151.5	0.00001[2)]	5.05	1.52
PP7	110	110	0.00001818	6.67	2.00
Sum:	697.264	694.194	/	35.27	10.58
Processing					
Pc1	0	118	1.75E-06	0.57	0.21
Pc2	0	12	1.46E-06	0.05	0.02
Pc3 [1)]	0	0	/	/	/
Pc4	0	116.631	1.03E-08	0.004	0.001
Pc5	0	9	0.001[2)]	30.00	9.00
Pc6	0	6	0.001[2)]	20.00	6.00
Pc7	0	23	5.65E-07	0.04	0.01
Pc8	0	40	0.001[2)]	133.33	40.00
Pc9	0	8.089	1.24E-05	0.42	0.10
Pc10	0	5	0.001[2)]	16.67	5.00
Pc11	0	130	5.92E-06	2.11	0.77
Pc12	0	200	0.001[2)]	666.67	200.00
Pc13	0	38	2.60E-05	3.29	0.99
Pc14 [1)]	0	0	/	/	/
Pc15	0	120	0.001[2)]	166.67	50.00
Pc16	0	5	0.001[2)]	16.67	5.00
Pc17[1)]	0	0	/	/	/
Pc18	0	5	0.001[2)]	16.67	5.00
Pc19	0	24	0.001[2)]	80.00	24.00
Pc20	0	3.4	0.001[2)]	11.33	3.40
Pc21	0	5	0.001[2)]	16.67	5.00
Pc22	0	5	0.001[2)]	16.67	5.00
Pc23 [1)]	0	0	/	/	/
Pc24	0	5	0.001[2)]	16.67	5.00
PC25[1)]	0	0	/	/	/
Sum:	0	878.12	/	1,447.81	434.5
Total	1,819.10	1,572.31	/	1,550.48	465.32

1) No phenol is processed; the company is only a trader.
2) Based on TGD default values (see Table 3.1)

Data on the release into the atmosphere during the production and/or processing of phenol are available for 12 companies. The total release is estimated at approximately 10.66 tonnes/annum.

No further data on the release into the atmosphere during the production and/or processing or use of the substance are available. In the case of the companies that have not submitted any data on the release of phenol into the atmosphere during production and/or processing, the release into the atmosphere can be estimated with the help of the TGD (see **Table 3.1**) in consideration of the production and/or processing quantity in each case. A release into the atmosphere of 465.32 tonnes/annum phenol is calculated for the companies without available exposure data (for the calculation see **Table 3.11**).

For the processing of 70,190 tonnes/annum phenol at unknown sites the default values from the TGD were used to estimate the emission of phenol to air. The direct emission to air amounts to 70.2 tonnes/annum.

In the following table representative sites with their local air concentration and deposition rates are summarised:

Table 3.12 Calculation of local air concentrations and deposition rates

Representative sites from Table 3.11	Emission to air [kg/d]	$PEClocal_{air\text{-}annual}$ [µg/m³]	$DEP\ total_{annual}$ [µg/m² d]
Pc12 (Maximum emission)	666.67	152	219
Pc4 (Minimum emission)	0.004	0.027	0.0013
P3 (Mean emission 40 kg/d)	33.33	7.6	11
Pc19 (90th percentile emission 75 kg/d)	80	18	26

3.1.4.2 Release from diffuse sources

Release through photochemical degradation of benzene

Investigations by Atkinson et al. (1989) revealed that in the presence of NO and NO_2 with OH radicals, benzene is converted to phenol with a yield of about 20%. Canton et al. (1986) performed a model calculation for the formation of phenol from benzene for the Netherlands using a reaction rate constant of 1,800 $ppm^{-1} \cdot min^{-1}$ (=$1.2 \cdot 10^{-12}$ $cm^3 \cdot molecule^{-1} \cdot s^{-1}$), a mean annual concentration for benzene between 2 and 3 µg/m³, an OH radical concentration of $5 \cdot 10^{-8}$ ppm and a mean reaction volume of $3 \cdot 10^{13}$ m³. A release of 1,100 tonnes/annum of phenol is therefore calculated for the Netherlands. According to the authors, this value only represents a rough estimate. It should, however, be used in an assessment for Europe.

In the draft RAR of benzene (January, 2002) the typical value of benzene in the EU are summarised as follow: in urban industrial areas 5 µg/m³ and in rural and pristine areas 1.5 µg/m³. Based on these monitoring data the mean annual concentrations for benzene of 2 to 3 µg/m³ used by Canton et al. (1986) are relevant for the present formation of phenol from benzene.

If an area of 42,000 km² is considered for the Netherlands and an area of 3,231,000 km² for the EU, using the same assumptions as in the estimation by Canton et al., a release of phenol due to the photochemical degradation of benzene in the atmosphere amounting to approximately 84,600 tonnes/annum results for the EU.

Release as a result of vehicle exhaust fumes

Phenol is formed during the incomplete combustion of motor fuels. Canton et al. (1986) starts from a mean value of 4.7 mg phenol/m^3 in vehicle exhaust fumes and calculates, on the basis of the petrol consumption and the exhaust fumes which are formed during combustion in the engine, an emission of 270 tonnes/annum for the Netherlands. If this calculation is related to the quantity of petrol consumed in the EU, amounting to 117,205,000 tonnes in 1994 (MWV, 1996), a phenol emission of approximately 8,814 tonnes is calculated.

This estimation does not permit differentiation on the basis of the number of vehicles with and without catalytic converters, nor is there consideration of the phenol emission from vehicle exhaust fumes arising from vehicles with diesel engines.

Extensive investigations into the emission of non-limited exhaust-gas components, inter alia, phenols, were performed on 11 passenger cars with Otto engines (4 without and 7 with catalytic converters) and 7 passenger cars with diesel engines by Schulze et al. (1989). In these investigations the total phenols as the sum of phenol, cresols and xylenols were determined analytically.

The mean emission factors for the total phenol emission for passenger cars with Otto engines without catalytic converters were determined to 18.29 mg/mile (11.36 mg/km), for passenger cars with Otto engines with catalytic converters to 0.81 mg/mile (0.50 mg/km) and for passenger cars with diesel engines to 1.63 mg/mile (1.01 mg/km). This investigation cannot be considered for the purpose of assessing the release of phenol via vehicle exhaust fumes because it does not provide any specific statements on the emission of phenol. However, it becomes clear that a considerable reduction in the emission of phenol can be achieved through the use of catalytic converters.

Release as a result of further combustion processes

Phenol is formed during the combustion of organic substances. However, investigations which can be used for the estimation of the quantity of phenol which is formed are only available for a very limited area. In the following there is a description of the available investigations and the quantity of phenol which is formed is roughly estimated for Germany. An extrapolation to the EU is only possible via the ratio of the population of Germany to that of the EU since no specific data on the consumption of the individual products in the EU are available.

In three independent measurement campaigns in 1991 the emission of phenol in the smoke gases from a detached family house (fuel: brown-coal briquettes) was determined by Engewald et al. (1993). The mean emission factor amounted to 29.05 mg phenol per kg briquette. A phenol emission of approximately 355 tonnes/annum is calculated in consideration of a brown-coal production in Germany of 12,224,000 tonnes/annum in 1992.

Phenol could be determined in smoke gas during the combustion of wood. During measurements in the smoke gas of wood-fired tile stoves Schubert and Keller (1987) found phenol concentrations from 8 to 26 mg/m^3. Investigations involving the smoke gas during the combustion of wood briquettes, air-dried and damp wood in open hearths and in hearth stoves revealed phenol concentrations ranging from 1.4 to 85.6 mg/m^3 (Hoffmann et al., 1994). Cooper (1980) gave 0.1 g phenol/kg wood as the emission factor for stoves and 0.02 g phenol/kg wood for hearths. If the emission factor of 0.1 g phenol/kg wood for stoves and the quantity of wood felled for fire-wood in Germany amounting to 4,366,000 m^3 (1 m^3 wood = 0.5 tonnes) are considered, a release of approximately 218 tonnes of phenol as a result of the combustion of wood in Germany can be estimated for 1992.

Larger quantities of phenol may be released into the atmosphere as decomposition products of lignin, above all in the case of bush and forest fires (Jordan et al., 1979). It is not possible to quantify the amount of phenol released via this route.

Phenol is contained in cigarette smoke in quantities which differ according to the particular type concerned. Starting from a mean phenol emission in cigarette smoke of 0.4 mg/cigarette (Canton et al., 1986), a phenol emission of approximately 50 tonnes/annum can be estimated for Germany on the basis of a national consumption of 124.4 thousand million pieces in 1991.

Further data on the release of phenol as a result of combustion processes, such as those involving hard coal, fuel oil or fuel gas, are not available.

A total emission of 623 tonnes/annum results for the territory of Germany from the above mentioned diffuse releases, from further combustion processes (355 tonnes/annum from the combustion of brown-coal briquettes, 218 tonnes/annum from the combustion of wood and 50 tonnes/annum as a result of cigarette consumption). If account is taken of the population of Germany at 80 million and of the EU at 370 million, this release quantity from further combustion processes can be extrapolated from Germany to the EU. A phenol release amounting to approximately 2,880 tonnes/annum results for the total territory of the EU. However, this figure only represents a rough approximation since nowhere near all of the areas in which a diffuse release of phenol occurs have been sufficiently investigated. Consequently, it is not possible to provide a complete quantitative estimation of the phenol emission.

Quantitative determinations of phenol in the ambient air are only available to a limited extent. For example, investigations of the air were carried out in Gladbeck near Phenolchemie GmbH in 1987. However, it was not possible to detect phenol with a detection limit of 2 µg/m^3 (RWTÜV, 1987). In the period 1967 to 1970 phenol concentrations of < 20 to 289 µg/m^3 were found in the air of the city of Cologne (Deimel and Gableske, 1973). In March 1991 a phenol concentration of 0.59 µg/m^3 was determined in the air in Rome (Ciccioli et al., 1992). In January 1977 studies of the air were carried out in Paris. In sunny weather 2.1 to 5.1 µg/m^3 phenol were found, in the case of a cloudy sky the detected quantity was 0.7 to 8.2 µg/m^3 and in rainy weather it amounted to 5.4 µg/m^3 (Hageman et al., 1978).

Investigations involving the air of 8 cities in the USA during the period 1974 to 1978 revealed phenol concentrations (as mean values derived from the individual values) of 0.1 to 305 µg/m^3 (Brodzinsky and Singh, 1983).

3.1.5 Terrestrial compartment

The topsoil terrestrial compartment receives input through the application of sludge dressing and continuous airborne deposition. The elimination from soil occurs via leaching, volatilisation and biodegradation. These removal processes are considered in the model calculation of the PECsoil.

3.1.5.1 Direct release during production and processing of phenol

No information was provided for the direct emission of phenol to soil during production and processing. Due to its minor relevance related to the release via air, water and agricultural soil a direct release into the industrial soil for the production and further processing in Europe has not to be considered for this initial approach.

3.1.5.2 Release from other sources

Phenol may enter the soil as a result of the spreading of sewage sludge and liquid manure from livestock farming.

For the spread of liquid manure derived from livestock farming over agricultural areas it is not possible to estimate a total release to soil due to insufficient data. Between 0.5 and 45 mg/l phenol were detected in fresh liquid manure produced by pigs (Yasuhara and Fuwa, 1983). The liquid manure derived from livestock farming is typically collected in large open tanks over a long time period before spreading over agricultural areas (one ore two times per year) for the purpose of fertilisation. The phenol would be rapidly eliminated in the collecting tanks and the concentration of phenol in the manure at the time of the spreading is much lower than in fresh manure. Therefore, an estimation of the soil exposure using the information on the phenol content in fresh manure will significantly overestimated the resulting soil concentrations and will not give any valuable information for the risk assessment.

Sewage sludges arising from the production and processing of phenol in the chemical industry are for the most part disposed of by incineration or landfilling. However, release into the soil as a result of the spreading of sewage sludge from municipal WWTPs is possible. These plants receive waste water from private households, containing phenol as a product of human metabolism. On the assumption that 3,780 tonnes/annum phenol are released into municipal WWTPs within the EU (see Section 3.1.3.4) and that 0.3% is eliminated through adsorption to sewage sludge (see Section 3.1.1, elimination in WWTPs), the resultant quantity of phenol in the sewage sludge in Europe amounts to 11.34 tonnes/annum. If it is assumed that 50% of the sewage sludge is incinerated and 50% are spread on agricultural areas, the resultant release of phenol into the soil via the spreading of sewage sludge is approximately 5.7 tonnes/annum.

Further diffuse release of phenol into the soil is to be expected as a result of deposition from the atmosphere. Production and further processing of the substance and formation of phenol from the photochemical degradation of benzene in the atmosphere, vehicle exhaust fumes and further exhaust gases from combustion are considered here (see Section 3.1.3).

A local air load of approximately 18 µg/m^3 is calculated for a typical company (90th percentile of the local concentrations from **Table 3.11**, at site Pc19). To this is added the regional background concentration of phenol in the air of approximately. 0.026 µg/m^3 resulting from the photochemical degradation of benzene, vehicle exhaust fumes and further exhaust gases due to combustion (see Section 3.1.6). The daily deposition rate is calculated from this amount to 0.026 mg/m^2 · day (for the calculation see Appendix B). If there is no spreading of sewage sludge on the soil in the immediate vicinity of a typical company (90th percentile of the local concentrations from **Table 3.11**, at site Pc19), a soil concentration (arable soil) of 1.35 µg/kg soil or a soil pore water concentration of 0.85 µg/l result from the deposition rate of 0.026 mg/m^2 · day (for the calculation see Appendix C).

If the application of sewage sludge with a concentration of 1.69 mg/kg (dry weight) for the fertilisation of the soil used for agricultural purposes (see Section 3.1.3.4) is considered in addition to the deposition rate of 0.026 mg/m^2 · day, a soil concentration (arable soil) of 2.13 µg/kg soil or a soil pore water concentration of 1.35 µg/l is calculated, in accordance with the TGD, after 30 days of sewage sludge spreading (for the calculation see Appendix C).

The ground water concentration can be calculated in accordance with the TGD as the soil pore water concentration under the agriculture soil. For a typical company (90th percentile of the local concentrations from **Table 3.11**, at site Pc19) and the use of sewage sludge with a concentration of 1.69 mg/kg (dry weight), a soil pore water concentration of 0.94 µg/l is calculated.

With regard to the occurrence of phenol in soils, an investigation into contaminated soils at a gasworks near Copenhagen exists which reveals concentrations between 0.05 and 29 mg/kg (Damborg, 1987). Other monitoring data of phenol in soils or ground water are not available.

3.1.6 Secondary poisoning

As phenol has only a low bioaccumulation potential it is not required to carry out a risk characterisation for secondary poisoning.

3.1.7 Regional concentrations

All releases, from point sources and diffuse sources, are considered in the determination of a regional background concentration. The calculations for the regional PECs are performed with SimpleBox 2.0.

Sources for the release into the aquatic compartment and the atmosphere

- the local emissions for the production and/or processing of phenol (32 sites in the EU) are summarised and distributed to the regional and continental area in a ratio of 10% to 90%.
- the diffuse releases from human metabolism, photochemical degradation of benzene, vehicle exhaust fumes and further combustion processes are distributed to the regional and continental area in a ratio of 10% to 90%.

Table 3.13 Emission of phenol from different sources

Source of phenol	Ratio reg./cont.	Release into the hydrosphere in t/a		Release into the atmosphere in t/a
	in %	direct	into WWTP	
Production and processing	10/90	-	1,351	535.5
Human metabolism	10/90	1,620	3,780	-
Photochemical degradation of benzene	10/90	-	-	84,600
Vehicle exhaust fumes	10/90	-	-	8,814
Further combustion processes	10/90	-	-	2,880
Total		**1,620**	**5,131**	**96,829.5**

Sources for the release into the soil

Due to its minor relevance related to the release via air, water and agricultural soil a direct release into the industrial soil for the production and further processing in Europe has not to be considered for this initial approach. The release into the agricultural soil as a result of the spreading of sewage sludge is considered with a release of approximately 5.7 tonnes/annum (see Section 3.1.4.). Further diffuse releases as a result of distribution processes, such as e.g. deposition from the air, are to be expected.

The following total releases are considered for the calculation of the regional environmental concentrations.

Table 3.14 Input data for the calculation of the regional exposure

Release to	Continental model in t/a	Regional model in t/a
Air	87,146.5	9,683
Agricultural soil	5.1	0.6
Water- Direct	1,458	162
- WWTPs	4,618	513

The input data for the model calculations are presented in detail in Appendix D. The following regional environmental concentrations result from the calculations:

$PECregional_{aquatic}$ = 2.41 µg/l
$PECregional_{air}$ = 0.026 µg/m^3
$PECregional_{agr.soil}$ = 0.172 µg/kg
$PECregional_{natural\ soil}$ = 0.59 µg/kg

3.2 EFFECTS ASSESSMENT: HAZARD IDENTIFICATION AND DOSE (CONCENTRATION) - RESPONSE (EFFECT) ASSESSMENT

3.2.1 Aquatic compartment (incl. Sediment)

Available effect data

Many investigations are available concerning the toxicity of phenol to aquatic organisms from different systematic classes including also several non-standard tests. Tests were regarded as valid if they were performed according to national or international test guidelines or if they are sufficiently documented and scientifically acceptable. Tests that were performed according to standardised methods are presented in tables while tests requiring more extensive description are described in the text.

Short-term toxicity to fish

The following table gives an overview of the sensitivity of different fish species to phenol in short-term tests. It covers the full range of species tested. For each species the lowest available valid tests were selected.

Table 3.15 Short-term toxicity of phenol to fish

Species	Duration	Effect value [mg/l]	Test system	Reference
Oncorhynchus mykiss	48 hours	LC_{50} = 5.4 - 9.8	Semistatic	Brown et al. 1967
Pimephales promelas	96 hours	LC_{50} = 24 -36 (measured)		Ruesink/Smith 1975
Rutilus rutilus	48 hours	LC_{50} = 10 (measured)	Flow-through	Solbe et al. 1985
Carassius auratus	96 hours	LC_{50} = 44.5 (nominal)	Static	Pickering/Henderson 1966

Table 3.15 continued overleaf

Table 3.15 continued Short-term toxicity of phenol to fish

Species	Duration	Effect value [mg/l]	Test system	Reference
Lepomis macrochirus	96 hours	LC_{50} = 17 (measured)	Static	Holcombe et al. 1987
Pimephales promelas	96 hours	LC_{50} = 24.9-67.5 (measured)	Flow-through	DeGraeve 1980
Phoxinus phoxinus	96 hours	LC_{50} = 9.5 (measured)	Flow-through	Oksama/Kristofferson 1979
Oncorhynchus mykiss	96 hours	LC_{50} = 10.5 (measured)	Semistatic	Holcombe et al. 1987
Oncorhynchus mykiss	96 hours	LC_{50} = 9.7 (measured)	Flow-through	Hodson et al. 1984
Oncorhynchus mykiss	96 hours	LC_{50} = 5.02	Semistatic	Mc Leay 1976
Lebistes reticulatus	96 hours	LC_{50} = 47.5 (measured)	Semistatic	Gupta et al. 1982
Oncorhynchus mykiss	96 hours	LC_{50} = 8.9 (measured)	Flow-through	DeGraeve et al. 1980
Leuciscus iduss	48 hours	LC_{50} = 14 (nominal)	Static	Juhnke/Lüdemann 1978
Brachydanio rerio	96 hours	LC_{50} = 29 (measured)	Flow-through	Fogels/Sprague 1977
Jordanella floridae	96 hours	LC_{50} = 36.3 mg/l (measured)	Flow-through	Fogels/Sprague 1977

Schulte and Nagel (1994) examined the acute toxicity of phenol to embryos of *Brachydanio rerio*. Fertilised eggs were individually exposed in multiplates to different phenol concentrations and the following parameters of egg development were observed: coagulation of the eggs, gastrulation, number of somites, movement, development of organs, pigmentation, heartbeat and circulation. After 48 hours the study was stopped to prevent hatching. EC_{50}-values in the range of 84 to 436 µmol/l (7.9-41 mg/l) were found for the different endpoints. The most sensitive parameter in the development of eggs exposed to phenol was "no circulation" (after 36 hours). An EC_{50}-value of 84 µmol/l equivalent to 7.9 mg/l was found for this endpoint.

96-hour LC_{50}-values are in the range of 5.02 mg/l to 47.5 mg/l. *Oncorhynchus mykiss* seems to be the most sensitive fish species. The lowest effect value of 5.02 mg/l was obtained with this species in a semi-static system.

The experimental values are in reasonable agreement with QSAR estimation according to the TGD (1996) which results in a fish (96-hour) LC_{50} of 55 mg/l for polar narcotic acting substances.

Long-term toxicity to vertebrates

Birge et al. (1979) examined the long-term toxicity of phenol in an embryo-larval test with *Oncorhynchus mykiss* as test organism with hard and soft water. In a flow-through system (temperature: 12-14°C; dissolved oxygen: 9-11 mg/l; water hardness: 50 and 200 mg/l $CaCO_3$; pH: 7.3-8.1) eggs were exposed to the test substance 20 minutes after fertilisation. Exposure was maintained through 8 days after hatching. Average hatching time for *Oncorhynchus mykiss* was 22 days. Phenol concentration was measured daily.

Test parameters were egg hatchability and survival 8 days posthatching.

Log probit analysis was used by the authors to determine the LC_1 and LC_{50} at hatching and 8 days after hatching. LC_{50}-values of 0.64 and 0.54 mg/l were obtained for soft water. For hard water the LC_{50} was 0.08 mg/l both at hatching and 8 days posthatching. The LC_1-values calculated at hatching were 0.2 and 9.0 µg/l in hard and soft water, respectively. No significant change occured when exposure was extended beyond hatching.

The LC_1-values cannot be used as NOECs in an effects assessment as an effect of 1% compared to the control seems not significant. Therefore EC_{10}-values were derived by probit analysis on the basis of the available test results (percent survival 8 days posthatching). EC_{10}-values of 2 µg/l for hard water and of 65 µg/l for soft water could be determined that can be regarded as NOECs for 22-30 days exposure.

With nearly the same test design the long-term toxicity of phenol to *Oncorhynchus mykiss*, *Pimephales promelas* and the three amphibian species *Ambystoma grazile*, *Rana temporaria* and *Xenopus laevis* was studied by Black et al. (1982; 1983). The tests were conducted using only one water hardness (100 mg/l $CaCO_3$).

The rainbow trout eggs were exposed 20 minutes after fertilisation. Average hatching time was 23 days. Exposure was maintained through 4 days after hatching. Using probit analysis an EC_{10}-value of 5 µg/l (survival 4 days posthatching) can be calculated from the available test results.

Eggs of the three amphibian species were exposed within 30 minutes of fertilisation, while eggs of *Pimephales promelas* were exposed 2 to 8 hours postspawning. Average hatching time was 5.5 days for *Ambystoma grazile*, 5 days for *Pimephales promelas* and *Rana temporaria* and 2 days for *Xenopus laevis*. Exposure was maintained through 4 days after hatching.

The following EC_{10}-values (survival 4 days posthatching) were calculated from the given test results:

Pimephales promelas:	EC_{10} = 282 µg/l
Ambystoma grazile:	EC_{10} = 14 µg/l
Rana termporaria:	EC_{10} = 5 µg/l
Xenopus laevis:	EC_{10} = 200 µg/l

By Birge et al. (1980) an EC_{10}-value of 5.2 µg/l was found for *Rana pipiens* using the same test system.

DeGraeve et al. (1980) examined the toxicity of phenol in embryo-larval tests using *Oncorhynchus mykiss* and *Pimephales promelas* as test species.

Eyed rainbow trout eggs (> 5 days after fertilisation) were exposed in flow-through system (hardness: 580 mg/l $CaCO_3$, pH: 7.8, dissolved oxygen: 72% of saturation) to 7 different phenol concentrations in the range of 0.2 to 13.8 mg/l. Within 24 hours the fry began hatching and hatching was completed by 48 hours. The larvae were exposed for further 58 days, and then surviving fish were counted and individually weighed and measured.

Fathead minnow eggs (no information on age) were also exposed in a flow-through system (hardness: 704-725 mg/l $CaCO_3$, pH: 8, dissolved oxygen: 82-106% of saturation) to 7 different phenol concentrations ranging from 0.23 to 68.5 mg/l. Exposure was maintained for 30 days.

In both tests larvae were fed with brine shrimp and powdered trout food. Phenol concentration was measured once a week.

For *Pimephales promelas* egg hatchability was significantly reduced by exposure to 68.5 mg/l phenol and growth was impaired by exposure to concentrations of 2.5 mg/l.

Hatchability of *Oncorhynchus mykiss* eggs was not measured. The lowest concentration found to reduce rainbow trout growth when compared to controls was 0.2 mg/l. From this a NOEC of 0.1 mg/l can be derived according to the TGD.

However, there are some problems with this study: the water hardness of 580-725 mg/l $CaCO_3$ is much higher than normally employed in bioassays. In addition, the survival of rainbow trouts in the control is given as 181%. It is not clear why the survival is more than 100%.

The toxicity of phenol to embryo-larval and early-juvenile stages of *Pimephales promelas* was studied by Holcombe et al. (1982) in a 32-day flow-through test (temperature: 25°C, water hardness: 46 mg/l $CaCO_3$, pH: 7.2-7.9, mean dissolved oxygen: 7.7 mg/l). Eggs (< 24 hours after spawning) were exposed to phenol concentrations ranging from 240 to 3,570 µg/l.

At complete hatch the number of normal larvae was recorded and 25 normal larvae per concentration were further exposed for 4 weeks. Surviving fish were counted after 96 hours and then each week.

Hatchability and survival of fish was not significantly affected at the tested phenol concentrations. However, growth of the 28-day-old fish was significantly reduced at 3,570 µg/l, the highest concentration tested. A NOEC of 1.83 mg/l is resulting from this study.

Verma et al. (1981) studied the toxicity of phenol to 3 day old larvae of *Cyprinus carpio*. The larvae (about 8 mm in length) were exposed for 60 days in a semi-static system (renewal of test solution every 24 hours; pH: 7.2, T: 20-23°C, hardness: 60-88 mg/l). After the exposure period survival and growth were determined. A MATC of 110-130 µg/l was found.

With a similar test system 2 day old larvae of *Cirrhina mrigala* were exposed to phenol concentrations in the range of 44-175 µg/l for 60 days (pH: 7.2-7.4, T: 21-25°C, hardness: 70-74 mg/l). A MATC related to survival and growth of 77-94 µg/l was found (Verma et al., 1984).

Short-term toxicity to invertebrates

The short-term toxicity of phenol to different invertebrate species is given in the following table.

Table 3.16 Short-term toxicity of phenol to invertebrate species

Species	Duration	Effect value [mg/l]	Test system	Reference
Daphnia magna	24 hours	EC_{50} = 12 (nominal)	Static	Bringmann/Kühn 1982
Daphnia magna	24 hours 48 hours	EC_{50} = 29 EC_{50} = 12 (nominal)	Static	LeBlanc et al. 1980

Table 3.16 continued overleaf

Table 3.16 continued Short-term toxicity of phenol to invertebrate species

Species	Duration	Effect value [mg/l]	Test system	Reference
Daphnia magna	24 hours 48 hours	EC_{50} = 21 EC_{50} = 10 (nominal)	Static	Kühn et al. 1989
Daphnia mgana	48 hours	EC_{50} = 4.2-10.7 (measured)	Static	Lewis et al. 1983
Daphnia magna	48 hours	EC_{50} = 12.6 (measured)	Flow-through	Holcombe et al. 1987
Daphnia magna	48 hours	EC_{50} = 13		Cowgill/Milazzo 1991
Ceriodaphnia dubia/affinis	48 hours	LC_{50} = 4.3 (24°C) LC_{50} = 12.1 (20°C)		Cowgill et al. 1985
Ceriodaphnia dubia	48 hours	LC_{50} = 20		Cowgill/Milazzo 1991
Ceriodaphnia dubia	48 hours	LC_{50} = 3.1 (measured)		Oris et al. 1991
Asellus aquaticus	96 hours	LC_{50} = 180 (measured)	Flow-through	Green et al. 1985
Gammarus pulex	96 hours	LC_{50} = 69 (measured)	Flow-through	Green et al. 1985
Artemia salina (marine)	24 hours 48 hours	LC_{50} = 157 LC_{50} = 56 (nominal)	Static	Price et al. 1974
Baetis rhodani	96 hours	LC_{50} = 15.5 (measured)	Flow-through	Green et al. 1985
Palaemonetes pugio (marine)	48 hours 96 hours	LC_{50} = 11 LC_{50} = 5.8 (nominal)	Static	Tatem et al. 1978
Brachinonus rubens	24 hours	LC_{50} = 600		Halbach et al. 1983

In addition to the tests cited in the table above there are additional tests with mussels, snails, worms and insects. Most effect values found for these species are much higher (mussels: 59-1,000 mg/l, snails: 51-580 mg/l, worms: 32-1,080 mg/l, insects: 7-1,800 mg/l) than the effect values for daphnids.

The most sensitive species to phenol seem to be *Ceriodaphnia dubia* and *Daphnia magna*. The lowest effect value of 3.1 mg/l was found by Oris et al. (1991) for *Ceriodaphnia dubia*. Cowgill et al. (1985) and Cowgill and Milazzo (1991) found EC_{50} values for the same species ranging from 4.3 to 20 mg/l. For *Daphnia magna* 48-hour effect values are in the range from 4.2 to 13 mg/l.

For the further risk assessment the 48-hour LC_{50} of 3.1 mg/l is used as effect value for short-term toxicity of phenol to invertebrates.

The experimental EC_{50}-values (48 hours) for *Daphnia* are in reasonable agreement with QSAR estimations according to the TGD (1996) which results in a Daphnia (48 hours) EC_{50} of 23 mg/l for polar narcotic acting substances

Long-term toxicity to invertebrates

Deneer et al. (1988) investigated the long-term toxicity of phenol to *Daphnia magna*, using growth of the animals as test parameter. As growth reduction will generally result in a lowered reproductive output this endpoint is of high relevance.

Daphnia magna (< 24-hour-old) were exposed to different phenol concentrations for 16 days. They were fed green algae each day. Three times a week daphnids were transferred in new test solution and all newly born daphnids were removed. After 16 days the length from the top of the head to the end of the tail was measured using binoculars equipped with an ocular micrometer. An EC_{10}-value of 0.46 mg/l and an EC_{50}-value of 10 mg/l was found. The effect values are related to nominal concentrations.

Both Oris et al. (1991) and Masters et al. (1991) studied the toxicity of phenol in 4-day and 7-day tests with *Ceriodaphnia dubia*. Survival and reproduction were the measured endpoints. Masters et al. found chronic values (geometric mean of NOEC and FOEC) of 1.77 mg/l and 3.5 mg/l for reproduction and survival in the 4-day test and of > 5 mg/l for both endpoints in the 7-day test. Oris et al. give 4-day and 7-day chronic values of 4.9 mg/l for survival and reproduction.

The sensitivity of *Ceriodaphnia dubia* and *Daphnia magna* to phenol was examined by Cowgill and Milazzo (1991) using the three-brood test. Test parameters were survival, total progeny, number of broods and mean brood size. The following results are reported:

Table 3.17 Long-term toxicity of phenol to invertebrate species

Endpoint	*Ceriodaphnia dubia*	*Daphnia magna*
Survival	8-day LC_{50} = 9 mg/l 8-day NOEC = 0.84 mg/l	11-day LC_{50} = 4 mg/l 11-day NOEC = 0.5 mg/l
Progeny	EC_{50} = 7 mg/l NOEC = 6.5 mg/l	EC_{50} = 6 mg/l NOEC = 1.4 mg/l
Number of broods	EC_{50} = 10 mg/l NOEC = 6.5 mg/l	EC_{50} = 7 mg/l NOEC = 0.8 mg/l
Mean brood size	EC_{50} = 8 mg/l NOEC = 6.5 mg/l	EC_{50} = 7 mg/l NOEC = 3.9 mg/l

The lowest long-term effect value was found for *Daphnia magna* by Deneer et al. for growth reduction as test parameter. Although this parameter is not a standardised endpoint the EC_{10}-value of 0.46 mg/l will be used as long-term effect value for aquatic invertebrates.

Short-term toxicity to plants

The following table shows the available valid effect values obtained in tests with aquatic plants:

Table 3.18 Short-term algae toxicity data

Species	Duration	Effect value[mg/l]	Effect	Reference
Selenastrum capricornutum	96 hours	EC_{50} = 61.1 (37.1-84.5) (nominal)	Growth inhibition	St-Laurent et al. 1992
Selenastrum capricornutum	120 hours	EC_{50} = 67 (nominal)	Growth inhibition	Cowgill et al. 1989
Selenastrum capricornutum	96 hours	EC_{50} = 150 (nominal)	Growth inhibition	Shigeoka et al. 1988
Selenastrum capricornutum	8 days	EC_{50} = 7.5 (nominal)	Growth inhibition	Beaubien et al. 1986
Selenastrum capricornutum	14 days	IC_{10} = 93 IC_{50} = 175 (nominal)	Growth inhibition	Gaur 1988
Skeletomena costatum	120 hours	EC_{50} = 49.6 NOEC = 13 (nominal)	Growth inhibition	Cowgill et al. 1989
Chlorella vulgaris	96 hours	EC_{50} = 370 (nominal)	Growth inhibition	Shigeoka et al. 1988
Scenedesmus quadricauda	8 days	TGK*= 7.5 (nominal)	Growth inhibition	Bringmann/Kühn 1978
Microcystis aeruginosa	8 days	TGK* = 4.6 (nominal)	Growth inhibition	Bringmann/Kühn 1978
Lemna minor	7 days	EC_{50} = 171 NOEC = 5 (nominal)	Number of plants	Cowgill et al. 1991

* TGK: toxic threshold concentration, defined as 3% effect compared to the control

EC_{50}-values for different algal species are in the range from about 7.5 to 370 mg/l. The lowest effect value was found by Beaubien et al. in a study conducted over 8 days with the green algae *Selenastrum capricornutum*. Bringmann/Kühn measured the same value as 8-day TGK for *Scenedesmus quadricauda*. As the TGK is defined as 3% effect compared to the control, this value can be considered as a NOEC. For the blue-green algae *Microcystis aeruginosa* a TGK of 4.6 mg/l was found by Bringmann/Kühn. However, after 8 days the algae may not longer be in the exponential growth phase and this can have a negative influence on the test result. Therefore these very low effect values should be used with care. The lowest EC_{50} from a test with a standardised exposure time of 96 hours is 61.1 mg/l obtained in a test with *Selenastrum capricornutum* (St-Laurent et al., 1992).

Toxicity to microorganisms

The following table shows the effect values that are available for microorganisms.

Table 3.19 Microorganism toxicity data

Species	Duration	Effect value [mg/l]	Effect	Reference
Pseudomonas putida	16 hours	TGK[1)] = 64 (nominal)	Cell multiplication inhibition	Bringmann/Kühn 1977/1979
Pseudomonas putida	6 hours	EC_{10} = 15.1 EC_{50} = 244 (nominal)	Growth inhibition	Slabert 1986
activated sludge	15 hours	IC_{50} = 1,100 (nominal)	Inhibition of oxygen uptake	Blum/Speece 1991
methanogens	48 hours	IC_{50} = 2,100 (nominal)	Inhibition of gas production	Blum/Speece 1991
Nitrosomonas spec.	24 hours	IC_{50} = 21 (nominal)	Inhibition of ammonia consumption	Blum/Speece 1991
activated sludge, industrial	30 minutes	EC_{20} = 100 EC_{50} = 300 (nominal)	Respiration inhibition	Strotman et al. 1994
activated sludge, industrial	4-5 hours	EC_{20} = 450 EC_{50} = 880 (nominal)	Growth inhibition	Strotman et al. 1994
Entosiphon sulcatum	72 hours	TKG[2)]= 33 (nominal)	Growth inhibition	Bringmann/Kühn 1981
Uronema parduczi	20 hours	TGK[2)] = 144 (nominal)	Growth inhibition	Bringmann/Kühn 1981
Chilomonas paramaecium	48 hours	TGK[2)] = 65 (nominal)	Growth inhibition	Bringmann/Kühn 1981

1) TGK= toxic threshold concentration, defined as 3% effect compared to the control
2) TGK= toxic threshold concentration, defined as 5% effect compared to the control

Determination of $PNEC_{aqua}$

Long-term tests with species from three trophic levels are available for phenol. The most sensitive group were fish. The lowest effect value was obtained in an embryo-larval test conducted with *Oncorhynchus mykiss* (Birge et al., 1979). In this test an EC_{10}-value of 2 µg/l was calculated for hard water. The EC_{10} for soft water was 65 µg/l, showing a high dependence of the toxicity on the water hardness.

The very low effect value of 2 µg/l is supported by results from embryo-larval tests conducted by Black et al. (1982; 1983) using nearly the same test design. For *Oncorhynchus mykiss* an EC_{10}-value of 5 µg/l was calculated.

The effect values found by Birge and Black for several substances are usually very low compared to effect values found by other authors. No explanation for these large discrepancies could be found. A careful examination of the entire information provided by Birge et al. and Black et al. gave no plausible reason for the inconsistency of the data. Nevertheless it was

decided by the EU member states not to use these data for a derivation of a PNECaqua if other valid fish early life stage tests are available.

Also the effect values found by Black et al. for the amphibian species *Rana temporaria, Ambystoma gracile* and *Xenopus laevis* are not used for the effects assessment for the same reason. As there are no other tests with amphibians from other authors available, it cannot be excluded that amphibian species may be more sensitive to phenol than other aquatic species.

Without the data obtained by Birge and Black the lowest NOEC was found by Verma et al. (1984) for *Cirrhina mrigala.* A MATC of 77-94 µg/l is reported. With the assumption that the MATC is given as the range between the NOEC and the LOEC, a NOEC of 77 µg/l can be derived from this test. This NOEC is supported by MATC of 110-130 µg/l found by Verma et al. (1981) for *Cyprinus carpio* and by the NOEC of 100 µg/l reported by DeGraeve (1980) for *Oncorhynchus mykiss*.

For the derivation of the $PNEC_{aqua}$ an assessment factor of 10 is applied to the NOEC of 77 µg/l:

Therefore $PNEC_{aqua}$ = 77 µg/l / 10 =7.7 µg/l

Determination of $PNEC_{microorganism}$

From the various test results the lowest three are chosen to show the derivation of this PNEC. According to the different endpoints and sensitivities of the test systems the following assessment factors have to be applied:

Pseudomonas putida NOEC (6-hour)	= 15.1 mg/l	F = 1	⇒ PNEC = 15.1 mg/l
Entosiphon sulcatum NOEC (72-hour)	= 33 mg/l	F = 1	⇒ PNEC = 33 mg/l
Nitrosomonas spec. IC_{50} (24-hour)	= 21 mg/l	F = 10	⇒ PNEC = 2.1 mg/l
Activated sludge IC_{50} (0.5-hour) (Industrial)	= 300 mg/l	F = 100	⇒ PNEC =3 mg/l

As a worst case assumption a $PNEC_{microorganism}$ of 2.1 mg/l has to be used in the risk characterisation for waste water treatment plants.

Sediment

Not enough data are available on the occurrence of phenol in sediment (only one study). Neither are there any test results with benthic organisms. According to the physico-chemical properties currently known, there is nothing indicating that phenol accumulates in sediment. Therefore a quantitative risk assessment seems not to be necessary for this compartment.

3.2.2 Atmosphere

Data on biotic or abiotic effects in the atmosphere are not available. Because of the short half-life adverse effects are not to be expected.

3.2.3 Terrestrial compartment

For terrestrial organisms in the following only those test results are presented which were conducted with soil as substrate. The effect concentrations given in the references are corrected for a standard soil with a content of organic matter of 3.4%, where possible.

Lactuca sativa	14-day EC_{50}	149 and 408 mg/kg dry weight
	16-dayEC_{50}	14 mg/l (test with nutrient solution)
	20-day EC_{50}	20 mg/l (test with nutrient solution)

effect: growth inhibition; nominal concentrations, soil contained 1.8% and 1.4% organic matter (Hulzebos et al., 1993)

Eisenia foetida	14-day LC_{50}	136 mg/kg dry weight

soil contained 10% peat (Neuhauser et al., 1985, 1986)

Soil microorganisms	NOEC	> 100 mg/kg dry weight

effect: reduction of hydrogenase activity; content of organic matter not stated (Maas and Auspurg, 1984)

Determination of $PNEC_{soil}$

As for earthworms and plants only results from acute tests are available the assessment factor has to be set at F = 1,000.

Therefore $PNEC_{soil}$ = 136 µg/kg dry weight

For comparison, the $PNEC_{soil}$ is also derived via the equilibrium partitioning method according to the following equation:

$$PNEC_{soil} = \frac{PNEC_{aqua} \cdot K_{soil-water} \cdot 1{,}000}{RHO_{soil}}$$

With a $PNEC_{aqua}$ of 7.7 µg/l, a K_{soil_water} of 2.683 and a RHO_{soil} of 1,700 kg/m³ the $PNEC_{soil}$ is calculated to 12.15 µg/kg ww. This value is equivalent to about 13.8 µg/kg dw. Although this value is more than a factor of 10 below the $PNEC_{soil}$ based on experimental data, it is not used for the further assessment as experimental data for two trophic levels (plants and earthworms) are available and these data are more relevant for the assessment.

3.2.4 Secondary poisoning

As phenol has only a low bioaccumulation potential it is not required to carry out a risk characterisation for secondary poisoning.

3.3 RISK CHARACTERISATION

3.3.1 Aquatic compartment (incl. Sediment)

Waste-water treatment plants

Production and processing of phenol

A WWTP effluent concentration above the $PNEC_{microorganisms}$ of 2.1 mg/l results for 8 of 32 sites (PP5, PP6, Pc6, Pc10, Pc16, Pc18, Pc20, and Pc22). For these sites the calculations are based on default emissions and default WWTP flow rates of 2,000 m^3/day. Since the ratio of $Clocal_{effl}/PNEC > 1$, there is an indication of a risk to the microorganism population of the industrial WWTPs.

Site specific data are available for 24 of 32 sites and for those the WWTP effluent concentrations are lower than the $PNEC_{microorganisms}$ and the ratio of $Clocal_{effl}$ /PNEC are < 1. There is currently no indication of a risk to the microorganism population of these industrial WWTPs (for the individual sites see **Table 3.20**).

Results of risk characterisation for the waste-water treatment plants

Conclusion (iii).

This conclusion applies to the industrial WWTPs at sites PP5, PP6 Pc6, Pc10, Pc16, Pc18, Pc20 and Pc22. For all these sites the $Clocal_{eff}$ is based on default values and could possibly be lowered by site-specific and traceable exposure data. However, all sites had been contacted and did not provide the required information. Therefore, it is not expected to obtain exposure data for all these sites with reasonable efforts and time expenditure.

In principle, a further possibility would be to improve the data basis by performing a nitrification inhibition test with industrial sludge, which may be more realistic for the effect assessment for industrial WWTP. On the other hand, a $PNEC_{microorganism}$ of 3 mg/l can be derived from a respiration inhibition test with industrial activated sludge. Using this PNEC a risk for the same 8 sites has to be assumed. Therefore, even if from a nitrification inhibition test with industrial sludge a higher $PNEC_{microorganism}$ can be derived, the concern cannot be removed due to the result from the respiration inhibition test with industrial sludge.

Conclusion (ii).

This conclusion applies to all municipal WWTPs and industrial WWTPs at site P1 to P5, PP1, PP2, PP3, PP4, PP7, Pc1, Pc2, Pc4, Pc5, Pc7, Pc8, Pc9, Pc11, Pc12, Pc13, Pc15, Pc19, Pc21 and Pc24 (24 of 32 sites, see **Table 3.20**).

Use of products containing phenol

For the release of phenol from processing and use of binders $C_{effluent}$ of 21.41 µg/l and 35 µg/l were estimated. Both values are below the $PNEC_{microorganism}$ of 2.1 mg/l.

Conclusion (ii).

Aquatic environments

Production and processing of phenol

A regional background concentration of 2.41 µg/l for phenol in the hydrosphere is calculated based on all releases of phenol into the environment (see Section 3.1.6). This background concentration is added to the $Clocal_{water}$ calculated in Section 3.1.2, thus obtaining the PEC_{local} concentrations for the individual point sources.

The data for the calculation of the $Clocal_{water}$ and the PEC/PNEC ratio for each individual company where phenol is produced and/or processed are summarised in **Table 3.20**. In the calculations it was assumed that all companies are connected to an in-house biological waste-water treatment plant. This means that considerably higher water concentrations have to be expected if individual companies release their waste water directly into the receiving stream as direct discharges.

Table 3.20 Site specific PEC/PNEC ratios for the aquatic compartment

Site	Site specific exposure data[1)]	Elimination in WWTP	Volume flow of WWTP[2)]	Dilution or river flow[3)]	$Clocal_{effl}$ / $PNEC_{microorg.}$	$PEClocal_{water}/PNEC_{aqua}$	Remark
Production							
P1	available	SimpleTreat	site specific	site specific	0.005	0.33	
P2	available	SimpleTreat	site specific	site specific	0.15	0.32	
P3	available	SimpleTreat	site specific	default	0.004	0.41	Emission to the sea
P4	available	SimpleTreat	default	default	0.08	0.32	
P5	available	SimpleTreat	site specific	default	0.48	0.37	
Production and Processing							
PP1	available	SimpleTreat	site specific	site specific	0.25	0.38	
PP2	available	SimpleTreat	site-specific	default	0.05	1.8	Emission to the sea
PP3	available	SimpleTreat	site specific	default	0.03	0.52	
PP4	available	SimpleTreat	site-specific	default	0.02	0.31	
PP5	not available	SimpleTreat	default	default	5.00	0.84	
PP6	available	SimpleTreat	site specific	site specific	6.33	0.34	
PP7	available	SimpleTreat	site specific	default	0.005	0.44	Emission to the sea
Processing							
Pc1	available	site specific	site specific	site specific	0.005	0.31	
Pc2	available	site specific	site specific	site specific	0.03	0.32	
Pc3	/	/	/	/	/	/	Trading company only, no processing
Pc4	available	SimpleTreat	site specific	site specific	0.0002	0.31	
Pc5	not available	SimpleTreat	site specific	site specific	0.03	0.37	
Pc6	not available	SimpleTreat	default	default	4.20	0.75	

Table 3.20 continued overleaf

Table 3.20 continued Site specific PEC/PNEC ratios for the aquatic compartment

Site	Site specific exposure data1)	Elimination in WWTP	Volume flow of WWTP2)	Dilution or river flow3)	Clocaleffl / PNECmicroorg.	PEClocalwater/PNECaqua	Remark
Pc7	available	SimpleTreat	site specific	site specific	0.02	0.32	
Pc8	available	site-specific	site-specific	default	0.12	0.33	
Pc9	available	SimpleTreat	site specific	default	0.24	0.38	
Pc10	not available	SimpleTreat	default	default	3.50	0.68	
Pc11	available	site specific	site specific	site specific	0.06	0.33	
Pc12	available	SimpleTreat	site specific	site specific	0.05	0.63	
Pc13	available	SimpleTreat	default	default	0.01	0.31	
Pc14	/	/	/	/	/	/	No processing
Pc15	available	site-specific	site-specific	site-specific	0.05	0.32	
Pc16	not available	SimpleTreat	default	Default	3.50	0.68	
Pc17	/	/	/	/	/	/	Trading company only, no processing
Pc18	not available	SimpleTreat	default	Default	3.50	0.68	
Pc19	available	/	/	/	/	/	No emission of wastewater
Pc20	not available	SimpleTreat	default	Default	2.38	0.56	
Pc21	available	/	/	/	/	/	No emission of wastewater
Pc22	not available	SimpleTreat	default	default	3.50	0.68	
Pc23	/	/	/	/	/	/	Import only, no processing

Table 3.20 continued overleaf

Table 3.20 continued Site specific PEC/PNEC ratios for the aquatic compartment

Site	Site specific exposure data1)	Elimination in WWTP	Volume flow of WWTP2)	Dilution or river flow3)	Clocaleffl / PNECmicroorg.	PEClocalwater/PNECaqua	Remark
Pc24	available	/	/	/	/	/	No emission of wastewater
Pc25	/	/	/	/	/	/	Trading company only, no processing

1) If no site specific and/or not traceable data on exposure were available, the default values from the TGD were used (see Table 3.1)
2) The default value is 2,000 m^3/day.
3) The default value is D = 10 for emission to the sea or the river flow is 60 m^3/s.

Taking into consideration the PNECaqua of 7.7 µg/l, there is only one site (PP2) for which a PEC/PNEC ratio above 1 (1.8) is calculated. The calculation is based on site-specific emissions into the WWTP, site-specific volume of the WWTP and default elimination rates and dilution factor. However, there are indications from non-representative measured effluent concentrations of this site that the actual emissions may be significantly lower than the estimated concentrations. In addition, the default dilution factor of 10 applied for releases into the sea is considered a conservative approach. As a weight of evidence, it can therefore be concluded that there is not an unacceptable risk arising from this site and that there is no need for further information and/or testing.

Use of products containing phenol

A PEClocal of 4.51 µg/l is estimated for the release of phenol from processing of binders. A PEC/PNEC ratio of 0.59 is resulting for this scenario.

For the release of phenol from the use of binders a PEClocal of 5.91 µg/l was roughly estimated. A PEC/PNEC ratio of 0.77 is resulting for this life-cycle step.

Sediment

A sediment concentration of approximately 0.0073 mg/kg phenol results from the estimation of exposure for the processing of phenol at a typical company (90^{th} percentile of the local concentrations from **Table 3.8**).

Since no effect values for sediment-dwelling organisms are available, it is not possible to perform a quantitative risk assessment for this compartment. But considering the low adsorption potential of phenol, the risk assessment for surface water covers also the sediment compartment.

Results of risk characterisation for the aquatic environment (incl. Sediment)

Conclusion (ii).

This conclusion applies to all sites that produce and/or process phenol (see **Table 3.20**) as well to the scenarios processing and use of binders containing phenol.

3.3.2 Atmosphere

On account of the atmospheric half-life ($t_{1/2}$ = approximately 42 minutes), abiotic effects on the atmosphere, such as global warming and ozone depletion, are not to be expected in the case of phenol.

The calculated concentration in air amounts to 18 µg/m^3 for a typical company (90^{th} percentile of the local concentrations from **Table 3.11**). In consideration of all known sources, a regional air load of 0.026 µg/m^3 results for phenol. Since no data are available on the ecotoxicological effect of the substance through exposure via air, it is not possible to carry out a quantitative assessment for this compartment. Considering the low atmospheric half-life of phenol and that there are no indications of specific toxicity in plants, the performance of further tests is not considered necessary.

Results of risk characterisation for the atmosphere

Conclusion (ii).

3.3.3 Terrestrial compartment

Releases into the terrestrial compartment are to be expected as a result of deposition from the atmosphere and the spreading of sewage sludge on soils, which are used for agriculture. The deposition rate results from the calculations for a typical company (90^{th} percentile of the local concentrations from **Table 3.11**) as well as from further diffuse releases into the atmosphere. The daily deposition rate amount to 0.026 mg/m^2 · day. If there is no spreading of sewage sludge on the soil in the immediate vicinity of a typical company (90^{th} percentile of the local concentrations from **Table 3.11**, at site Pc19), a soil concentration (arable soil) of 1.35 µg/kg soil or a soil pore water concentration of 0.85 µg/l result from the deposition rate of 0.026 mg/m^2 · day

With regard to phenol in the soil, a regional background concentration of 0.59 µg/kg is calculated from all of the releases of phenol into the environment (see Section 3.1.6). This background concentration relates to soils that are not contaminated as a result of the spreading of sewage sludge or are not located in the immediate vicinity of a point source (production/processing of phenol).

In consideration of the $PNEC_{soil}$ of 136 µg/kg, a PEC/PNEC < 1 results for soils without direct entry of phenol (i.e. without the spreading of sewage sludge), and a risk to terrestrial organisms is not to be expected. (For agricultural soil subjected to fertilisation with sewage sludge see Section 3.3.5).

Groundwater

The ground water concentration can be calculated in accordance with the TGD as the soil pore water concentration under the agriculture soil. For a typical company (90^{th} percentile of the local concentrations from **Table 3.11**, at site Pc19) and the use of sewage sludge with a concentration of 1.69 mg/kg (dry weight) soil pore water concentration of 0.94 µg/l is calculated. With an odour and taste threshold value of 1 µg/l for drinking water proposed by the Federal Environmental Agency of Germany, no risk for this compartment has to be assumed.

Results of risk characterisation for the terrestrial environment

Conclusion (ii).

This conclusion applies to all emission scenarios.

3.3.4 Secondary poisoning

As phenol has only a low bioaccumulation potential it is not required to carry out a risk characterisation for secondary poisoning.

3.3.5 Unintentional releases

Phenol is eliminated by humans as a product of metabolism in the urine and faeces. For this assessment it is assumed that a person eliminates about 40 mg phenol per day via the urine.

Waste Water treatment plants

A WWTP effluent concentration of 0.0252 mg/l results for the continuous release of phenol into the environment via municipal WWTPs.

In consideration of the $PNEC_{microorganisms}$ of 2.1 mg/l, a ratio of $Clocal_{effl}$ /PNEC of 0.012 results for the diffuse source of release of phenol as a product of human metabolism via municipal WWTPs. Since the ratio of $Clocal_{effl}$ /PNEC < 1, there is currently no indication of a risk to the microorganism population of the municipal WWTPs.

Conclusion (ii).

Aquatic compartment

In the case of the release of phenol as a product of human metabolism, water concentrations of 22.57 µg/l results for direct discharges of municipal waste water into a receiving stream and 5.1 µg/l for indirect discharges into the receiving stream via municipal WWTPs (see Section 3.1.3.4). With regard to Europe it is assumed that approximately 70% of the population release their waste water into the receiving stream via municipal WWTPs and that 30% discharge directly into a receiving stream.

Taking into consideration the $PNEC_{aqua}$ of 7.7 µg/l, a PEC/PNEC ratio > 1 results for the direct discharges of phenol as a product of human metabolism without purification of the municipal waste water in a biological treatment plant. However, this emission path is not the subject of this risk assessment, but further investigations, i.e. measurement of the phenol content in the influent of municipal WWTPs or in untreated municipal waste water and/or monitoring of the phenol content in streams of direct discharges should be considered by the responsible authorities.

It was not possible to provide an estimation of exposure for the aquatic environment with regard to the areas relating to the coking, gasification and liquefaction of coal, refineries and pulp manufacture (see Section 3.1.3.4).

It was not possible to estimate the exposure to the aquatic environment from landfills without landfill leachate collecting system (see Section 3.1.3.4).

Conclusion (i).

Atmosphere

There are considerable unintentional diffuse sources for the release of phenol into the atmosphere (see Section 3.1.3.2). Although these releases are not subject of this risk assessment, they had to be considered to derive a realistic background concentration.

A regional background concentration of 0.026 µg/m^3 in the atmosphere is calculated from all of the releases of phenol into the environment (see Section 3.1.6). From the qualitative risk characterisation (see Section 3.3.2) it can be concluded that no unacceptable risk for the atmosphere arises from diffuse emissions of phenol.

Conclusion (ii).

Terrestrial compartment

Releases into the terrestrial compartment are to be expected as a result of spreading of sewage sludge on soils, which are used for agriculture. The sewage sludge concentration (1.69 mg/kg

dry weight) results from the release of phenol into the municipal waste water as a product of human metabolism (see Section 3.1.3.4). The resultant soil concentrations (arable soil; 30 days after the spreading of sewage sludge) for phenol amount to 0.0021 mg/kg or 0.0013 mg/l soil pore water, if both sewage sludge application as well as deposition is considered. For the spread of liquid manure derived from livestock farming over agricultural areas it is not possible to estimate a total release to soil due to insufficient data (see Section 3.1.4.2).

In consideration of the $PNEC_{soil}$ of 136 µg/kg, a PEC/PNEC ratio < 1 results for soils on which sewage sludge is spread.

Conclusion (ii).

Phenol may enter the soil as a result of the spreading of liquid manure from livestock farming. For the spread of liquid manure derived from livestock farming over agricultural areas it is not possible to estimate a total release to soil (see Section 3.1.4.2).

It was not possible to estimate the exposure to the terrestrial environment from landfills without landfill leachate collecting system (see Section 3.1.3.4).

Conclusion (i).

4 HUMAN HEALTH

4.1 HUMAN HEALTH (TOXICITY)

4.1.1 Exposure assessment

4.1.1.1 General discussion

Phenol is mainly (about 100%) used as a chemical intermediate in synthesis. Approximately 65% of the produced phenol is processed further to organic chemicals for example, to bisphenol A, caprolactam, salicylic acid, diphenyl ether, alkyl phenols, nitrophenols and other chemicals. About 30% is used to manufacture phenolic resins and a non-quantifiable part serves as a component in cosmetics and medical preparations. In Germany, phenol is no longer used as a disinfection component in laundry, cleaning, scouring and care agents (Industrieverband, 1996).

Use of phenol-containing disinfectants, antiseptics, medicinal products, cosmetics, paints, floor waxes, polishes etc., and other consumer products or application of phenol-formaldehyde resins (IARC, 1989) may result in dermal and/or inhalatory exposure of consumers to unbound phenol. Further exposure scenarios are described in Section 3.1.2.2.

For workers the inhalation and dermal routes of exposure are likely to occur.

4.1.1.2 Occupational exposure

Industrial activities using phenol present opportunities for occupational exposure. Exposure ranges depend on the particular operation and the risk reduction measures in use.

The following occupational exposure limits are applied for phenol (ARIEL 2002):

Table 4.1 8-hour time weighed average (8-hour TWA)

FIN, SP, UK	20 mg/m^3
D, B, F, CH, US (NIOSH/OSHA AGGIH)	19 mg/m^3
NL	8 mg/m^3
AU, IR, IT	7.8 mg/m^3
S, DK, NO	4 mg/m^3

Table 4.2 Short-term exposure levels (STEL)

FIN, UK	39 mg/m^3
D, CH	19 mg/m^3
S	8 mg/m^3

General

The exposure assessment generally aims at assessing exposure levels representing the reasonable worst-case situation. The reasonable worst case is regarded as the level of exposure which is exceeded in a small percentage of cases over the whole spectrum of likely circumstances of use for a specific scenario.

The assessment of inhalation exposure is mainly based on measured exposure levels from which, if possible, 90th or 95th percentiles are derived as representing reasonable worst case situations. For the purpose of exposure assessment only data measured later than 1990, if available, are taken. If quantitative exposure data are not available, model estimates are taken. Scenarios are clustered as far as possible to make the description transparent.

Beside inhalation exposure, dermal exposure is assessed for each scenario. Two terms can be used to describe dermal exposure:

Potential dermal exposure is an estimate of the amount of a substance landing on the outside of work wear and on the exposed skin.

Actual dermal exposure is an estimate of the amount of a substance actually reaching the skin.

There is an agreement between the EU-member states, within the framework of existing substance, to assess, as a rule, dermal exposure as exposure to hands and parts of the forearms. In this, the main difference between both terms, potential and actual, is the protection of hands and forearms by work wear and, more importantly, the protection by gloves. Within this exposure assessment, the exposure reducing effect achievable by gloves is only considered if information is provided, that for a certain scenario gloves are a widely accepted protective measure and that the gloves are fundamentally suitable for protection against the substance under consideration. As a measure for the latter, tests according to DIN EN 374 are taken as a criteria. For most down stream uses it is commonly known, that gloves are not generally worn. In these cases, dermal exposure is assessed as actual dermal exposure for the unprotected worker. In case of substances and preparations classified as corrosive, the experience of skin damage due to the corrosive properties of a substance leads to reduced dermal exposure. For phenol, the situation is more complex: beside the corrosive properties, phenol has local anaesthetic properties; therefore afflicted persons described reduced experience of pain after dermal contact.

According to the revised TGD (Technical Guidance Documents), for classified corrosives, it is not necessary to assess the risk from repeated dermal exposure (only occasional exposure). If, during the use of the corrosive substance or formulation diluting/mixing occurs which results in a substance or formulation which has no corrosive properties then dermal exposure should be taken into account, i.e. repeated dermal exposure cannot be neglected.

Since often quantitative information on dermal exposure is not available, the EASE model is mostly used for assessing dermal exposure.

Exposure scenarios

Exposure to phenol is to be expected during the handling of pure phenol and phenolic resins. In the case of phenolic resins phenol is released especially during the hardening process at elevated temperatures (≤ 180°C). The following scenarios are regarded to be relevant for occupational exposure:

Scenario 1: Production and further processing as a chemical intermediate (see Section 4.1.1.2.1)
Scenario 2: Production of phenolic resins (see Section 4.1.1.2.2)
Scenario 3: Use of phenolic resins (see Section 4.1.1.2.3)

The exposure as a result of phenol vapours from cosmetic products and medical preparations at room temperature is assessed as low due to the relatively low vapour pressure of the pure substance itself (20 Pa), the low concentration of phenol (< 2% phenol) and the circumstance, that works with aerosols and processes at elevated temperatures are not probable.

4.1.1.2.1 Production and further processing as a chemical intermediate (Scenario 1)

Today phenol is produced almost predominantly by oxidation of cumene with air or oxygen-enriched air to cumene hydroperoxide and a following acid-catalysed cleavage to phenol and acetone. Finally the reaction mixture is worked up by distillation. In addition, during the processing of coal tar, after the primary distillation phenol occurs continuously in several fractions which are processed by means of extraction, refining, precipitation and distillation (Collin et al., 1995). A multi-stage, continuous process, for which closed process technology is also assumed, is involved here. For filling processes of pure phenol it is assumed, that the molten form is handled at 70°C (melting temperature 40.9°C).

As a rule, the production and further processing of phenol takes place continuously in closed plant. The substance as such is placed on the market in a solid and a molten form as well as an aqueous solution.

Exposure of workers to vapours of the pure phenol is to be expected during weighing and metering, sampling, the analysis of samples, drumming as well as during cleaning, maintenance and repair work.

Inhalation exposure

Workplace measurements

The results which have been submitted in connection with workplace measurements performed in the area of production are presented in the following table separately according to shift averages and short-term values.

Table 4.3 Phenol exposure at workplaces during production and further processing (scenario 1)

Work area / activities	Years of measurements	Number of measurements	Range of measured values [mg/m³]	Median [mg/m³]	90th percentile [mg/m³]	Duration and frequency
8-hour TWAs						
Sampling and sample analysis during processing by distillation	1988 1989	4 3	0.3-1.5 0.5-0.6	--- ---	--- ---	--- ---
Loading (not specified further)	1988	4	1.0-4.4	---	---	---
Production	1997 1997 1990 ---	24 116 1 ---	0.04-1.0 0.003-0.45 0.85 < 0.39	--- --- --- ---	--- --- --- ---	--- --- --- ---
Distillation of coal tar	1984	11	0.4-10.3	2.56	---	---
Processing	1997 1997 1995 1995	4 20 14 69	0.04-0.4 0.0008-0.008 < 0.4 < 0.4-1.2 (s)	--- --- --- < 0.4	--- --- --- ---	--- --- --- ---
Filling	1990	1	0.05	---	---	---
Chemical industry	1990-1993	107	max: 19 (p)	0.5 (50th percentile)	3.3	---
Short term values						
Sampling during distillation	1988	6	0.16-9.6	---	---	5 minutes
Loading, connection of a tanker	1988	5	< 0.9	---	---	5 minutes
Disconnection of a tanker and sampling	1988	5	0.8-17.8	---	---	5 minutes
Repair work (exchanging a defective pump)	1988	2	0.4; 0.5	---	---	6 minutes; 17 minutes
Truck loading	1994/95	8	0.2-2.5 (p) 0.2-59 (s)	0.6 0.4	--- ---	--- ---

P Personal sampling
S Stationary sampling

The measuring results which were submitted by industry are to be regarded as valid. The sampling and analytical procedure as well as the workplaces, activities and duration of exposure are essentially described. Since 2 of 3 producers and users submitted measurement results which cover different activities, the measurement results are regarded to be representative for the Scenario 1.

According to information provided by a German manufacturer, in observance of the Hazardous Substances Ordinance which applies in the Federal Republic of Germany, sampling is performed using personal protective equipment comprising face protection, long-sleeved gloves and work shoes. If greater amounts of phenol may escape, work is performed employing the extended range of personal protective equipment comprising PVC suit, rubber boots, face protection, long-sleeved gloves and, where necessary, a compressed-air breathing set.

Based on the available measurement results, 3.3 mg/m^3 (90th percentile of a collective of measured results with highest exposure level) is regarded to represent a reasonable worst-case situation for all activities during production and further processing in the chemical industry. In addition, the short-term value 17.8 mg/m^3 (sampling time 5 min) obtained during tanker filling is taken for assessing inhalation exposure.

Conclusions

Inhalation exposure has to be assessed for the production and further processing of phenol in the large-scale chemical industry.

For the assessment of health risks of daily inhalation exposure 3.3 mg/m^3 (90th percentile of a measurement collective) should be taken to represent a reasonable worst case situation. For short term exposure, 17.8 mg/m^3 (sampling time 5 minutes) obtained during tanker filling should be taken for assessing exposure.

Dermal exposure

When producing and further processing phenol dermal exposure could occur during activities like drumming, bagging, sampling, cleaning, maintenance and repair work. Due to the corrosive effect of phenol and of its preparations (classified as corrosive for concentrations ≥ 3%); dermal exposure is limited to occasional skin contacts.

Liquid phenol is transported and drummed at elevated temperature due to its melting point of 40.9°C (assumed temperature: ≥ 70°C). In this, worker will avoid repeated skin contact and dermal exposure is reduced to accidental contacts.

For the assessment, bagging of corrosive solid phenol is regarded to be the activity with highest dermal exposure. For the unprotected worker, according to the EASE model, potential dermal exposure is assessed as follows:

Input parameters:	Non dispersive use, direct handling, incidental
Level of exposure:	0-0.1 mg/cm^2/day.

Considering an exposed area of 210 cm^2 (half of the palms of both hands) the model yields an exposure level of 2.1-21 mg/person/day. A rather small skin area is taken because of the corrosive effect of phenol. The upper value is regarded to represent the reasonable worst case situation.

Conclusion

For the production of liquid phenol, due to the high melting temperature of the substance of 40.9°C, dermal exposure is limited to accidental situations. In case of the handling of solid phenol, dermal exposure is assessed in consideration of the corrosive effect of phenol for the assessment; bagging of the solid is regarded to be the activity with highest dermal exposure. The assessment of dermal exposure yields to 21 mg/person/day (non-daily exposure).

Exposure to the eyes is largely avoided by using eye protection.

4.1.1.2.2 Production of phenolic resins (Scenario 2)

Gardziella (1979) describes the production, modification and processing of phenol formaldehyde resins (novolaks, resols) and modified phenolic resins as performed in closed plant. As a rule, resols remain liquid and are drummed at temperatures < 25°C (Bakelite AG, 1996). In case of novolaks, the production comprises the mixing of the components, melting and homogenisation at elevated temperatures (100-200°C), cooling and milling to granules or powders. Continuous processes are used in the production of large amounts (e.g. resols for wood materials); in the case of relatively small amounts, discontinuous modes of working are mainly appropriate due to the great variety of types involved (Gardziella, 1979). As a rule, resols contain higher percentages of free phenol (up to 15%) than novolaks (Vianova Resins, 1995). For all assessments for novolaks and resols, a concentration of 15% is taken as the basis.

According to information from CEFIC 50 companies produce phenolic resins in Europe (CEFIC 1996). There is no typical company but small, medium and large companies are involved. Detailed information on the technical realisation of the processes is not available. In SRI (1993) it is described that 100 companies produce phenol resins in Western Europe. Since for the production of resins often formaldehyde is used it is to be assumed that the workplaces are designed to observe the occupational exposure limit (OEL) of formaldehyde (Germany: 0.5 mg/m³). Since to a lesser extent, also other aldehydes are used, it is assumed, that beside companies with high levels of protection also companies with lower level of protection produce phenolic resins.

Based on the information available, it is concluded that the typical exposure situation is similar to the production and further processing of phenol as described in Scenario 1. As described above, possible lower levels of protection may lead to higher exposure levels representing the reasonable worst case situation of Scenario 2.

Exposure of workers to vapours of phenol is to be expected during filling, transfer, sampling, drumming as well as during cleaning, maintenance and repair work. The produced resins with phenol contents up to 15% are an additional source of exposure, e.g. when they cool down at elevated temperature outside the closed systems.

Inhalation exposure

Workplace measurements

Only limited exposure measurements on the production of resins is available. One company submit measurement results from 1997 (n = 10) with a range of 0-1.2 mg/m³ (mean: 0.1 mg/m³, 90th percentile 0.4 mg/m³). The duration of the measurement is not mentioned.

EASE estimation

EASE for Windows 2.0, Aug. 1997 was used.

EASE estimation for the production of phenolic resins. Exposure situation a) is regarded to be representative for works before and during the reaction since phenol can be released if the closed system is breached.

a)	Input parameters:	T = 60°C, closed system, significant breaching, LEV present
	Level of exposure:	2-3.9 mg/m^3 (0.5-1.0 ppm).

Similar exposures are obtained if it is assumed that solid phenol is used (LEV present):

b) Exposure to dust
Input parameters: T = 20°C, exposure-type is dust, dry manipulation, LEV present
Level of exposure: 2-5 mg/m^3

Exposure situation c) with the control pattern "segregation" is assumed to represent working situations when the resin containing up to 15% phenol cools down or granules are produced. The temperature of 80 °C is chosen as representing the temperature of the heated resins when cooling down.

c) Input parameters: T = 80°C, non-dispersive use, segregation, (vapour pressure 515 Pa at 80°C)
Level of exposure: 20-39 mg/m^3 (5-10 ppm).

A comparison of the estimates of the exposure situations (a-c) reveals that inhalation exposure is determined by situation c).

Taking into account the vapour pressure of phenol (515 Pa at 80°C) located at the lower range of the volatility class of 500-1,500 kPa, it is assumed that the exposure is at the lower end of the estimated range (20 mg/m^3). In view of the low content of phenol in the resins, exposure might be lower due to the reduced partial vapour pressure of phenol. This depends on the composition of the resin, especially on other volatile substances.

Conclusions

Inhalation exposure has to be assessed for the production of phenolic resins for the typical case as well as for the reasonable worst case situation.

Measured data are only available from one company which is probably not representative for all companies producing resins. Therefore, exposure is estimated by means of the EASE model. For the assessment of health risks from daily inhalation exposure to phenol during the production of phenolic resins an 8-hour time weighed average concentration of 20 mg/m^3 (EASE estimate, expert judgement) should be taken. It should be considered that the typical value is expected to be considerable lower. If the level of protection is similar to the situation described in Scenario 1 for the production of phenol, the typical value is expected to be in the range of 3 mg/m³ (reasonable worst-case for Scenario 1).

Dermal exposure

For the large scale production of resins, it is assumed that automated processes are employed. In this, worker load the bags on conveyer belts. The further steps, opening and emptying the bags are performed automatically. But beside the large scale production, also smaller amounts of special resins are produced. In this, phenol is manually dumped into reaction vessels. Due to the corrosive effect of phenol and its preparations (≥ 3%), workers avoid daily dermal exposure and skin contacts are limited to occasional events:

Input parameters: Non dispersive use, direct handling, incidental
Level of exposure: 0-0.1 mg/cm^2/day.

Considering an exposed area of 210 cm^2 (half of the palms of both hands) the model yields an exposure level of 2.1-21 mg/person/day. A rather small skin area is taken because of the

corrosive effect of phenol. The upper value is regarded to represent the reasonable worst-case situation.

For bagging resins not labelled as corrosive (< 3% phenol) the corresponding dermal exposure is assessed based on literature data summarised in the revised TGD (Annex 1E) as follows: The field study includes manual dumping of calcium carbonate (several grades) from bags of into paint mixers in ten paint producing facilities (n = 19; Lansink et al., 1996). Calcium carbonate is a relatively dusty powder. The dumping lasted for 1-15 minutes and 2-24 bags, containing 10-1,000 kg calcium carbonate were dumped. Local exhaust ventilation was generally used during dumping. Bags were cut open using a knife and the powder was allowed to flow into the mixer. Exposure is due to direct contact with the flow of powder, deposition of the dust and contact with contaminated surfaces, including the outside of the bags. These values are based on only one study (though in ten facilities) and they may therefore be less representative for the scenario than the other values. For manual dumping of powders a reasonable worst case estimate of 3,000 mg/person was derived (exposed skin surface area: 1,600 cm²). Taking into account a phenol content of 3%, dermal exposure amounts to 90 mg/person/day. Because calcium carbonate is a relatively dusty powder, dermal exposure to phenol might be lower. For the corresponding duration of dermal exposure, it is assumed that manual dumping can be performed during the whole shift.

Conclusions

For assessing the health risks of daily dermal exposure, handling corrosive phenol and corrosive resins (≥ 3% phenol) as well as bagging non-corrosive resins have to be taken into consideration. In the first case (corrosive substance and preparation) non-daily dermal exposure is assessed to 21 mg/person. For bagging non-corrosive resins (< 3% phenol) an exposure level of 90 mg/person should be taken as representing the reasonable worst case situation of repeated daily exposure. This exposure assessment is based on the assumption that gloves are not worn. For the purpose of risk assessment, the higher level of 90 mg/person is taken forward.

It cannot be presupposed that eye protection is regularly used. For assessing the risks, hand eye contacts as well as possible splashes to the eye should be considered.

4.1.1.2.3 Use of phenolic resins (Scenario 3)

From a chemical point of view, phenol resins (in the main phenol formaldehyde resins) can be subdivided, inter alia, into the acid and heat reactive resols and the thermoplastic novolaks. Resols may include percentages of free phenol ranging from < 1% to approximately 15%. In the case of the novolaks, the cross-linking to the hardened product is achieved through the addition of a hardener (mostly hexamethylene tetramine) at temperatures < 180°C, in the case of resols, through the addition of an acid or under the influence of heat (Bakelite-Phenolharze, 1993). During the hardening process the free phenol is in part chemically bound, in part released. The resins are used as liquids, in powdery form or as granules. The content of phenol in resins is up to 15%.

Resins are used:

- as moulding materials for plastic articles,
- as adhesives and impregnating resins for wood materials,
- as binders for insulating materials for car construction and house building,

- as impregnating resins,
- as core sand and moulding sand binders in foundries (use of resols, e.g. during “hot-box” and “no-bake” processes),
- as binders for coated abrasives,
- as binders for friction materials (brake and clutch linings),
- as binders for paints (anticorrosive primers, inner can coatings),
- as binders for single-package contact adhesives (nitrile-butadiene rubber adhesives, rubber/ metal bonds and sealing compounds) and
- in acid-protection construction in chemical-resistant cements and laminates and apparatus engineering (e.g. gas scrubbers, acid towers).

As a rule, resols contain different amounts of free phenol (up to approximately 15%). For some applications, the phenol content of the resols is known

- resols used in foundries contain up to 4.5% free phenol,
- phenolic resols for paper filters and laminates for the electrical engineering industry contain up to 6% free phenol,
- resols for the production of coated abrasives contain up to 8%,
- resols used for paints (protection against corrosion, inner can coatings) up to 10%
- and resols for friction materials in particular for clutch linings up to 14%

Exposure of workers to vapours is assumed to occur during the mixing of phenol-containing preparations and in the processing of resins at elevated temperatures. It is to be assumed that not every plant is equipped with suitable technical ventilation systems.

In addition, dermal exposure through immediate skin contact during the handling of phenolic resins is considered.

Inhalation Exposure

Workplace measurements

Measurements in the further-processing industry relating to the data-acquisition period 1990-1995 were evaluated by the BGAA (Berufsgenossenschaften`s working group on existing commercial chemicals, directed by the Berufsgenossenschaft for the chemical industry working group of the Workers´ Compensation Fund for the chemical industry). Here, activity-related measurement results with exposure duration > 1 hour were brought together from various branches. Shift averages are clustered in consideration of work areas and processes. The data are represented in a differentiated manner according to the technical ventilation systems. 40% of these measurement results were derived from personal sampling. In part, similar 8-hour TWA were measured at workplaces with and without LEV (local exhaust ventilation) (see **Table 4.4**). For a better understanding, it should be kept in mind, that occupational exposure levels at similar workplaces depend inter alia on the level of technical protection (here: LEV) and on the amount of the substance in use. Often, if the handling of large amounts of a substance is required, workplaces are equipped with LEV, whereas workplaces at which small amounts are handled are possibly not equipped with LEV. This circumstance might lead not only to similar exposure

levels at workplaces with and without LEV but also to the situation, that exposure is higher at workplaces with LEV than at those without LEV.

The measured results which are submitted are to be regarded as valid. The sampling and analytical procedures, as well as the activities, are essentially described.

Table 4.4 Phenol exposure at different workplaces

Job category / activities	Years of measure-ment	Number of samples (number of premises)	Technical measures	50th percentile [mg/m³]	90th percentile [mg/m³]	95th percentile [mg/m³]
8-hour TWA						
Processing of phenolic resins in the plastics processing and woodworking industries [1]	1990-1995	329 (136) 196 (91) 128 (56)	In total no LEV LEV	[2]	1.0 1.0 1.0	1.3 2.0 1.0
Processing of phenolic resins in foundries, levels above the 90th percentile during manufacture of cores [1]	1990-1995	236 (98) 98 (47) 158 (65)	In total no LEV LEV	[2]	2.0 2.0 1.1	2.9 2.0 3.0
				Range	Geom. mean	---
Aluminium foundries	1992-1995	61 (s,p)	---	< 0.04-2.1	0.1	
Aluminium sand foundries:						
moulding		5	---	0.14-0.5	0.3	
core making		7	---	0.06-0.3	0.1	
pouring		8	---	< 0.04-0.3	0.1	
shake out [3]		5	---	< 0.09-2.1	0.7	
Aluminium static die casting:						
core making		8	---	0.05-0.12	1.4	
static die casting		10	---	0.1-0.7	2.0	
core knock out [3]		2	---	0.08, 0.09	0.09	
Mechanical machining processes [1]	1990-1995	76 (41) 36 (18) 35 (23)	In total no LEV LEV	[2]	1.0 [1] 0.8	1.0 0.6 1.0
Surface coating [1]	1990-1995	234 (137) 77 (49) 148 (89)	In total no LEV LEV	[2]	1.5 1.5 1.2	2.0 2.0 2.6
Dryers, box / smelting and hardening furnaces [1]	1990-1995	93 (45) 45 (22) 43 (23)	In total no LEV LEV	[2]	2.0 1.8 2.0	3.3 4.0 2.0
Decanting, weighing, mixing [1]	1990-1995	91 (51) 33 (21) 50 (26)	In total no LEV LEV	[2]	5.0 2.6 8.0	8.5 3.0 12.0
Gluing [1]	1990-1995	60 (42) 38 (27) 21 (17)	In total no LEV LEV	[2]	1.0 1.0 [1]	2.0 2.0 3.8

Table 4.4 continued overleaf

Table 4.4 continued Phenol exposure at different workplaces

Job category / activities	Years of measure-ment	Number of samples (number of premises)	Technical measures	50th percentile [mg/m³]	90th percentile [mg/m3]	95th percentile [mg/m3]
Spraying:						
Surface coating 1)	1990-1995	234 (137) 77 (49) 148 (89)	In total no LEV LEV	2)	1.5 1.5 1.2	2.0 2.0 2.6
Short-term values						
All types of work areas 1)	1990-1995	18	17	1.2	7.6	12.2

1) BGAA (1999)
2) Below detection limit (1 mg/m³)
3) Westberg et al. 2001

Additional statements to the measured results:

Processing of phenolic resins in the plastics processing and woodworking industries: the measurements were taken for moulding, kneading, extrusion and injection moulding. More than 90% of the measurements were in the region of the analytically detectable concentration. Levels above the analytically detectable concentration (1.0 mg/m³) were measured during the moulding of wooden panels and abrasive discs.

Processing of phenolic resins in foundries: around 90% of the measurements were in the region of the analytically detectable concentration. Levels above 90% were measured during the manufacture of cores using phenol-containing resins.

The publication Westberg et al. (2001) included two remelting plants, four sand foundries, one static-die casting, and three die-casting foundries. The most frequently used aluminium-silicon alloys were all represented. All job titles – smelting, moulding, pouring, core making, shake-out operations, and fettling – were represented in the survey.

Additional information provided by the Institutes of and Occupational Safety and Health of the Länder in D (Federal States of Germany) reveal exposure levels between 0.03-1.8 mg/m³ (personal sampling, one measurement 6 mg/m³).

Mechanical machining processes: the measurements were taken in the metalworking, mechanical engineering, vehicle manufacture and electrical engineering industries. No levels above the analytically detectable concentration were measured.

Surface coating (spraying): the majority of the measurements came from the metalworking/mechanical engineering, woodworking and plastics processing industries. In more than 95% of cases the measurements were in the region of the analytically detectable concentration. Levels above the analytically detectable concentration were measured for the application of phenol-containing materials using compressed-air spray guns and brushes (coatings for the preservation of tanks, drums and floors).

Dryers, box/smelting and hardening furnaces: around half of the measurements were taken during the manufacture of abrasive products. 85% of the measurements were in the region of the analytically detectable concentration.

Decanting, weighing, mixing: the majority of the measurements came from the metalworking/mechanical engineering, woodworking and plastics processing industries. 75% of

the measurements were in the region of the analytically detectable concentration. Levels above 90% were measured during the mixing of phenol-containing materials (manufacture of abrasive discs, ceramic compounds, phenolic resins).

Gluing: the majority of the measurements came from the metalworking/mechanical engineering, woodworking and plastics processing industries. In more than 95% of cases the measurements were in the region of the analytically detectable concentration.

BGAA had performed a different clustering of exposure data from a slightly different time period (1990 – 1993) according to industries (e.g. chemical industry, processing of plastics) This clustering revealed that high exposure levels (> 1 mg/m^3) occur in the production of abrasive wheels (use of bakelite, n = 36, 9 companies, 50th percentile: 0.5 mg/m^3, 90th percentile: 5 mg/m^3, maximum: 42 mg/m^3), as well as during the production of abrasive coverings (n = 114, 6 companies, 50th percentile: 0.5 mg/m^3, 90th percentile: 2 mg/m^3, maximum: 2 mg/m^3) and in the production of coating agents, fillers and adhesives (n = 13, 10 companies, 50th percentile: 0.5 mg/m^3, 90th percentile: 2.0 mg/m³, maximum: 5 mg/m^3). These high exposure levels are, in part, confirmed by information provided by the Institutes of Occupational Safety and Health of the Länder in D (Federal States of Germany). Measured values obtained during the production of abrasive discs reveal exposure levels of 0.001-15 mg/m^3 (8-hour TWA, personal sampling, n = 5).

From the given information in **Table 4.4** and the corresponding descriptions and the different clustering of exposure data described above it can be concluded that the following exposure scenarios are associated with exposure levels > 1 mg/m^3:

- Manufacture of abrasive discs, ceramic compounds (activities: decanting, weighing, mixing, levels above 90th percentile were measured during the mixing of phenol-containing materials) (see **Table 4.4** and corresponding description)
- Dryers, box/smelting and hardening furnaces (half of the measurements were taken during the manufacture of abrasive disks) (see **Table 4.4** and corresponding description)
- Production of abrasive coverings and wheels (see different clustering)
- Production of coating agents, fillers and adhesives (see different clustering)
- Surface coating performed in different industries (metalworking/mechanical engineering, woodworking and plastics processing industries). Relatively high exposure levels were measured for the application of phenol-containing materials using compressed-air spray guns and brushes (coatings for the preservation of tanks, drums and floors) (see **Table 4.4** and corresponding description).

Further information on spraying processes is not available. The exposure levels do not differ largely from the other exposure levels. Therefore, no separate inhalation exposure level is given for spraying.

In this scenario, different activities and uses of different phenolic resin are clustered. Based on all available data, the 90th percentile of 5 mg/m^3 (with/without LEV) of a collective with highest exposure levels is taken. The collective is related to mixing, decanting and weighing in metalworking/mechanical engineering, woodworking and plastics processing industries and is regarded to represent the reasonable worst case situation for Scenario 3. Some of the clustered uses might lead to a health risk whereas others do not.

As short term exposure, 7.6 mg/m³ is taken.

Conclusions

From the available data it is seen that relevant exposure occurs at open handling of phenol containing materials, at processes at elevated temperature and during spray-techniques. The industries involved are the manufacture of abrasive disks and abrasive coverings, of ceramic compounds, coating agents, fillers and adhesives. Surface coating is performed in different industries (metalworking/mechanical engineering, woodworking and plastics processing industries). Relatively high exposure levels were measured if compressed-air spray guns and brushes were used (coatings for the preservation of tanks, drums and floors).

For the assessment of the health risks from daily inhalation exposure to phenol during the uses of phenol containing materials, a 8-hour TWA of 5 mg/m^3 (90th percentile of a measurement collective with highest exposure levels, with/without LEV, this levels includes spraying activities) should be taken. The results relate to decanting, weighing, and mixing activities. The majority of the measurements of this collective came from the metal working/mechanical engineering, woodworking and plastics processing industries. 75% of the measurements were in the region of the analytically detectable concentration (1 mg/m^3). Levels above the 90th percentile were measured during the mixing of phenol-containing materials (manufacture of abrasive discs, ceramic compounds, phenolic resins). Due to clustering different uses, some of the uses might lead to a health risk whereas others do not.

As short term exposure, 7.6 mg/m³ is taken.

Dermal exposure

For the assessment of dermal exposure the exposure scenario is subdivided into activities without the formation of aerosols (Scenario 3a) and spray techniques (Scenario 3b). Additionally, it has to be considered, that dermal contacts to resins classified as corrosive (≥ 3% phenol) is limited to occasional events with rather small skin areas exposed and that skin contacts to non-corrosive resins (< 3% phenol) may occur repeatedly on a daily scale.

a) Activities without the formation of aerosols

- - non-corrosive preparations

According to literature, measurements of dermal exposure were made in the plywood production using phenol-formaldehyde resin-glues (Mäkinen et al., 1999). Exposure measurements of potential dermal exposure of 4 workers at 4 days revealed, that dermal exposure is mostly at hands and chest. In total, exposure varies between 0.31 mg/hour and 2.663 mg/hour for the whole body and between 0.012 and 0.127 mg/hour for the hands. As a shift average for the whole body, 22 mg per day is given.

For the use of non-corrosive phenolic resins (< 3% phenol), it is to be assumed, that PPE (here gloves and eye protection) are not regularly worn. The corresponding dermal exposure is assessed for the unprotected worker in application of the EASE model. Liquid or solid resins are drummed or bagged. The following model estimation is in accordance with the revised TGD (Table 3, Annex 1E).

Input parameters:	T = 20°C, non dispersive use, direct handling, intermittent
Level of exposure:	0.1-1 mg/cm^2/day

Considering a phenol concentration of 3%, dermal exposure is assessed to 0.003-0.03 mg/cm²/day. Taking into account an exposed area of 420 cm^2 (palms of two hands), this dermal exposure amounts to 1.3-13 mg/person/day for daily dermal exposure during handling (e.g. filling). For the purpose of risk assessment, the higher value should be taken as representing the reasonable worst case situation. The level estimated in the literature (see above) is in good agreement with the EASE estimate.

– - corrosive preparations

If corrosive resins containing higher phenol concentrations (≥ 3% - < 15%) are used, dermal exposure is restricted to occasional dermal contacts:

Input parameters:	Non dispersive use, direct handling, incidental
Level of exposure:	0-0.1 mg/cm^2/day.

Considering an exposed area of 210 cm^2 (half of the palms of both hands) and a concentration of 15 % phenol the model yields an exposure level of 0.3-3 mg/person/day. A rather small skin area is taken because of the corrosive effect of phenol.

b) Spray techniques:

– non-corrosive preparations

Dermal exposure during spray painting is due to the deposition of spray mist, back bouncing, contact with contaminated spray gun and possibly also with freshly painted surfaces. The estimates are based on an experimental study in 3 off-shore facilities where containers were painted (Lansink et al., 1998) and on studies by HSE and IOM on airless spray application of antifouling paint (HSE, 1999). The Lansink et al. (1998) study involved 12 painters, using 3-13 l of paint with a duration of 4-21 minutes. A fluorescent tracer was added at 0.0074% (w/w). Exposure levels were presented based on the tracer and a linear extrapolation of exposure related to duration (3 hours, in which 150-200 l could have been applied) was done to compare the study with the other studies. The HSE compilation included a total of 70 exposure data provided by 18 separate surveys. The amounts of paint used during spray sessions in the HSE document ranged between 25 and 800 l and the spray session ranged from 40 to 360 minutes (median about 180 minutes). On the basis of the 90^{th} percentile of the extrapolated results of Lansink et al. (1998) and the 95^{th} percentile of the HSE data a reasonable worst case estimate of 10,000 mg on an exposed area of 840 cm² was derived. In consideration of content in formulations of 3% dermal exposure through direct skin contact during spraying of the formulations is estimated to 300 mg/person/day.

– corrosive preparations

If corrosive resins are sprayed, exposure is considerably reduced. There is no accepted methodology for assessing dermal exposure in this case. The assessment is made in comparison with the exposure levels assessed for the handling of resins without the formation of aerosols. There is a ratio of 4 between both subscenarios: non-corrosive: 13 mg/person/day and corrosive: 3 mg/person/day (see above). Taking this ratio of 4 and the assessed 300 mg/person/day for spraying non-corrosive resins into account, an exposure level of 75 mg/person seems to be appropriate for spraying corrosive resins. Due to the corrosive properties, exposure occurs only occasionally.

Conclusions

For assessing the health risks of daily dermal exposure in the area of use of non-corrosive phenolic resins (Scenario 3a) an exposure level of 13 mg/person/day should be taken. In case of spraying non-corrosive resins, daily dermal exposure amounts to 300 mg/person/day. This exposure assessment is based on the assumption that suitable gloves are not worn.

For handling corrosive resins (≥ 3% - 15% phenol), dermal exposure is limited to occasional events. Due to the low contact level (incidental) and a rather small exposed skin area, dermal exposure is assessed as 3 mg/person/day for activities without the formation of aerosols. For spraying corrosive resins, dermal exposure is expected to be higher. Based on a comparison of the assessed exposure levels (see above) an exposure level of 75 mg/person seems to be appropriate (expert judgement).

For the purpose of risk assessment, the higher exposure levels regarding exposure to non-corrosive resins are taken forward.

It cannot be presupposed that eye protection is regularly used. For assessing the risks, hand eye contacts as well as possible splashes to the eye should be considered.

4.1.1.2.4 Summary of occupational exposure

Phenol is mainly (about 100%) used as a chemical intermediate in synthesis. Approximately 65% of the produced phenol is processed further to organic chemicals, for example, to bisphenol A, caprolactam, salicylic acid, diphenyl ether, alkyl phenols, nitrophenols and other chemicals. 30% is used to manufacture phenol resins and a non-quantifiable part serves as a component in cosmetics and medical preparations.

Exposure to phenol occurs during the handling of pure phenol and phenolic resins containing up to 15% phenol. In the case of phenolic resins phenol is released especially during the hardening process at elevated temperatures (≤ 180°C). The following scenarios are regarded to be relevant for occupational exposure:

Scenario 1: Production of phenol and further processing as a chemical intermediate in the large-scale chemical industry (see Section 4.1.1.2.1)
Scenario 2: Production of phenolic resins (see Section 4.1.1.2.2)
Scenario 3: Use of phenolic resins (see Section 4.1.1.2.3)

The exposure as a result of phenol vapours from cosmetic products and medical preparations at room temperature is assessed as low due to the relatively low vapour pressure of the pure substance itself (20 Pa), the low concentration of phenol (< 2% phenol) and the circumstance, that works with aerosols formed and processes at elevated temperatures are not probable.

For the assessment of dermal exposure, it has to be considered that phenol and its preparations containing ≥ 3% phenol are classified as corrosive. The experience of skin damage due to the corrosive properties of a substance leads to reduced dermal exposure. For phenol, the situation is more complex: beside the corrosive effect, phenol has local anaesthetic properties; therefore afflicted persons described reduced experience of pain after dermal contact with phenol. According to the revised TGD, dermal exposure was assessed on a non-daily basis for the handling of phenol and its preparations classified as corrosive (≥ 3% phenol). More important might be dermal exposure to non-corrosive preparations (< 3% phenol), because in this case exposure occurs daily.

Relevant inhalation and dermal exposure levels are given in **Table 4.5** and **4.6**.

For the large scale chemical industry, it is assumed that the production and further processing of phenol is mainly performed in closed systems. Exposure occurs if the systems are breached for certain activities, e.g. filling (Scenario 1, **Table 4.5**). Due to the high melting temperature of phenol (40.9°C), transfer and drumming of the liquid substance are performed at temperatures of > 60°C and dermal contacts are avoided. Non-daily exposure is assessed for handling corrosive solid phenol.

For scenario 2 (production of phenolic resins) there is a lack of information concerning the processes and companies involved. Measurement data are available from only one company. These limited data cannot be regarded representative for the different types of companies producing phenolic resin. The typical exposure situations are assumed to be similar to Scenario 1. The manifold uses of phenolic resins are clustered in Scenario 3. In part, the resins contain up to 15% phenol. Some of the uses lead to a health risk at the workplace, whereas others do not. From the available data it is seen that highest exposure occurs at open handling of phenol containing materials, at processes at elevated temperature (processing of phenolic resins in foundries, hardening in furnaces) and during spray-techniques. The industries involved are the manufacture of abrasive disks and abrasive coverings, ceramic compounds, coating agents, fillers and adhesives. Surface coating (spraying) is performed in different industries (metalworking/mechanical engineering, woodworking and plastics processing industries). Relatively high exposure levels were measured if compressed-air spray guns and brushes were used (coatings for the preservation of tanks, drums and floors).

Table 4.5 Summary of inhalation exposure data (reasonable worst case) of phenol which are relevant for occupational risk assessment

Inhalation exposure								
Scenario number, Area of production and use	**Form of exposure**	**Activity**	**Duration**	**Frequency**	**Shift average [mg/m³]**	**Method**	**Short-term concentration [mg/m³]**	**Method**
Production an use as a chemical intermediate								
1. Production and further processing as a chemical intermediate	Vapour	Charging, drumming, cleaning, repair, maintenance	Shift length (assumed)	Daily	3.3	90th percentile	17.8	Workplace measurements (Duration: 5 min)
Formulation								
2. Formulation of phenolic resins	Vapour	Charging, drumming, cleaning, repair, sampling	Shift length (assumed)	Daily	20[1)]	EASE	---	---
Use of formulations								
3. Use of phenolic resins, (up to 15% phenol) novolaks, resols (processes at elevated temperatures)	Vapour	Decanting, mixing, surface coating, spray techniques, hardening	Shift length (assumed)	Daily	5	90th percentile	7.6	Workplace measurements (Duration: < 1 h)

1) Typical value is comparable to Scenario 1: 3mg/m³

Table 4.6 Summary of dermal exposure data (reasonable worst case) of phenol which are relevant for occupational risk assessment

Dermal exposure								
Scenario number, Area of production and use	**Form of exposure**	**Activity**	**Frequency [days/year]**	**Contact level** [1)]	**Level of exposure [mg/cm²/day]**	**Exposed area [cm²]**	**Shift average [mg/person/day] RWC**	**Method (use of gloves)**
Production and further processing								
1. Production and further processing as a chemical intermediate [2)]	solid	bagging, drumming, sampling cleaning, repair, maintenance	not daily	incidental	0.1	210	21	EASE corrosive substance
Further processing to formulations								
2. Formulation of phenolic resins, bagging non-corrosive resins (< 3 % phenol)[3)]	powder,	bagging	daily	-	1.9	1,600 (not completely exposed)	90	Analogous data
Use of formulations								
3a). Use of phenolic resins (non-corrosive, up to 3% phenol), novolaks, resols [3)]	liquid, paste	decanting, mixing, hardening	daily	intermittent	0.03	420	13	EASE (without gloves)
3b) Spraying techniques (non-corrosive, up to 3% phenol)[3)]	liquid	spraying, surface coating	daily	--	--	840	300	Analogous data

1) Contact level according to the EASE model
2) Due to the high melting temperature of phenol (40.9°C), transfer and drumming of the substance are performed at temperatures of > 60°C and dermal contacts are avoided.
3) Dermal contact to phenol and preparations labelled as corrosive (≥ 3 - 15%) is restricted to occasional events
Scenario 2 21 mg/person/day for pure phenol and corrosive resins
Scenario 3a 3 mg/person for resins containing ≥ 3% - 15% phenol
Scenario 3b 75 mg/person/day for resins containing ≥ 3% - 15% phenol

4.1.1.3 Consumer exposure

4.1.1.3.1 Exposure from uses

Phenol is used in paints and polishes, products used for floor covering materials, glues, 2-component adhesives and printing inks (Swedish product register, 1995; Berufsgenossenschaft der Bauwirtschaft, 1995). The product data base of the BfR is listing some phenol-containing products used by consumers: primers (content < 1.0%) and two-component adhesives (content < 2.5%). The exact number of paints/primers being on the market and containing phenol is not known. In the US, 14,000 exposures to phenol-containing products have been reported between 1988 and 1990. The content of phenol was reported to amount up to 26% (Spiller et al., 1993).

Inhalation exposure

Floor waxes, polishes

30 g of such products containing 2.5% of phenol will be used every day for a period of 0.144 hours. The EPA-SCIES all-purpose liquid cleaner scenario was taken for estimation using the following defaults: air exchange rate 0.2, room volume 20 m³, house volume 408 m³. The estimate revealed a peak room concentration of ~ 12.7 mg/m³, an average concentration during use of ≈ 4.0 mg/m³ and an average of 1.1 mg/m³ after use.

The results of the exposure estimation are displayed in the **Table 4.7**, for a female active user and a ten year old child as bystander.

Table 4.7 Exposure to phenol by use of polishes/floor waxes

	Room air concentration (mg/m³)	Inhalation rate (m³/h) (1)	Bodyweight (5th percentile) (2)	Estimated exposure (mg/kg)	Duration of stay (h) (3)	Exposure (mg/kg)
User during use (female, moderate activity)	12.7	1.6	45	0.45	0.14	0.063 during use
Bystander (child, 10 years, during use, light activity)	4	1	25	0.16	0.14	0.022 during use
After use (female, light activity)	1.1	1	45	0.024	20	0.48 per day
After use (child, 10 years, light activity)	1.1	1	25	0.044	15	0.7 per day

1) EPA (1997);
2) AIHC (1994);
3) Behörde für Arbeit, Gesundheit u. Soziales (1995)

From this estimation, the active user will be exposed to a maximum of 0.063 mg/kg, and to 0.48 mg/kg per day after use. This means that exposure during use can be neglected; however, the daily use of products should be mentioned as the most important source of exposure.

Bystanders, e.g. children may also be exposed to considerable amounts of about 0.7 mg/kg/bw/day.

Use of phenol containing disinfectants

For estimation exposure due to the disinfectants scenario a weekly use has been assumed. The EPA-SCIES estimate reveals an average concentration in room air of 0.08 mg/m³ after use. This means that a female person staying for 20 hours in that room would have an exposure of 0.018 mg/kg per day, a child staying 15 hours 0.048 mg/kg per day.

Table 4.8 Exposure to phenol by use of disinfectants

	Room air concentration (mg/m³)	Inhalation rate (1)	Bodyweight (5th percentile) (2)	Estimated exposure (mg/kg)	Duration of stay (h) (3)	Exposure (mg/kg)
User during use (female, moderate activity)	10.2	1.6	45	0.363	0.14	0.05 during use
Bystander (child, 10 years, during use, light activity)	3.4	1	25	0.136	0.14	0.019 during use
After use (female, light activity)	0.08	1	45	0.0016	20	0.036 per day
After use (child, 10 years, light activity)	0.08	1	25	0.0032	15	0.048 per day

1) EPA (1997);
2) AIHC (1994);
3) Behörde für Arbeit, Gesundheit u. Soziales (1995)

Use of other products

There are no quantitative data on consumer exposure from the use of phenol containing printing inks and 2-component-adhesives. As a worst case, it is assumed that the exposure is about 10 times lower than that due to floor waxes (mentioned above); the exposure would amount to about 0.02 mg/kg per event.

Cigarette smoke

In a non-ventilated room having a volume of 50 m³, the smoke from 10 cigarettes (main share of phenol in the side-stream) will result in a phenol concentration of 0.06-0.08 mg/m³ (Kuwata et al., 1980), resulting in human exposure of about 0.02 mg/kg bw/day (respiratory volume 19 m³ within 20 hours).

Dermal exposure

Phenol vapours are absorbed by the dermal route, thus contributing to the total dermal exposure.

Dermal exposure can occur by putting hands into disinfectant solutions, which can lead to 52.5 mg/event (assuming 420 cm^2 · 25 mg/cm^3 (concentration of phenol in the product) · 0.5 (a dilution factor of 2, arbitrary value) · 0.01 (thickness of layer on the skin). The dermal exposure may account for 0.9 mg/kg bw per event.

For water based waxes it is assumed that hands will be immersed in the solution for short time. Waxes can also be applied by immersing wiping cloth into a solution containing phenol for further cleaning actions. In this scenario, the maximum possible concentration on the wiping

cloth will be similar to that in the cleaning solution. Using wiping cloth with hands will result in contact of 210 cm^2 · 25 mg/cm^3 (maximum concentration of phenol on wiping cloth) · 0.01 (thickness of layer on skin) · 0.5 (dilution factor) revealing an exposure of 26.25 mg/event corresponding to 0.44 mg/kg bw per event.

Cosmetics

In EU member states the use of phenol and its alkali salts in soaps and shampoos is permitted in concentrations up to 1% (calculated as phenol); such products must be labelled containing phenol (EU Cosmetics Directive 76/768/EEC and amendments).

For dermal exposure of phenol from soap, the normal case scenario has been assumed as follows: the frequency of use is 6 times per day using 0.8 g of soap. Thus, a consumer using soap is exposed to 800 mg soap product · 6 times/day = 4.800 mg product/day. 4.800 mg product · 0.01 (fraction of phenol) · 0.01 (retention on the skin) = 480 µ/day which corresponds to about 0.01 mg/kg bw/day. Related to the exposed surface area of 840 cm^2 (hands) the external dermal exposure has been estimated to be 0.57 $\mu g/cm^2$/day and referring to a body weight of 60 kg 8 µg/kg bw/day.

Based on the SCCNFP-guideline the daily exposure with the use of phenol containing shampoo (one event per day) is calculated at 0.08 g/day (8 g/day and retention factor on skin 0.01), there from 1% (fraction of phenol) leads to 800 µg/day. Related to the exposed surface area of 1,430 cm^2 (hands and 1/2 of the head) the external dermal exposure has been estimated to be 0.56 $\mu g/cm^2$/day and referring to a body weight of 60 kg 13.3 µg/kg bw/day.

Thus, use of soaps and shampoos containing 1% phenol for their intended purposes will result in a total external dermal exposure of a consumer of 21.3 µg/kg bw/day.

Oral exposure

Phenol has also been detected as a contaminant in whipped cream dispensers (Sahenk et al., 1978). There is no detailed information available. Therefore this scenario would not be taken forward to the risk characterisation.

Exposure via medical treatment

In the case of the medicinal product, Labiosan Med ® (marketed in a package size of 9 g) having a phenol content of 0.5% (Hänselwerk, 1995), application to the lips of 300 mg ointment per day will result in a human exposure of 0.02 mg/kg bw/day (assuming a 100% absorption).

Phenol is also used as a preservative in pharmaceutical preparations for parental administration in a concentration up to 0.5% (Danish Medicines Agency, 2003).

In insulin preparations used by many diabetics throughout the EU, phenolic compounds are used as a preservative in concentrations of 2.15 mg/ml (metacresol 1.5 mg and phenol 0.65 mg/ml). Insulin is dosed on a individual basis, but at an average daily dose for an adult of about 40 IE of insulin/day a diabetic will inject about 0.6 mg metacresol and 0.26 mg phenol (0.004 mg/kg bw) subcutaneously each day. (Lægemiddelkataloget; www.lmk.dk).

Exposure by this type of use is not brought forward to the risk characterisation because it is regulated under another EU legislation.

Total phenol exposure of the consumer

Chronic exposure by use of phenol-containing consumer products may occur via the inhalation and dermal route.

During the application of floor waxes/polishes, and disinfectants consumers may be exposed via inhalation to maximum average concentrations of about 4 mg/m^3 (< 10 minutes) with possible peak values of 12.7 mg/m^3 and 10.2 mg/m^3, respectively. The average concentration after use of floor waxes was calculated to be 1.1 mg/m^3. This concentration will be used in the risk characterisation of chronic exposure. Considering all uses, it can be assumed that chronic inhalation exposure by use of consumer products may not exceed 0.48 mg/kg bw/day and 0.7 mg/kg bw/day for female adults and 10-year-old children, respectively. A very rare acute exposure by using high amounts of paints containing phenol as a conservation agent may lead to higher values. However, the frequency of occurrence of acute exposure cannot be assessed exactly because there is not sufficient information on the number of phenol-containing products available on the market. It is considered to be low.

Dermal exposure of the consumer via cosmetics (soaps and shampoos) can be assumed to be about 0.021 mg/kg bw/day. The dermal exposure from use of phenol containing waxes and disinfectants can account respectively 0.44 mg/kg bw/event and 0.9 mg/kg bw/event.

4.1.1.4 Humans exposed via the environment

In accordance with the TGD, humans exposed via the environment, such as e.g. via food, drinking water and the air, is to be determined for phenol. As a "worst-case' scenario, a point source (90th percentile of the local concentration in water and air, see Section 3) and application of sewage sludge from municipal waste water is used in the calculation. This result is compared with a second calculation which is based on the regional background concentrations (see Section 3.1.6).

The results of these calculations, together with the corresponding input values, are summarised in Appendix E. However, it is necessary to draw attention to the fact that the utilised calculation model is as yet only provisional in character. It will have to be revised when further information is available. The following input parameters were selected:

Table 4.9 Input data for the calculation of the indirect exposure

	Local scenario (point source)	Regional background concentrations
Annual average PEC in surface water in mg/l	2.3E-3	2.41E-3
Annual average PEC in air in mg/m^3	18.0 E-3	2.60 E-5
PEC in grassland in mg/kg	2.1 E-3	-
PEC in agriculture soil in mg/kg	-	1.72E-4
PEC in porewater of grassland in mg/l	1.3 E-3	-
PEC in groundwater under agriculture soil in mg/l	9.4 E-4	1.10 E-4

The resultant daily doses for the substance are:

- DOSEtot = 46.4 µg/kg bodyweight and day (local Scenario)

– DOSEtot = 0.15 μg/kg bodyweight and day (regional background concentrations)

Table 4.10 The calculated intake quantities result from the following routes:

Intake route	% of total intake	
	Local	Regional
Drinking water	0.14	45.6
Air	8.32	3.69
Plant shoot	91.47	40.88
Root	0.01	0.51
Meat	<0.01	<0.01
Milk	0.02	0.01
Fish	0.03	9.29

The most significant intake routes for the local approach to the indirect exposure are the plant shoot and for the regional approach of the indirect exposure it is the drinking water.

4.1.2 Effects assessment: Hazard identification and dose (concentration) - response (effect) assessment

4.1.2.1 Toxicokinetics, metabolism and distribution

4.1.2.1.1 Absorption and distribution

Phenol is well absorbed via gastrointestinal and respiratory tract and the dermal route.

In rats, sheep and pigs 90, 85 and 84% of the orally administered dose of 25 mg ^{14}C-phenol/kg bw were absorbed after 8 hours (Kao et al., 1979).

Rats (3-4 animals) were dosed with 0.03 mg/kg bw ^{14}C-phenol via oral, dermal, intratracheal or intravenous routes. Absorption of phenol was extensive. Of the recovered dose, 75-95% was excreted in the urine by 72 hours after administration by each of the four routes. The lowest total amount of radioactivity excreted in urine by 72 hours was after dermal administration (approximately 75% of the recovered dose). After oral administration, approximately 85% of the recovered dose was eliminated within 4 hours. Urinary elimination was essentially complete by 12 hours. After dermal application of phenol, however, only 40% of the dose was excreted in the urine by 4 hours, 70% by 12 hours and the excretion was essentially complete (~ 75%) by 24 hours. The content of radioactivity detected in the skin at 72 hours was 1.6%. Totally after dermal application about 75% of the dose is excreted via urine and 3% via faeces (Hughes and Hall, 1995).

Rapid (maximum concentration in serum after about 10 minutes) and efficient resorption (about 53%) of phenol via lungs was reported to occur in isolated organs (Hogg et al., 1981).

Volunteers were exposed to 6-20 mg/m^3 phenol via inhalation (dermal absorption was excluded) and the individuals retained from 60 to 88% of the phenol to which they were exposed. The mean values obtained from 12 experiments in groups exposed to the above mentioned

concentrations of phenol did not show significant differences. Fractional retention decreased from about 80% at the beginning to approximately 70% after 8 hours (Piotrowski, 1971).

Percutaneous absorption of 4 µg phenol/cm^2 was determined in in-vitro-experiments to about 26% in rats and about 19% in humans (Hotchkiss et al., 1991). Skin permeability is enhanced with increasing temperature (10-37°C) of the phenol solution (Jetzer et al., 1988).

After absorption phenol is rapidly distributed in body tissues.

After oral administration of 207 mg/kg bw ^{14}C-phenol to rats the total amount of radioactivity in the tissues reached a peak at 0.5 hours. For liver, spleen, kidney and adrenal gland the concentration ratios between tissue and plasma were greater than 1 at all times, and the thyroid gland and lung had ratios that were mostly greater than 1. About one half of the phenol in serum is conjugated (Liao and Oehme, 1981).

Male and female F 344 rats were exposed to single and repeated (8 days) doses of ^{14}C-phenol by (1) gavage, 1.5, 15, 150 mg/kg; (2) drinking water, 5,000 ppm; (3) inhalation 25 ppm, 6 hours. The concentrations of free phenol (vs. metabolite) in blood of male rats receiving either 1.5 or 150 mg/kg single oral bolus doses of ^{14}C-phenol were attained 0.02 µg/g blood within 1-3 minutes after dosing following the low doses and 46.4 µg/g blood following the high doses. Clearance of ^{14}C-phenol from the blood was rapid in both the 1.5 mg/kg and the 150 mg/kg dose group. The terminal half-life time was of 8 versus 12 minutes. 24 hours post oral administration of 150 mg/kg bw concentrations of radioactivity were < 0.024% in all tissues sampled, including the liver kidneys and brain and < 0.003% in the ovaries and testes. Low concentrations of radioactivity were found after repeated oral and drinking doses (< 0.0005% in bone) and inhalation exposure (< 0.004% in bone) (Dow, 1994).

Hughes and Hall (1995) found similar results in rat after administration of 0.03 mg/kg bw ^{14}C-phenol by the oral and dermal routes. Phenol was retained in low amounts (1-2% of the recovery of the dose administered) in the rat 72 hours after oral exposure. After oral or dermal administration the highest content of radioactivity was in the large intestinal contents (0.02% versus 0.07% of administered dose/g tissue). Low amounts were found in several of the larger organs including the liver (0.003%), lung (0.002%), and kidney (0.006%).

4.1.2.1.2 Metabolism

Phenol was extensively metabolised to its sulfate and glucuronide conjugates after administration via all the routes and species for which data available.

In a comparative study in 17 different mammalian species, being administered via gavage by 20-50 mg phenol/kg bw, significant differences of metabolites in urine was found after 24 hours. Conjugation of phenol in cat occurred only with sulfuric acid, in pig only with glucuronic acid. In carnivores' 13-32% and different rodents 3-28% of the administered dose was detected as conjugates with hydrochinone (Capel et al., 1972).

Metabolism of phenol predominantly occurs in liver, gut and kidneys (Cassidy and Houston, 1980; Houston and Cassidy, 1982). Enhanced metabolism by extrahepatic tissue, particularly in gut due to saturation of liver enzymes was observed in rats after dosage of more than 5 mg phenol/kg bw (Cassidy and Houston, 1984).

Male and female mice were exposed by 1.4 to 21.2 mg ^{14}C-phenol/kg bw by intravenous administration. First pass intestinal metabolism of phenol was evaluated by comparison of

urinary excretion of phenol metabolites following iv administration with additional groups of male mice that received the same dose levels by oral gavage. The major urinary metabolites were phenol sulfate, phenol glucuronide, and hydroquinone glucuronide. While sulfateion was the dominant pathway for phenol elimination at the lowest dose level, there was a decrease in sulfateion and concomitant increase in glucuronidation as the dose level increased. The ratio of sulfate/glucuronide excreted in urine of male mice decreased from 3.3 to 1.2 over a dose range of 1.4 to 21.2 mg/kg bw. Male mice consistently excreted a higher portion of phenol as the oxidised conjugated metabolite, compared to female mice. There are significantly greater percentage of phenol glucuronides excreted in the urine following oral compared to intravenous administration (38% versus 17%) and the significantly lower percentage of hydroquinone (8% versus 17%). Excretion of other metabolites of phenol, that is, hydroquinone sulfate and mercapturic acid conjugates of hydroquinone was significantly higher following intravenous compared to oral administration (11% versus 1%) (Kenyon et al., 1995).

Hughes and Hall (1995) have shown in rats that phenol was extensively metabolised to the sulfate and glucuronide conjugates after absorption from the four routes of exposure (oral, dermal, intratracheal or intravenous). The sulfate conjugate was excreted in higher amounts than the glucuronide conjugate at 4 and 8 hours post-exposure irrespective of the route of exposure (Koster et al., 1981).

Similar results are shown in another study in rats with several routes of administration (Dow, 1994). Regardless of dose or route of administration, the urinary metabolites of phenol consisted predominately of sulfate and glucuronide conjugates of phenol itself. However, the ratio of glucuronide to sulfate conjugates was dose-dependent. At low doses of phenol the sulfate conjugate predominates over the glucuronide conjugate in urine. With increasing phenol dose, saturation of sulfate conjugation results in predominance of the glucuronide conjugate. Repeated low-dose oral bolus treatment had no effect on the ratio. A small amount (2-4% of total recovered radioactivity) of the urinary radioactivity was recovered as an unidentified metabolite (Dow, 1994).

The capacity-limited sulfatation of high dosages of phenol appears to be due to the reduced availability of hepatic 3-phosphoadenine-5-phosphosulfate (PAPS), which in turn is limited by the availability of sulfate (Kim et al., 1995).

After oral administration of 0.01 mg phenol/kg bw in humans after 24 hours 77% of the dose was excreted via urine as phenolsulfate and 16% as phenolglucuronide. Only traces of conjugated hydroquinone were detected in the metabolic profiles for humans and rats (Capel et al., 1972).

The metabolic conjugation of phenol in humans after dermal absorption is not known.

In vitro incubations of phenol with various tissue preparations results in covalent binding of phenol to protein and DNA (Subrahmanyam and O'Brian, 1985; Reddy et al., 1990; Kolachana et al., 1993). However, Reddy et al. (1990) could not detect any evidence of *in vivo* DNA binding in several rat tissues (bone marrow, Zymbal gland, liver or spleen) after oral administration of 75 mg/kg bw phenol or 150 mg/kg bw phenol/hydroquinone (1:1).

Phenol is a metabolite following oxidation of benzene. Benzene-induced myelotoxicity and hematotoxicity are generally not found following phenol oral exposure. The quantity of produced benzene metabolites is the result of subtle interplay among various enzymes competing for substrates at a given location, the distribution of those enzymes in the liver, and the relative rates of perfusion in different species. As an explanation for the different toxicity following phenol and benzene exposure Schlosser et al. (1995) concluded that the residual phenol available for

oxidation in the centrilobular region is very low when phenol is administered because most of it is conjugated upstream of this region. Following administration of benzene, phenol is produced in the centrilobular region thus being more available for subsequent oxidation to the following metabolites.

4.1.2.1.3 Excretion

Excretion via urine is the main elimination pathway of phenol metabolites in humans and animals.

In rabbits, exposed to high oral dosage of phenol (300 mg/kg bw) about one half of the administered dose was excreted via urine as unmetabolised compound. Less than 1% of the administered dose was excreted via faeces, only low amounts were exhaled (Deichmann, 1944).

In comparative studies by Capel et al. (1972) the rate of ^{14}C excretion via the 24-hour urine in different species were found ranging from 31% of the doses in monkeys to 90% in rats and 95% in humans.

Fast excretion of radioactivity after 12.5 or 50 mg ^{14}C phenol/kg bw, administered in the ureter-cannulated rat intraduodenally was reported. 77% of the dosage was excreted via urine within the first 2 hours. After oral administration of 25 mg phenol/kg bw 90 versus 96% of the dosage were detected as phenolic metabolites in urine by 8 hours (38.1% phenol glucuronide, 49.7% phenol sulfate, 2.1% hydroquinone glucuronide and 0.9% hydroquinone sulfate). Less than 0.5% was excreted in the faeces. At 24 hours the elimination of the radioactivity was 87%, 86% and 97% for the sheep, pig and rat respectively (Kao et al., 1979).

The urinary excretion profile in rats was similar between the animals administered phenol by intravenous, oral and intratracheal routes (about 95% of the recovered dose by 72 hours). The lowest total amount of radioactivity excreted in urine by 72 hours was measured after dermal administration (about 75% of the dose). Faecal elimination of phenol-derived radioactivity was considerably lower than urinary elimination (about 2-3% at 72 hours for all routes) (Hughes and Hall, 1995).

Similar results were found in further studies in rats (Dow, 1994). For all exposure routes radioactivity was rapidly eliminated in urine (> 94% by 24 hours). Faecal elimination amounted about 0.8-3.3% of the radioactivity. Small amounts of unconjugated phenol were consistently recovered only in urine of high oral bolus females (1.3% of radioactivity) and in urine collected from male rats during inhalation exposure (2.7%).

After dermal and inhalative exposure of volunteers to phenol (5-25 mg/m^3) during 8-hour half-life of excretion of about 3.5 hours was estimated. Nearly 100% of the absorbed dosage was excreted after 24 hours from starting exposure (Piotrowski, 1971).

Conclusion

Phenol is well absorbed via gastrointestinal and respiratory tract and the dermal route. Concerning the oral route a high absorption was measured in rats, sheep and pigs with 90, 85, and 84% of the orally administered phenol dose of 25 mg/kg bw after 8 hours. Volunteers exposed to phenol concentrations of 6-20 mg/m^3 via inhalation absorbed 60 to 88% of the substance. After dermal application of phenol to rats, 40% of the applied dose was excreted in the urine by 4 hours, 70% by 12 hours and the excretion was essentially complete (with 75%) by 24 hours. In body tissues phenol is rapidly distributed. It is metabolised to sulfate and

glucuronide conjugates. The ratio of sulfate/glucuronide conjugates excreted in urine is species and dose-dependent with a capacity-limited sulfatation at high dosages in rats and mice. Cats showed a poor glucuronidation of phenol, only conjugation with sulfate occurred. Small amounts of conjugated hydroquinone were only detected in the metabolic profiles for humans and rats. Metabolism predominantly occurs in liver, gut and kidneys. Excretion via urine is the main elimination pathway of phenol metabolites in humans and animals for the different exposure routes.

For risk assessment purposes the rates of oral and inhalation absorption are assumed to be 100%, whereas for dermal exposure the rate was set to 80%.

4.1.2.2 Acute toxicity

4.1.2.2.1 Studies in animals

Bruce et al. report (1987) that in humans and experimental animals the signs and symptoms of acute toxicity are similar regardless of the route of administration. Muscle weakness, convulsions, and coma are the predominant symptoms associated with exposure to lethal concentrations of phenol. For animals, dermal and oral LD_{50} values are reported in the literature, most falling within one order of magnitude according to the sensitivity of species with the cat being the most sensitive and the guinea pig most resistant. Although LC_{50} values are not available in literature, rats are reported to have tolerated phenol concentrations as high as 236 ppm (900 mg/m^3) for 8 hours, resulting in ocular and nasal irritation, loss of co-ordination, tremors, and prostration. The odour recognition threshold (100% response) of phenol is approximately 0.05 ppm, a concentration far below the levels where toxic effects have been reported; thus, the chemical has good warning properties for inhalation exposure. Regardless of the route of exposure, absorption is rapid, as illustrated by the fact that acute doses of phenol can produce symptoms of toxicity within minutes of administration.

Acute oral toxicity

Oral LD_{50} values of 340-530 mg/kg body weight resulted for phenol (Merck's reagent quality) in an acute oral toxicity test with Wistar rats, conducted comparable with international guidelines: Aqueous preparations containing 2, 5, 10 and 20% of phenol were administered by gavage to 5-15 rats per dose group (equal numbers of male and female rats used). The first three of these preparations showed the same degree of toxicity, the LD_{50} being 0.53, 0.53 and 0.54 g/kg. The 20% emulsion was somewhat more toxic, the corresponding LD_{50} being 0.34 g/kg. All of the animals that died within the study were found dead within 5 to 150 minutes. Clinical signs observed were fluctuating body temperature, pulse and respiration became slow, irregular and weak, pupils first contracted and later on dilated. Salivation, marked dyspnea, tremor and convulsions, lethargy, and coma were reported (Deichmann and Witherup, 1944).

Oral application of phenol (no data on purity) to mice (with vehicle olive oil) in a test conducted comparable to international guidelines resulted in an oral LD_{50} of approximately 300 mg/kg body weight. The following mortalities are reported: 5/10 mice died after administration of 300 mg/kg, 8/10 mice each died after administration of 400 and of 500 mg/kg, 6/10 after 600 mg/kg and 10/10 after 700 mg/kg, death occurring up to 7 days after test substance administration. Clinical signs were excitement shortly after the administration, within a short time tremors and convulsions were observed (von Oettingen and Sharpless, 1946).

An oral LD_{50} of less than 620 mg/kg body weight resulted for rabbits in a test comparing the toxicity of aqueous preparations of phenol in different concentrations: Single doses (0.28, 0.42, 0.62 and 0.94 g/kg body weight) of melted crystals of phenol (Merck's reagent grade) or of aqueous solutions and emulsions prepared so as to contain 2, 5, 10, 20, 50, 75 and 90% of phenol were administered by gavage to 1-10 Albino rabbits per dose group (equal numbers of males and females used). The results show that there is very little difference in the toxicity of dilute and concentrated preparations of phenol when administered orally. Lethal effects were produced uniformly by the dose of 0.62 g/kg, sometimes by the dose of 0.42 g/kg, but never by the dose of 0.28 g/kg. Clinical signs observed were fluctuating body temperature; pulse and respiration become slow, irregular and weak; pupils first contracted and later on dilated. Salivation, marked dyspnea, tremor and convulsions, lethargy, and coma were observed (Deichmann and Witherup, 1944).

On the basis of mortality during a 14-day post-exposure period, an oral LD_{50} of 650 mg/kg was estimated (95% confidence limits of 490-860 mg/kg) for male albino rats in a test according to FHSA (of August 12, 1961) with 4 doses of phenol in water (no data on purity) and with 5 rats per dose group: following oral administration of 200 mg/kg bw and 398 mg/kg bw respectively no deaths were observed, after a dose of 795 mg/kg bw 4/5 and after 1,580 mg/kg bw all rats died on the day of administration. All of the rats which died during the observation period revealed hyperemia and distention of the stomach and intestines upon autopsy. The majority of the rats which survived the observation period showed body weight gains which were significantly less than those of the control rats. None of the rats sacrificed following the holding period exhibited any gross lesions upon pathological examination (Flickinger, 1976).

Acute inhalation toxicity

Data on relevant acute inhalation toxicity tests with animals are not available.

The acute toxic effects of catechol-, resorcinol- and phenol-water aerosols were investigated at comparable airborne concentrations. Samples were dissolved in distilled water and the resulting solutions were aerolised using a D18 Dautrebande aerosol generator operated at 30 psi. At this operating pressure, the D18 generator delivers droplet diameters of 1µ size and smaller. The concentration of the sample solutions was adjusted so that airborne concentrations approximated 2,000 mg/m^3 of the sample in air. Airborne concentrations were determined by measurement of the volume loss of solution following aerosolisation. The weight of sample present in that volume was then calculated and related to the total volume of air used in generating the aerosol to obtain chamber concentrations. Six female Harlan-Wistar albino rats weighing 87-126 g were subjected to an 8-hour inhalation period of the aerolised sample of phenol (no data on purity) in water (containing 8% concentration of phenol in the solution). The nominal airborne concentration of the sample was calculated to be 900 mg/m^3. The following toxic signs were observed within the period of exposure: Ocular and nasal irritation, slight loss of co-ordination with spasms of the muscle groups within 4 hours, tremors and one prostrate within 8 hours, but no deaths. The animals seemed to be normal on the day following exposure. Animals were held for 14 days following exposure and were then weighed (normal weight gains) and sacrificed for gross autopsy (no lesions attributable to inhalation of the aerosol were seen) (Flickinger, 1976).

In a sensory irritation test with male Swiss OF1 mice as developed by Alarie (1966). A RD_{50} of 166 ppm was detected for phenol (high-purity grade): Systematic determination of the concentration associated with a 50% decrease in respiratory rate (RD_{50}) was used as an index of sensory irritation. Test atmosphere was generated by injecting the test compound at the entry of each inhalation chamber using two different methods: an injector was used and heat was added as needed to obtain the vaporisation of the substance, or vapours were produced by bubbling an

additional air flow through a vial containing the test compound. Decrease in respiratory rate was measured with 6 mice per group: The animals were secured in individual body plethysmographs, with their heads placed through a perforated latex dam. During exposure, the plethysmographs were inserted through the wall of the exposure chamber; the head of each animal was extended into inhalation chamber. Each of the six plethysmographs was connected to a pressure transducer which sensed pressure changes due to inspiration and expiration of the confined mice. The resulting signals were then amplified and displayed on a six-channel oscillograph. A control level was first established, during which time the mice were exposed to room air. A continuous recording was made, beginning 10 minutes before exposure; the mice were then rapidly placed in the stabilised cell with a predetermined concentration of irritant and were exposed for about 5 minutes. During the exposure, the respiratory rate decreased and the maximum percent decrease from the control values was calculated. The responses obtained for various concentrations were used to develop concentration-response relationships by plotting the maximum percent decrease in respiratory rat versus the logarithm of the exposure concentration of irritant. From this relationship, the concentration associated with a 50% decrease in respiratory rate, RD_{50}, was calculated for phenol as 166 ppm, uncomfortable but tolerable concentration was found at 17 ppm and minimal or no effect was detected at a concentration of 2 ppm (de Ceaurriz et al., 1981).

Acute dermal toxicity

A dermal LD_{50} of 660-707 mg/kg body weight resulted from a study with female Alderley Park Wistar rats conducted comparable to international guidelines (with the exception of an observation period ending already 7 days after application of the substance): Five rats per dose group (dose groups of 1.0, 0.5, 0.25 or 0.1 ml phenol /kg body weight) received single occlusive applications of molten phenol ("laboratory reagent grade", warmed in a water-bath until melted and maintained in this state at approximately 40°C) to the shorn backs. After 24 hours the dressings were removed and the skin was cleaned with a mild detergent. In a second experiment a non-occlusive technique was employed in which the treated area was left uncovered, and the animals were prevented from cleaning the site of application by means of a rigid plastic collar applied round the neck. The dose levels in this case were 1.0, 0.75, 0.3 and 0.1 ml/kg bw and the skin was again cleaned after 24 hours. Percutaneous toxicity of solutions of phenol in water, in 2-5% cetrimide, in methylated spirit and in olive oil were tested using the non-occlusive technique. All animals which survived were observed for seven days and were then killed and subjected to post-mortem examination. The kidneys and skin were examined histologically. Both occlusive and non-occlusive techniques revealed a dermal LD_{50} of 0.625 ml/kg (660-707 mg/kg) for molten phenol. Clinically, all the animals behaved similarly: between 5-10 minutes after dosing they developed severe muscle tremors causing marked twitching which developed into generalised convulsions with loss of consciousness and prostration. At varying times between 45-90 minutes, depending upon the dose administered, the animals developed severe haemoglobinuria. Rats receiving 1 ml, and 2 of those receiving 0.5 ml, died within 4 hours of treatment by the occlusive technique; by the other method, all receiving 1 ml and 0.75 ml died within 24 hours, but there were no other deaths. All animals showed severe skin lesions with immediate onset of oedema followed within 4 hours by necrosis associated at 24 hours with discoloration and surrounding erythema. At necropsy, those animals dying in the acute stage from phenol poisoning showed renal congestion, and the urinary bladders were distended with blood-stained fluid. On histological examination, the kidneys showed haematin casts in the distal convoluted tubules and in the tubules of the medulla and papillae. The skin showed extensive epidermal necrosis characterised by a hyaline appearance of the cells, loss of intercellular processes, and deposition of eosinophilic debris in the intercellular spaces. There was extensive superficial necrosis of the dermis, which was stained a purple colour by haematoxylin and eosin

suggesting a coagulative type necrosis. The severity of the dermal effects of phenol was markedly influenced by the type and of concentration. The most toxic mixtures were not necessarily those containing the highest proportion of phenol. At each concentration, a phenol/water mixture appears to be more toxic than any other mixture studied. An explanation for the variation in toxicity possibly lies in the ability of phenol to provoke a coagulative necrosis which may well slow further penetration, thus allowing time for the residual material to be removed from the epidermis and upper dermis (Corning and Hayes, 1970).

On the basis of mortality during a 14-day post-exposure period, the single dose skin penetration LD_{50} was estimated to be 850 mg/kg bw (95% confidence limits 600-1,200 mg/kg) for male albino rabbits whose abraded skin and intact skin was in contact with the phenol (no data on purity) for a maximum period of 24 hours (method according to FHSA of August 12, 1961): After dermal application of 252 mg/kg bw (vehicle water, no data on method of occlusion) and of 500 mg/kg bw to 4 male rabbits per dose group no deaths were observed. After dermal application of 1,000 mg/kg bw 3/4 and after application of 2,000 mg/kg bw all rabbits died on the day of application. The material produced necrosis of the skin in all of the exposed rabbits. The majority of the rabbits that survived the 14-day observation period exhibited body weight gains significantly less than those of the control rabbits. No internal gross lesions were observed upon autopsy of the sacrificed animals (Flickinger, 1976).

4.1.2.2.2 Studies in humans

NIOSH (DHEW/NIOSH, 1976) gives a historical overview on human experience following exposure to phenol. Liquid phenol in contact with the skin rapidly enters the bloodstream. From a variety of case reports clinical signs are known being documented for various occupationally exposed persons. These signs and symptoms can develop rapidly with serious consequences including shock, collapse, coma, convulsions, cyanosis, damage to internal organs, and death. Skin contact of humans with solutions, emulsions, or preparations containing 80-100% phenol for 5-30 minutes has been reported to result in death**.**

Phenol is reported to cause poisoning by skin absorption, vapour inhalation and ingestion (Kania, 1981). Primary route of entry is the skin. Vapours readily penetrate the skin surface with absorption efficiency equal to that of inhalation. Absorption from spilling phenolic solutions on the skin may be very rapid, and death results from collapse within 30 minutes to several hours. Death has resulted from absorption of phenol through a skin area of 64 $inch^2$. Where death is delayed, damage of the kidneys, liver, pancreas and spleen, and oedema of the lungs may result. The symptoms develop rapidly, frequently within 15-20 minutes following spilling of phenol on the skin. Initial skin contact produces a white wrinkled discoloration with no experience of pain due to the local anaesthetic properties of phenol, with the affected area turning brown and subsequently becoming gangrenous. Prolonged exposure may result in deposition of dark pigment (ochronosis). Phenol vapours are also well absorbed by the lungs. Inhalation causes dyspnea, cough, cyanosis, and pulmonary oedema. Ingestion of even small amounts of phenol causes severe burns of the mouth, esophagus, and abdominal pain. Patches, first white then brown with areas of necrosis, may be noted about the face and oral cavity.

A 47-year-old male had 90% phenol spilled over his left foot and shoe (3% of body surface area). After a 4.5-hour exposure, manifestations included confusion, vertigo, faintness, hypotension, ventricular premature beats, atrial fibrillation, dark-green urine, and tense swelling, blue-back discoloration, hypalgesia, and hypoesthesia of the affected area. Peak serum phenol concentration was 21.6 µg/ml, considered in the fatal range. Peak urine phenol plus

urine-conjugated phenol was 13,416 mg/g creatinine, indicating a major absorption. An elimination half-life of 13.9 hours was reported (Bentur et al., 1998).

Oral toxicity of phenol in humans leading to the death of the victim is reported for doses as low as 140-290 mg/kg body weight (Bruce et al., 1987).

Tanaka et al. (1998) reported the case of a 27-year-old male student, who had died after ingestion of a waste fluid containing phenol of DNA extraction. He was found in the laboratory the next day. At autopsy, the body surface was greyish in colour; the skin in the large area extending from the right arm to both legs had changed colour to dark brown, and some parts of its surroundings were chemically burned. There were also blisters in the skin across the burned area. The lips, oral mucous membranes and the walls of the oropharynx, larynx, brochus, esophagus and stomach were dark brown and inflamed. Histology revealed inflammatory changes in the lungs, interstitial edema and renal tubular hemorrhage in the kidneys, interstitial hemorrhage in the pancreas and adrenal glands.

In an effort to determine the various complications and frequency of occurrences of chemical face peeling, Litton and Trinidad sent a questionnaire to US plastic surgeons and reported the experiences submitted: Out of 794 plastic surgeons responding to this questionnaire, 588 (74%) used solutions containing approximately 50% phenol for face peeling purposes (oil/water emulsions containing 50% phenol). As a consequence of face peeling with these solutions, 87% of the surgeons did not encounter any systemic complications. Abnormal local skin pigmentation was observed as the most common local complication, and 21% of the surgeons announced that scarring of the skin is frequently seen after skin peeling. 13% of the surgeons noted cardiac complications, with tachycardia being the most frequent observation (Litton and Trinidad, 1981).

Conclusion

Signs and symptoms of acute toxicity in humans and experimental animals are similar regardless of the route of administration. Absorption is rapid, as illustrated by the fact that acute doses of phenol can produce symptoms of toxicity within minutes of administration: Oral toxicity of phenol in humans leading to the death of the victim is reported for doses as low as 140-290 mg/kg body weight (Bruce et al., 1987). Absorption from spilling phenolic solutions on the skin of humans may be very rapid, and death results from collapse within 30 minutes to several hours. Death has resulted from absorption of phenol through a skin area of 64 $inch^2$ (Kania, 1981). For animals, dermal and oral LD_{50} values are given in the literature: An oral LD_{50} of 340 mg/kg bw for rats (Deichmann and Witherup, 1944), of approximately 300 mg/kg bw for mice (von Oettingen and Sharpless, 1946) and of less than 620 mg/kg bw for rabbits (Deichmann and Witherup, 1944) are reported. A dermal LD_{50} value of 660-707 mg/kg bw was determined for female rats (Corning and Hayes, 1970). Although LC_{50} values are not available in the literature, rats are reported to tolerate phenol concentrations as high as 236 ppm (900 mg/m^3) for 8 hours, resulting in ocular and nasal irritation, loss of co-ordination, tremors, and prostration. Based on the frequent reports on human experience with occupational exposure to phenol in earlier times (since 1871), phenol has been classified as “toxic” and labelled with “R 23/24/25 (Toxic by inhalation, in contact with skin and if swallowed)”.

4.1.2.3 Irritation

4.1.2.3.1 Studies in animals

Skin irritation

Due to the extreme corrosive properties of phenol no data on skin irritation are available.

Eye irritation

Upon the application of 0.1 g of phenol (no data on purity) into the eyes of male, albino rabbits (number of animals not given), the conjunctivae became inflamed, the corneas opaque, and the rabbits gave evidence of marked discomfort. Examination of the exposed eyes 24 hours following exposure showed severe conjunctivitis, iritis, corneal opacities occluding most of the iris, and corneal ulcerations extending over the entire corneal surface. There was almost no perceptible improvement in the condition of the eyes during the observation period, and by the 14^{th} day all of the exposed eyes exhibited keratoconus and pannus formation (Flickinger, 1976).

In an eye irritation test conducted similar to international guidelines, two groups of at least 6 rabbits were exposed to a 5% aqueous solution of phenol (reagent grade): The first group received 0.1 ml solution and the eyes were gently washed for 2 minutes with 300 ml of tap water 30 seconds after exposure to the test material. The second group received 0.1 ml of the solution and the eyes remained unwashed. All of the animals treated with this 5% aqueous solution of phenol produced corneal opacity. Washing enhanced the recovery of eyes damaged by phenol. The washing procedure increased the number of eyes demonstrating pannus but decreases in some cases the severity and duration of corneal opacities (Murphy et al., 1982).

4.1.2.3.2 Studies in humans

No data on local irritation effects available.

Conclusion

Phenol causes severe chemical burns, occasionally skin necrosis is seen with solutions as dilute as 1% (Kania, 1981). Eye irritation in rabbits caused by a 5% aqueous phenolic solution was irreversible after an observation period of 7 days (Murphy et al., 1982). Thus, data on local irritation caused by phenolic solutions cannot be assessed properly.

4.1.2.4 Corrosivity

4.1.2.4.1 Studies in animals

No data on relevant skin irritation/corrosion tests with animals are available.

In a study with 5 male and 5 female rats per test group, conducted in order to assess skin decontamination procedures, moderate to severe chemical burns were observed after a 1-minute uncovered application of undiluted (molten) phenol: Five male and five female rats were treated

with 1 ml phenol AR per kg body weight (used as a liquid by maintaining at 45°C in a water bath) for exactly one minute. After this application, the contaminated area was sprayed for 45 seconds with appropriate solvents: After treatment with water no mortality occurred, hematuria, convulsions and moderate burns were documented; after treatment with PEG 300 no hematuria, no convulsions and very mild burns were observed. If the application site was quickly wiped over after the 1-minute contact, no animal died but hematuria, convulsions and severe black burns were documented (Brown et al., 1975).

The contact of 0.5 g of phenol (no data on purity) moistened with physiological saline with the intact and abraded areas of the skin of the bellies of rabbits (no data on number of animals) for a maximum period of 24 hours produced necrosis of the intact skin, it is not classified as a primary irritant but as a "corrosive" substance, no more information on the test is given (Flickinger, 1976).

Severe chemical burns - even with dilute solutions - were documented after contact of rabbit eyes with phenol in a study conducted in 1928: Using an 87% aqueous solution of phenol (no data on purity of phenol) the eye was completely destroyed. When the test substance was left in the eye for 10 seconds or longer before treatment with water, 60% of the treated eyes resulted in transparent corneas. A 50% solution of phenol in glycerine left in the eye without treatment caused a very opaque cornea. After a burn of 10 seconds or longer, 30% of the eyes treated with any treatment had transparent corneas in 3-5 days (Cosgrove and Hubbard, 1928).

4.1.2.4.2 Studies in humans

Initial skin contact with phenol produces a white wrinkled discoloration with no experience of pain due to the local anaesthetic properties of phenol, with the affected area turning brown and subsequently becoming gangrenous. Ten percent solutions regularly produce corrosion, and occasionally skin necrosis is seen with solutions as dilute as 1%. Concentrated solutions are severely irritating to the eyes and cause conjunctival swelling with the cornea becoming white and hyperaesthetic; loss of vision has occurred in some cases. Concentration is more critical than volume with respect to local response (Kania, 1981).

From 1871 onwards cases of carbolic acid gangrene of the fingers were reported frequently. In most cases survival of affected fingers was unusual and amputation had to be carried out. A case of a male laboratory assistant aged 18 years is reported by Abraham (Abraham, 1972): This assistant conducting a chemical experiment at home was wearing rubber gloves in the right thumb of which were accidentally present some crystals of phenol (no data on purity). He felt no pain or discomfort. After completing the experiment, he removed the gloves and found that his right thumb was quite white over the pulp, and was completely insensitive, no blistering was present. Approximately 41 hours after the injury he was referred to a plastic surgery department. On examination most of the skin of the pulp of the thumb was quite black, the surface of the affected portion being dry and hard. Full movement was present, and examination of the nail bed showed a normal colour with a normal colour return on pressure. Circulation in the base of the thumb, which was not swollen, and in the remainder of the hand and upper extremity was normal. Twenty-six days after the injury a clear line demarcation had formed, there was a full thickness skin loss but a considerable bulk of fibro-fatty pulp tissue had survived. No bone, joint capsule or tendon was exposed. A thin split skin graft from the inner aspect of the upper arm was applied in strips transversely on tulle gras to the raw area, ten days later the thumb was completely healed, 2 month later sensation over the grafted thumb-pulp was apparently normal.

Conclusion

Initial skin contact with phenol produces a white wrinkled discoloration with no experience of pain due to the local anaesthetic properties of phenol. Phenol causes severe chemical burns, occasionally skin necrosis is seen with solutions as dilute as 1% (Kania, 1981). Eye irritation in rabbits caused by a 5% aqueous phenolic solution was irreversible after an observation period of 7 days (Murphy et al., 1982). Thus, data on local irritation caused by phenolic solutions cannot be assessed properly.

The existing classification with the R-phrase: Causes burns (R 34) is confirmed.

4.1.2.5 Sensitisation

4.1.2.5.1 Studies in animals

In a modified Buehler Test ten female Hartley albino guinea pigs were treated with phenol (purity: 99.9%) as follows: For induction a 10% phenol concentration in white petrolatum was applied to the skin for 48 hours. This procedure was repeated three times a week for two weeks. Two weeks after the end of the induction procedure 1% and 0.1% phenol concentration in white petrolatum was used for challenge treatment. Exposure time was 48 hours. None of the animals showed a positive response. Control animals were not included in the study (Itoh, 1982).

In a Mouse Ear Swelling Assay (MESA) 15 female Balb/c mice received a topical application of a 5% phenol concentration on both sides of the right ear on days 0 and 2, and a scapular subcutaneous injection of 0.05 ml Complete Freund´s Adjuvans on day 2. On day 9, left ear thickness was measured immediately before topical application of a 5% phenol concentration on both sides of the ear, and again 24 hours later (day 10). Ear thickness was not affected by phenol treatment demonstrating that phenol has no skin sensitising potency. The purity of phenol and the vehicle were not mentioned (Descotes, 1988).

4.1.2.5.2 Studies in humans

There is no evidence of allergic contact dermatitis caused by phenol. No specific Ig-E-reaction to phenol was measured for 45 students before and after a 4-week exposure to phenol during an anatomy course (no further details on the exposure; Wantke et al., 1996).

Conclusion

Phenol did not cause any signs of skin sensitisation in tests conducted with guinea pigs (modified Buehler Test, Itoh 1982) and mice (Mouse Ear Swelling Assay, Descotes 1988), and there is no evidence of allergic contact dermatitis in humans. Therefore, labelling with R 43 is not warranted.

4.1.2.6 Repeated dose toxicity

4.1.2.6.1 Studies in animals

Up to now, there is no test on repeated dose toxicity of phenol available which was carried out in full compliance with the minimum requirement of a 28-day standard test.

Nevertheless, the cancer studies of the National Institutes of Health (NIH, 1980) were assessed for the requirements of the regulation 793/93/EEC as valid studies with some restrictions. A range of additional studies with oral, inhalative, dermal, subcutaneous, intraperitoneal application modus, and with short repeated (only few days) up to subchronic exposure (90 days) on several species (rat, mouse, rabbit, guinea pig) were evaluated as further information looking for consistency of phenol-related effects. From these studies the following target organs or organ systems showed effects: central nervous system, bone marrow (hemopoietic system and stromal cell function), immune system, liver, lung, kidneys, heart, and skin.

Oral studies

- In NIH studies (1980), 50 animals/sex/group of F344 rats and B6C3F1 mice were administered drinking water containing 2,500 or 5,000 ppm phenol (equivalent to an assumed phenol uptake of 200 and 450 mg/kg/day for rats and 281 and 375 mg/kg/day for mice) for 103 weeks. Examinations included clinical signs (twice daily), presence of palpable masses (weekly), mean body weights and food consumption (every 2 weeks, monthly after 12 weeks), and water consumption (weekly). After necropsy of moribund and survived animals gross and microscopic examinations were performed on major organs and tissues (> 28) and all gross lesions. No treatment-related effects on the survival rate were observed in rats and mice. Treated animals showed reduced body weights (rats at high dose, mice at both doses) and reduced water consumption (both species and sexes at both doses, -10 and –20% in rats, -25 and -40 to –50% in mice). No other relevant toxic effect was seen related to non-neoplastic lesions. As parameters on haematology, clinical biochemistry as well as on urinanalysis were not investigated, data from further studies with deviation from actual standard testing methods were considered to indicate further effects of phenol-related local and systemic toxicity. Because the reduction of body weight gain was attributed to the reduced water consumption, the No-observed-adverse-effect-level (NOAEL) from this study is 450 mg/kg bw/day for rat and 375 mg/kg bw/day for the mouse. With respect to target organs identified from other studies, no indication on phenol-related effects were observed in the heart, liver, and immune system (spleen, thymus, lymph nodes, brain) in male and female rats. Incidences of chronic inflammation in the kidney of treated rats (74%, 74%, 96% in male rats and 14%, 26% and 56% in female rats of the control, low and high dose groups) were increased in treated rats. They are interpreted as of questionable toxicological significance because of high spontaneous rates in rats and because of the lack of grading for any of the histopathology findings of these studies. In mice, none of the presumed target organs showed dose-related increased incidences of alterations.
- Immunotoxicity screening and clinical pathology tests were conducted in male Sprague-Dawley rats as part of a two generation oral (drinking water) reproductive toxicity study of phenol (IITRI, 1999, see Section 4.1.2.9 - reproductive toxicity). A subset of male study population administered to phenol at concentrations of 0, 200, 1,000 or 5,000 ppm in the drinking water (approximately 0, 15, 71 and 301 mg/kg/day) for at least 13 weeks prior to assessing clinical pathology or immune competence. The clinical pathology consisting of

standard clinical chemistry and haematology parameters was performed on 9-10 rats/group, of which at least 8-9 rats/group were later used in the antibody-forming cell (AFC) assay. An additional five rats served as positive controls for the AFC assay. They received daily intraperitoneal injections of cyclophosphamide (20 mg/kg/day) for four days prior to assay. All AFC animals received app. 2 · 108 sheep red blood cells (SRBC) by intravenous injection four days prior to assay. In the positive control, there was a significant reduction of AFC and spleen cellularity compared to the drinking water exposed control animals. No significant effects were observed on spleen weight, cellularity (cells/spleen), or AFC (no. of antibody producing plasma cells per spleen or per 106 cells) for any of the phenol-administered groups compared to the control group.

- Clinical pathology examinations revealed significantly increased levels of blood urea nitrogen (BUN) in the high dose group following 13 weeks. Any other treatment related alterations of clinical chemistry parameters (including creatinine) and of haematology parameters were observed.
- Administration of up to 5,000 ppm phenol (301 mg/kg bw/day) for at least 13 weeks did not result in any significant alteration in the T-cell dependent humoral response as measured in the AFC assay. No significant changes other than increased BUN concentrations at 5,000 ppm were detected in clinical chemistry and haematology parameters. Increases of BUN and creatinine may indicate extensive renal dysfunction. Hence, both parameters are relatively insensitive. Data on morphologic damage of renal tubule were not available in this part of the study. Because creatinine concentrations were normal in all dosed groups, elevated BUN levels were regarded to be of minimal to questionable biological significance. For the parameters examined, the NOAEL was accepted to be 5,000 ppm (301 mg/kg bw/day).
- In CD-1 mice (5 males/group), a 28-day administration of phenol (reagent grade, no data on impurities) in drinking water revealed significant reduced red blood cell counts (-54%) and reduced hematocrite values (-8%) at an analytical concentration of 95.2 mg/l (equivalent to 33.6 mg/kg/day). A significantly dose-dependent decrease of erythrocyte counts was also evident in low and mid dose group (-32% at 4.7 mg/l, equivalent to 1.8 mg/kg/day, -35% at 19.5 mg/l, equivalent to 6.2 mg/kg/day). At high dose level, tests on immune functions revealed a decreased lymphoproliferative response to B-cell and T-cell mitogens and in mixed lymphocytes cultures. At 19.5 mg/l (equivalent to 6.2 mg/kg/day) and at 95.2 mg/l (equivalent to 33.6 mg/kg/day) antibody production against T cell-dependent antigen (sheep erythrocytes) was suppressed as determined by the number of IgM antibody plaque-forming cells and serum antibody levels. No significant effects on food and water consumption, body weight gain, white blood cells (number and differential counts), spleen cellularity and no gross lesions were found in liver, kidney, spleen, thymus, lung, heart and brain of mice in any treatment group. No changes were reported to be found on the weight of selected organs including spleen, kidney, thymus and liver (data not shown). Neurochemical investigations revealed decreased levels of neuro-transmitters in several brain regions at all dosages tested. In the hypothalamus, a major norepinephrine-containing compartment, the concentrations of norepinephrine were significantly decreased by 29 and 40% in groups dosed with 19.5 and 95.2 mg/l, while in the corpus striatum dopamine concentrations decreased by 21, 26, and 35% at 4.7, 19.5 and 95.2 mg/l, respectively. Phenol also decreased 5-hydroxytryptamine in the hypothalamus, medulla oblongata, midbrain and corpus striatum. Levels of monoamine metabolites decreased in the hypothalamus (5-hydroxyindoleacetic acid), midbrain (vanillylmandelic acid), corpus striatum (vanillylmandelic acid and dihydroxyphenylacetic acid), cortex (vanillylmandelic acid), and cerebellum (dihydroxyphenylacetic acid) (Hsieh et al., 1992).

- Toxic phenol effects were examined in multiple organs of 77-day old F344 rats after 14 day oral dosing (Berman et al., 1995; Moser et al., 1995; MacPhail et al., 1995). Doses of 0, 4, 12, 40, and 120 mg/kg bw of phenol (analytical grade purity, > 99%) in deionised water were applicated by gavage to groups of eight females each group for 14 consecutive days. H&E-sections of liver, kidneys, spleen, and thymus were examined microscopically. All rats of the high dose group died premature (one at day 1, 2, 3, 4, 8, and 11, two at day 6, without any data on organ toxicity). Body weight loss of 14% was reported in the 120 mg/kg dose group, tissue sampling was not done in this dose group. At the 40 mg/kg dose, one female showed vacuolar degeneration of liver cells, two females had necrosis or atrophy of spleen or thymus (not further specified), and three females had renal tubular necrosis, protein casts, and papillary hemorrhage. One female of the 12 mg/kg dose group showed a necrosis of atrophy of spleen or thymus (not exactly reported). The NOAEL of this oral 14-day study was considered to be 4 mg/kg bw/day. This study included examinations of blood and serum and organ weight determination, but did not describe results. Examinations of the neurobehaviour revealed inhibited pupil response in the 120 mg/kg group at day 4 of treatment and slightly non-significant decreased motor activity levels at day 9 and 15. Increased rearing was obtained in the 40 mg/kg female group at day 15.

Inhalation studies

- A 14 day-inhalation study on phenol (CMA, 1998a) specifically designed to examine effects on the respiratory tract was conducted in F344 rats (20 animals/sex/group). Phenol vapour was administered by nose-only exposures for 10 exposures (5 days/week, 6 hours/day) at target concentrations of 0 (air control), 0.5, 5.0 and 25 ppm (1 ppm ≈ 0.00385 mg/l). Sacrifices were performed for 10 animals/sex/group after 10 exposures, and after a 14-day recovery time for the remaining animals. Physical observations for each animal were performed for viability (prior to exposure and 30 minutes following exposure viability) and for clinical signs (during each exposure and twice daily at cage side). Body weight were measured twice in the pre-test weeks, just prior to the exposure, weekly during the exposure time and before sacrifice. Food consumption measurements were conducted weekly once prior to the exposure and during the treatment weeks. Blood samples for analysis of haematology and clinical chemistry parameters were collected just prior to sacrifice at termination and recovery. Complete macroscopic postmortem examinations were conducted on all animals. Microscopic evaluations were conducted on the liver, kidney, respiratory tract tissues (lungs with mainstem bronchi, trachea, larynx, pharynx and 4 sections on nasal turbinates) and gross lesions for animals in the control and high-exposure groups, at termination and recovery. The test conditions were similar to a 14-day inhalation study design of OECD Guideline 412. However, the number of organs which were examined by histopathology was reduced in this study, and in comparison to the Annex V, B.8 method the study duration was 14 days instead of 28 days.
- The mean analytical exposure concentrations determined by HPLC analysis at 6 times per chamber per day were 0.00, 0.52 ± 0.078, 4.9 ± 0.57 and 25 ± 2.2 ppm for the air control and exposure groups. The study revealed no remarkable differences between control and phenol vapour exposed animals for clinical observation, body weights, food consumption, clinical pathology, organ weights and macroscopic and microscopic postmortem examinations, at termination and recovery. Based on the conditions of this study, no adverse effects were seen at phenol concentrations up to 25 ppm in the respiratory tract or in any other organ system (NOAEClocal and systemic, ≈ 0.09625 mg/l).

- A 14 day-inhalation study with phenol concentration of 0.1 mg/l on rats (age 12-13 months, strain unknown, no data on number of animals and exposure duration per day) induced clinical signs of motor disorders with impaired function of the balance regulation (Dalin and Kristoffersson, 1974). On day 1 increased activity, on day 3 and 4 appearance of motor disorders with impaired balance and disordered walking rhythm, labile sitting position, disturbed grooming behaviour. Symptoms passed off during day 5, after that animals seemed more sluggish. CNS effects on equilibrium and motor co-ordination studied in a tilting-plane method before and after treatment revealed a significant decreased sliding angle after exposure to phenol. Increased serum liver enzymes (LDH, ASAT, ALAT, GLDH) were indicative of liver damage. Additionally, serum levels of potassium and magnesium were increased. The study was incomplete with respect to parameters of haematology and clinical chemistry (no data on necropsy, organ weights and histopathology).
- Subchronic inhalation studies showed no pathological lesions in 15 rats, although bronchopneumonia and degenerative cell alterations of the myocard, liver and kidney were observed in six rabbits and 12 guinea pigs at vapour concentration of 0.1-0.2 mg/l (7 hours/day, 5 days/week, all species). Rabbits were exposed on 63 days over a period of 88 days. Liver changes were characterised as centrolobular necrosis, little exsudative inflammation. Myocard degeneration with necrosis of muscle bundle, interstitial fibrosis and inflammatory cell infiltrations were found in the heart. The kidneys demonstrated diffuse tubular swelling and casts of cell debris of granular material, focal cortical tubular degeneration, tubular atrophy and dilatation, glomerular degeneration/sclerosis and interstitial fibrosis. Guinea pigs were most sensitive, after 3 to 5 exposures decreased activity and paralysis of the hind quarters were observed. Myocardial degeneration and inflammation, lobular purulent pneumonia, and similar lesions of the liver and kidneys were reported for the guinea pigs. A premature limit of the treatment of the guinea pigs was necessary because of respiratory disturbances and sudden deaths of five beginning after 20 days of exposures during a treatment period of 28 days. Rats exposed on 53 days over a period of 74 days did not show any clinical symptoms or any morphologic abnormality. The study is of limited validity because of the absence of data on phenol purity, growth, haematology, clinical chemistry, organ weights and a list of organs examined microscopically. The data from the rabbits and guinea pigs were considered of low reliability because purulent bronchopneumonia may also indicate a primary infectious disease. The lesions of the other parenchyma might be related to this. However, there were consistence with another study of limited quality (Deichmann et al., 1944), however an association to the phenol treatment can not be totally excluded.

Dermal studies

- Phenol absorption after repeated dermal applications on 18 days at concentrations of 1.18-7.12% aqueous phenol solutions produced tremors (≥ 2.37%) as well as epidermal hyperkeratosis and ulceration in rabbits at concentrations > 3.56 per cent. Four animals per dose group were exposed to preparations of 1.18, 2.37, 3.56, 4.75, 5.93, and 7.12% phenol on 5 hours/day and 5 d/w; up to 4.75% two of four animals obtained an occlusive application. The hair was clipped from the abdomen, and an area of 10 by 15 cm was exposed initially to 5 ml of the solutions, followed every 20 minutes by 2 ml. Assumed daily total volume was 33 ml/day, based on an assumed body weight of 3 kg the 7.12% solution corresponded to 783 mg/kg bw/day of phenol. Signs of moderate to systemic intoxications (not further characterised) were described at concentrations of 5.93 and 7.12% phenol solutions, one rabbit of the high dose died after six exposures (Deichmann et al., 1950). No other data were reported, no laboratory or postmortem investigations were incorporated. Based on the scarce

observations provided, the NOAEL for systemic toxic effects was 1.18% (130 mg/kg bw/day), the NOAEL for local effects on the skin was 2.37% (260 mg/kg bw/day). Although the confidence in these data was low due to very limited study design/reporting and few animals tested, the study was mentioned because of the lack of other valid data for the dermal route.

Studies with other application routes

- Phenol applicated intraperitoneally in mice from two strains on 4 days at daily dosages of 200 mg/kg suppress bone marrow stromal cell function to support *in vitro* hemopoiesis of granulocyte/monocyte precursors in cocultured bone marrow cells from untreated animals (Gaido and Wierda, 1985).
- *In vivo* studies in mice demonstrated a decreased concentration of granulopoietic stem cells in the bone marrow of mice, which were injected subcutaneously on 6 days with dosages of 50 mg/kg/day (Tunek et al., 1981).
- Bolcsak and Nerland (1983) confirmed the inhibition of erythropoiesis by phenol. 48 hours after a subcutaneous injection of 0.5 ml phenol in corn oil (calculated dose 245 mg/kg) to male Swiss-Webster mice iron incorporation into developing erythrocytes was inhibited. Intraperitoneal administration of phenol at lower doses (25-100 mg/kg) in female Swiss albino mice did not result in a significant reduction of iron uptake into erythrocytes.
- However, the combined treatment of phenol with its metabolites hydroquinone or catechol yielded greater depressions of 59Fe-uptake into erythrocyte hemoglobin than could be accounted for on a simple additive basis (Guy et al., 1990).
- A direct toxic effect of phenol on the proximal tubules of the kidneys was demonstrated after infusion of phenol solutions of 0.1, 1.0, and 5.0% concentrations directly to the renal circulation in rats (Coan et al., 1982).
- 2.5% and 5% phenol in water or glycerol solutions were injected into the rectovesical pouch in 35 male rats. After 3 weeks the bladders were excised and the effects on the density of acetylcholinesterase-enzyme-containing nerves were reduced by 20% in the phenolised animals (Parkhouse et al., 1987). Transient convulsions were seen in the aqueous subgroup within 1 min post dosing.

Specific studies on neurotoxicity

- In a recently performed study on potential neurotoxicity of phenol (> 99%) (CMA, 1998b), three groups of 15 male and female Sprague-Dawley rats were treated for 13 weeks via drinking water with phenol concentrations of 0, 200, 1,000 or 5,000 ppm, respectively (≈ 0.77, 3.85 or 19.25 mg/ml). Acceptable concentrations (± 10%) were recorded in analysis of the dosing solutions for phenol content during weeks 1, 7, and 13. The average intake of phenol during the treatment period was 0, 18, 83 and 308 mg/kg bw/day for males and 0, 25, 107 and 360 mg/kg bw/day for females. A 4-week recovery period followed the treatment phase. During the study, body weights and food consumption were recorded weekly, water intake was measured daily and any abnormal clinical sign was recorded daily. A functional observational battery (FOB) and motor activity test were conducted prestudy and once during each of weeks 4, 8 and 13, and for recovery animals during week 17 as well. Following 13 weeks of treatment, 5 rats/sex/group were given a whole-body perfusion and later those animals in the control and 5,000 ppm groups underwent a neuropathological evaluation. Brain weight, length and maximum coronal width were recorded prior to trimming. Paraffin embedded sections from brain (6 levels) and spinal cord (cervical and lumbar) were

processed for H&E staining. Toluidine blue stained epoxy sections were examined from sciatic, sural and tibial nerves (longitudian and cross sections) and from central nervous system (Gasserian ganglion and dorsal and ventral root and root ganglions of cervical and lumbar regions). Other tissues were preserved, but were not examined microscopically. The remaining animals were euthanised at the end of the recovery period; 5 rats/sex/group were given a whole-body perfusion (not examined) and all others from every group were subjected to a gross pathological examination. Laboratory investigations on parameters of hematology, clinical biochemistry and urinalsis were not conducted.

One female in the 5,000 ppm group was euthanised on day 14 due to poor condition. Clinical signs observed for this animal included dehydration, hunched posture/prominent backbone, thin/weak appearance, uncoordinated movements, tremors, reduced activity, pallor, partly closed eyes, reduced body temperature, decreased feces and ungroomed fur/fur staining. No other animals were euthanised early and none died prior to scheduled euthanasia. Primarily during the first three weeks of treatment, another female and male of the 5,000 ppm group showed dehydration, hunched posture/prominent backbone/thin appearance, reduced activity, decreased feces and fur staining, tremors, pallor and partly closed eyes; reduced body temperature were also noted for the female rat. Dehydrated appearance commencing at the end of week 1 was seen for seven males and nine females in the 5,000 ppm group and for two males and two females in the 1,000 ppm group. In addition, one male and six females in the 5,000 ppm groups showed a prominent backbone/thin appearance.

The mean body weight of the 5,000 ppm males was slightly lower from day 8-57 and significantly lower from day 64 until treatment termination on day 92. The mean body weight of the 5,000 ppm females was significantly lower from day 8 and thereafter until treatment termination on day 92. Marked body weight gains were seen during the recovery period for both sexes and the mean body weights of the 5,000 ppm males were not significantly different from control values throughout this period. The mean body weight of the 5,000 ppm females was significantly lower on day 99 of the recovery period but there was no significant difference to the control values thereafter. No significant differences in mean body weight were detected between the control and 200 or 1,000 ppm groups for either sex at any time during the study.

The mean food consumption of the 5,000 ppm males was significantly lower on day 1-8, 43-50 and 71-85 and insignificantly lower for all other periods. The mean food consumption of the females was significantly lower throughout the treatment period, which exception of days 15-22 which was only slightly lower. Marked improvement occurred during the recovery period and the mean food consumption in the 5,000 ppm was slightly or significantly increased throughout this period. No significant decrease in mean food consumption was detected between the control and 200 or 1,000 ppm groups for either sex at any time during the study. Females in the 1,000 ppm group showed slightly lower values throughout the study. No data on food efficiency were reported.

The mean daily water consumption of the 5,000 ppm males and females was significantly reduced throughout the treatment phase with the exception of days 52-53 which was only slightly lower for females. Marked improvement was seen immediately at the start of the recovery period and the mean daily water consumption in this group was slightly or significantly increased throughout this period. Generally slight or on occasion significant reductions in water intake were noted for the 1,000 ppm males and females during treatment, however, values were similar to controls during recovery. No significant reduction in mean

daily water consumption was noted between the control and 200 ppm males or females throughout the study.

The FOB evaluation did not reveal any findings of neurotoxicological significance following qualitative (observations in home cage, removal from home cage, observations in arena, handling observations, on surface, and on top of box) or quantitative (grip strength, hindlimb splay) measurements throughout treatment or following recovery except a significant decrease in body temperature noted for males in the 1,000 and 5,000 ppm groups at the week 13 evaluation. These values were reported to be within the historical control range and together with the absence of other FOB findings, the author concluded that this was not of neurotoxicological significance. To our opinion this conclusion can not be accepted. As a general rule, data from internal control groups are of higher relevance unless it is obvious that their values are abnormal. This was not the case. The reduction at week 13 was dose-related and there already was a tendency to lower body temperatures of dosed males at week 8. After recovery, the values returned to the control level. Therefore it can not be excluded that the reduction of body temperature was a treatment-related effect.

No significant differences in group mean activity counts were detected for males in any of the treated groups following each evaluation throughout treatment (week 4, 8 and 13) or following recovery (week 17). The motor activity test indicated a significant reduction in total group mean activity counts at the week 4 and 8 evaluation for the 5,000 ppm females and for females of the 1,000 and 5,000 ppm group at week 17 during recovery. At week 13 total mean activity counts were significantly higher in 1,000 and 5,000 ppm females. The author found that these changes were likely secondary to the reduction in water and/or food consumption and given the generalised nature of the changes and the lack of FOB findings they were considered not to be of neurotoxicological significance. However, the likeliness of this hypothesis is unclear, because in general altered motor activity is not necessarily be associated to reduced food/water uptake (Gerber and O-Shaugnessy, 1986). In addition, there was only a minor decrease in water uptake and normal feed consumption at 1,000 ppm. In opposite to this, it can also be assumed, that lowered food/water intake may occur secondarily to reduced motor activity. The lack of significant changes in the motor activity counts for dosed males does not support the second assumption. Thus, an interference between motor activity and water consumption can not be clarified. Also, the discrepancy of increased counts at week 13 only could not be explained. However, due to the neurotoxic potential of phenol that was known from other studies, a phenol-associated reduction in motor activity could not be ruled out.

At week 14 and recovery (week 18), there were no significant differences in brain weight for males or females in any of the treatment groups. The brain width of males in the 1,000 and 5,000 ppm groups were significantly increased; the relevance of this finding is unclear. No gross or histopathological lesions were found in central or periperal nervous tissue that were attributed to treatment with phenol. The premature killed female showed small spleen and thymus, dark areas on the stomach mucosa and discoloration of multiple organs (adrenal, kidney, liver, pituitary).

The NOAEL for neurotoxicity study on rats was 200 ppm (18 mg/kg bw/day for males, 25 mg/kg bw/day for females).

- Dose-related signs of encephalopathy were observed in male Sprague-Dawley rats (300 ± 50 gm) after single intraperitoneal injections of 70 µmol phenol (≈ 0.313 mg/kg bw) and above (Windus-Podehl et al., 1983). Changes in general body movement, body control,

leg control, muscle tone, and response to external stimuli were evaluated in 3-6 males per dose after single ip. injections of 70, 180, 200, 420, 480, 540 or 600 µmol phenol (dissolved in saline, pH-adjusted to 7.4). At a dose of 600 µmol, all animals became deeply comatose within 5 minutes continued until recovery within 20-60 min later or death. At 540 µmol, 50% of animals were comatose. At 480 µmol, none of the animals became comatose, but the shaking of limbs was present. Doses below 420 µmol produced slight decrease in general body movement, loss of back leg control, and shaking of limbs. The loss of back leg control was discernible with as little as 180 µmol, and the shaking of limbs with as little as 70 µmol. The intensity of the shaking increased as dose increased between 70 and 200 µmol.

- Histopathological changes after single injection of 0.5 ml solutions containing 3% or 6% phenol or three injections of 3% phenol in the epidura of the lumbar spinal cord were examined in 11 cynomologus and rhesus macaque monkeys (Katz et al., 1995). Five primates remained untreated and 5 others received epidural administration of radiographic contrast material. Two weeks after single or final phenol injections animals were killed and the spinal cord and thoracolumbar roots were removed and immersion fixated with Karnovsky's fixative. Tissue sections were stained routinely for hematoxylin and eosin or with myelin stains, selective sections were stained with immunoperioxidase techniques using an antibody to glial fibrillary acid protein (GFAP) or CD68 (macrophage marker). One animal that received 6% phenol showed ataxia and profound flaccid paralysis of both legs and died on day 3 post injection. Other primates developed motor or leg weakness after phenol injection. Axonal swelling, myelin sheath degeneration, spare inflammatory cell infiltration and fascicle injury observed in phenol-injected monkeys was characteristic for nerve fibre degeneration of the posterior and to a lesser extent of the anterior nerve roots at the lumbar and thoracic level and in some animals in the lower cervical or sacral levels. Similar multifocal or confluent lesions along with prominent vacuolisation and gliosis were also found in the spinal cord. The severity of lesions increased gradually in animals receiving single 3% phenol < repeated 3% phenol < single 6% phenol injections. The severity of clinical symptoms did not correlate with the morphological lesions; a well known phenomenon of many neurotoxic substances.
- A single unilateral needle injection of 0.01 or 0.015 ml of 5% phenol in saline directly into the sciatic nerve of rats causes persistent loss of motor function showing gait abnormalities immediately after treatment (Burkel and McPhee, 1970). Clinical symptoms gradually improved during the next 8 weeks after treatment, and were not longer evident after 14 weeks. A total of 29 animals killed sequentially after 10 minutes, 1 hour, 1 day, 1, 2, 4, 8, and 14 weeks postinjection were examined with light microscopy and electronmicroscopy of toluidine blue stained sections. After 10 minutes to 1 day postinjection hemorrhage and vessel occlusion was severe next to the injection area. Wallerian degeneration of axons and desintegration of myelin sheaths were seen reaching a maximum extent after 1 week postinjection. Other consequences were muscle atrophy and endoneural fibrosis. Most of the nerve fibres regenerated until the 14th week after injection.
- Another more recently conducted study confirmed the nonselective neurolysis of phenol on a peripheral nerve (Westerlund et al., 1999). 0.01-0.02 ml of a 7% phenol-aqua solution was injected intra- or perineural to the sciatic nerves of male adult Sprague-Dawley rats (groups of 16 rats). Lidocaine or saline injections were used as controls. Clinical evaluation as measured by a muscular function score was performed under blind conditions at 2, 4, and 7 days and 2, 4, and 8 weeks. Tissue samples were taken after 1, 2, 4, and 8 weeks post injection for the evaluation of the degree of neurolysis by light- and electronmicroscopical examinations. In the phenol-treated groups, severe muscle dysfunction (moderate-severe paresis up to total paralysis, severe plantar flexion) was noted immediately after recovery

from anesthesia and persisted up to 4 weeks; severity scores remained at higher levels during the whole study period in the group with intraneural administration. After 8 weeks, individual rats still showed slight weakness. Moderate to severe gastrocnemius muscle atrophy developed within 2 weeks and was still present after 4 weeks in rats with intra- and perineural phenol injection. Atrophy persisted until the end of study at week 8 in one rat of the intraneural group. Trophic skin changes such as redness (evident in rats of the perineural group during the first week) or redness and roughness was notable in most rats of the intraneural group after 2 weeks. Peri- and intraneural injection of phenol-aqua solution induced total endoneural damage of the cross-sectional area at the injection site. Axonal regeneration started after 1 week in rats of the perineural injection group and after 2 weeks in rats receiving intraneural injection of phenol.

- On 67 saphenous nerves of 42 cats acute electrophysiological studies alone, in combination with histology/electronmicroscopy or histology/electronmicroscopy alone were performed during or after 10-30 minutes of *in vivo* perfusion of phenol solutions with concentrations of 0.1, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, and 5% (Schaumburg et al., 1970). Within 1-2 minutes after injection, phenol solutions of 0.25% or higher diminished the action potential until the baselines were almost reached. After perfusion with saline the impulses returned to control values. Complete disappearance of the potential occurred within 2 minutes at 1%, recovery after washing with saline was slow and incomplete. At sacrifices 3-4 weeks post infusion, electronmicroscopical examination revealed Wallerian degeneration, demyelination and remyelination of the nerve fibres at 0.5% phenol for 30 minutes, or at higher concentrations and shorter perfusion time.
- Two out of six rats that received two single subcutaneous injections of 200 mg/kg phenol (≥ 99%) with 1 week rest between the injections showed neuropathic damages in the sacral spinal cord and dorsal or ventral spinal roots at a lower cord level whereas no effect at any cord level was seen in 10 control animals (Veronesi et al., 1986).

4.1.2.6.2 Studies in humans

Reports on humans with repeated oral, inhalative or dermal exposures to phenol described mucosal irritation, diarrhea, dark urine, weakness, muscle pain, loss of appetite and body weight, liver toxicity resulting in a bad general state of health (Baker et al., 1978; Merliss, 1972).

- Accidental spillage of 37,900 l of 100% phenol in July, 16, 1974 caused chemical contamination of wells in rural areas of Southern Wisconsin. Several families continued to drink their well water for several weeks after the spill (Baker et al., 1978). Human illness characterised by diarrhea, mouth scores, dark urine, and burning of the mouth was subsequently reported by 17 individuals who consumed the contaminated water. Their approximate daily intake of phenol was 10 to 240 mg/person/day (0.14-3.42 mg/kg bw/day). Systemic evaluation of persons exposed to phenol contaminated drinking water was performed about 7 months after the accident.
- There was a case report of a laboratory technician working for 13.5 years for a company engaged in the processing of phenol, cresol, and xylenol in their pure state (Merliss, 1972). He distilled phenol in a 99% solution on several times a day, was exposed to phenol vapour, and spilled phenol on his trousers. Gradually his health deteriorated with loss of appetite, weight loss, occasional dark urine, muscle pain. Slow improvement was seen after absence from the laboratory for several months, but symptoms as weakness, muscle aches and pain still remained. After return to work, symptoms recurred immediately. Medical evaluation

revealed emaciation, enlarged liver, dark urine and increased levels of liver enzyme activities.

- In a case report a 41-year old female with back and chest pain was treated with two series of weekly intramuscular injections for 37 and 18 weeks of a 10 ml solution of 25% dextrose, 25% glycerol, 2.5% phenol, and 47.5% sterile water mixed with 10 ml of 0.5% lidocaine (Kilburn, 1994). Following the treatment the patient noted the onset of extreme fatigue, chest pain and burning, dizziness, light-headedness and somnolence, memory loss, inability to concentrate, and instability of mood.
- Spiller et al. (1993) reported a 5-year retrospective review of all exposures to a high concentration phenol disinfectant (up to 26% phenol) reported to a regional poison control centre. Of a total of 96 located cases, 16 cases were lost to follow-up, leaving 80 cases for evaluation. Ages ranged from 1 to 78 years, with a mean of 10 years; 75% of the patients were < 5 years. There were 60 oral-only exposures, 7 dermal-only exposures, 12 oral/dermal exposures and 1 case was inhalation exposure. 52 cases were evaluated in a hospital. 11 patients (all oral exposures) experienced some form of central nervous system depression. Nine patients experienced lethargy (the time to onset was 15 minutes to 1 hour, with a mean time of 20 minutes); onset of lethargy progressed to unresponsiveness within 1 hour. Coma was seen in two patients (information on the ingested dose was not available). Burns were noted in 17 patients with oral exposure and 5 patients with dermal exposure. No cardiovascular complications were noted. A distinct change in urine colour to dark green/black was noted in 5 patients with oral exposure; oliguria or anuria was not seen. Recovery was complete in all cases. By history, the oral dose of exposure ranged from 2 to 90 ml disinfectant (520 mg to 23.4 g phenol). The largest dose without effect was 30 ml (8.8 g phenol) and the smallest dose with any effect was 5 ml (1.3 g phenol).
- Fasting blood samples were collected at the end of the shift of the last working day of the week from 20 workers (mean exposure duration 13.5 ± 6.55 years) exposed to time weighted average concentration of 5.4 ppm phenol (0.021 mg/l) alone during aromatic extraction from distillates containing wax, oil and impurities according to the factory reports (no further data on exposure). Hematologic and clinical chemistry parameters were examined (transaminases, total proteins, prothrombine time, bleeding time, clotting time, fasting blood sugar, serum creatinine, copper, zinc, iron, magnesium, manganese, calcium and complete blood picture) (Shamy et al., 1994). Urine samples were analysed for phenol, hippuric acid and methyl ethyl ketone (not reported here). The effects were compared to 32 workers of combined exposure to phenol, benzene, toluene and methyl ethyl ketone (not reported here) and 30 control subjects with similar mean age. Workers exposed to phenol alone showed significantly higher levels of ALAT, ASAT and clotting time, and lower levels of serum creatinine than control subjects. Significantly higher levels of haemoglobin, hematocrite, colour index, MCH, MCV, basophils and neutrophils and lower levels of monocytes than the control subjects were observed in the workers exposed to phenol alone. They also demonstrated significantly higher serum levels of Mg, Mn and Ca. Urinary phenol concentrations in the phenol-only group was significantly elevated (68.60 ± 47.06 mg phenol/g creatinine) in comparison to the background levels in the nonexposed control group (11.54 ± 4.7 mg phenol/g creatinine). Weaknesses of this study are the lack of data on the recording time points and duration, on individual exposure data, ranges of exposure height, and daily exposure duration. No information on the type of exposure measurements (either workplace or personal recording) was given. The strength of the study is the verification of an increased external phenol exposure by increased urinary concentrations in the phenol-only group.

Table 4.11 Mean levels of serum and hematological findings

	Exposed workers (n=20)		Control subjects (n=30)	
Test parameters	**Mean**	**SD**	**Mean**	**SD**
Serum				
ALAT (U/ml)	24.50*	4.11	15.81	14.92
ASAT (U/ml)	27.06**	716.87	14.71	10.70
Creatinine (mg/dl)	0.85**	0.20	0.99	0.20
Clotting time (min)	6.13**	0.82	4.06	0.46

* $p < 0.05$,
** $p < 0.01$ significant against control group

- Since 1920 phenol has been applied in medical practice as a topical anaesthetic or for relief of chronic pain and spasticity by intrathecal, epidural, intraneural, perineural or intramuscular injections (for review see Wood, 1978). Depending on the concentration and treatment schedule, phenol solutions caused protein coagulation and necrosis resulting in non-selective neurolysis of efferent and afferent nerve fibres and damage of perineural vessels.

Other information: Results from *in vitro* studies

Effects on the nervous system, bone marrow, immune system and lung were supported by data from some additional *in vitro* tests.

- A section of the sural nerve of adult cats was exposed to phenol solution showing a reversible block of nerve conduction on A- and C-fibres at low concentrations (0.05-0.125%) and persistence conduction on C-fibres at higher concentrations (0.6-1%) (Dodt et al., 1983).
- Phenol is toxic to mouse bone marrow stromal cells *in vitro* at a high concentration of $1 \cdot$ 10-4 M (Gaido and Wierda, 1984).
- In purified peritoneal macrophages, RNA synthesis was inhibited after exposure to phenol. This was interpreted as an indicator of reduced protein growth factor release required in the co-operation of bone marrow stromal cells and hematopoietic stem cells (Post et al., 1986).
- The cell viability of three leukaemic cell lines (human, rat, mouse) was 50% of that of control cultures after 48 hours of incubation with phenol concentrations of 0.2-1.9 mM (IC_{50}) (Ruchaud et al., 1992).
- Fan et al. (1989) demonstrated that phenol at concentrations of $1 \cdot 10^{-7} \sim 5 \cdot 10^{-5}$ M inhibit natural killer cell activity in an *in vitro* test on mouse spleen cells.
- An inhibitory effect on leukocyte chemotaxis was shown in a chemotactic activity model on peritoneal neutrophils of guinea pigs (Azuma et al., 1986).
- In an *in vitro* vapour model, phenol was cytotoxic to cell line derived lung epithelial cells from the rat (Zamora et al., 1983).
- A dose-related increase of cytotoxicity by phenol was reported at concentrations between 1 and 10 mM in a culture of rat dental pulp cells (RPC-C2A) (Kasugai et al., 1991).
- Phenol solutions with concentrations ≥ 8% induce contraction in isolated rings of lumbar segmental arteries from dog (Brown and Ororie, 1994).

– Concentrations of ≥ 1.25 mM Phenol were toxic on colonic epithelial cells when exposed to cell cultures from ulcerative colitis and control patients for 24 hours (Pedersen et al., 2002).

4.1.2.6.3 Summary on repeated dose toxicity

General state of health/Mortality

Body weight loss and premature deaths occurred in all of eight female rats which received gavage doses of 120 mg/kg bw/day during the first 11 days in a 14-day study (Berman et al., 1995, Moser et al., 1995, MacPhail et al., 1995). A single unscheduled death occurred in a female rat receiving phenol in drinking water at a concentration of 5,000 ppm (360 mg/kg bw/day) on 14 days (CMA, 1998b). Respiratory distress and unscheduled deaths of guinea pigs led to a premature study end after 20 days of inhalation exposure to phenol vapour at 0.1-0.2 mg/l (Deichmann et al., 1944). A single early death of a rabbit occurred after six dermal applications of 7.12% phenol in aqueous solutions (783 mg/kg bw/day) (Deichmann et al., 1950). In contrast to this, survival rates of F344 rats exposed to 200 and 450 mg/kg bw/day phenol and B6C3F1 mice exposed to 281 and 375 mg/kg bw/day were comparable between treated and control groups at the end of study after 103 weeks (NIH, 1980).

Nervous system

Although the quality of exposure data are limited, there are human data indicating that phenol adversely affects the nervous system after prolonged oral, dermal or inhalation exposure. Reduction of spontaneous activity, muscle weakness and pain, disordered cognitive capacities were observed in case reports (Merliss, 1972; Kilburn, 1994).

After dermal, oral or inhalation administration of phenol to experimental animals, there were several clinical symptoms. Results from neurobehavior tests indicate that the central and peripheral nervous system is affected by repeated phenol exposure. Muscle tremor (rabbit, dermal, 18 exposures, ≥ 2.37% phenol ≈ 260 mg/kg bw/day, Deichmann et al., 1950, rat 13 weeks, 308 mg/kg/day, CMA, 1998b), transitory uncoordinated movements and balance deregulation (rat, inhalation, 14 days, 0.1 mg/l, Dalin and Kristoffersson, 1974, rat, 308 mg/kg/day, CMA, 1998b), reduced body temperature (male rats, 13 wk, 83 mg/kg/day, CMA, 1998b), ptosis (rat, 13 weeks, 308 mg/kg/day, CMA, 1998b), reduced pupil response (rat, 14 days, 120 mg/kg bw/day by gavage, Berman et al., 1995, Moser et al., 1995, MacPhail et al., 1995), reduced motor activity (female rat, 13 weeks, 107 mg/kg/day (CMA, 1998b); rat, 14 days, 120 mg/kg bw/day by gavage, Berman et al., 1995, Moser et al., 1995, MacPhail et al., 1995), increased rearing (rat, 14 days, 40 mg/kg bw/day, Berman et al., 1995, Moser et al., 1995, MacPhail et al., 1995) and/or initial increase of spontaneous activity and final sluggish behaviour (rat, inhalation, 14 days, 0.1 mg/l, Dalin and Kristoffersson, 1974), decreased spontaneous activity and paralysis of hind legs (guinea pigs, 3-5 inhalation exposures, 0.1-0.2 mg/l, Deichmann et al., 1944) have been reported for laboratory animals. Transient convulsions were seen in rats injected with a 2.5 or 5% aqueous solution of phenol in the rectovesical pouch (Parkhouse et al., 1987). Clinical symptoms observed in two generation studies on mice provide additional evidence for neurotoxicity potential of phenol. Tremor was reported to be the primary clinical sign observed in all pregnant female CD-mice of a preliminary toxicity study receiving phenol at dosages ≥ 200 mg/kg/day within distilled water by gavage on gestation day 6-15. In the following teratology study, clinical signs of tremor during the first treatment days were already seen in dams of the same strain at 70 and 140 mg/kg/day; at 280 mg/kg/day tremor was observed

during the complete treatment period of gestational day 6 to 15 and was associated with severe ataxia (Jones-Price et al., 1983b, no histopathological examinations conducted).

Hypothermia observed in male rats of the study of CMA (1998b) seemed not to be a species or sex-specific effect. Besides clinical symptoms of twitching and tremor, disturbed thermoregulation was also reported as a long lasting dose-depending effect in male and female mice after single i.p. injections of 50-300 mg/kg phenol with maximum reduction of 5°C after 1-2 hours (Dose range finding study, Dow Chemical, 2001, see Section 4.1.2.7). In this species females were more sensitive than male animals, doses of 200 mg/kg induced delayed recovery after 24 hours, normal body temperature was not retained within 48 hours after treatment at 300 mg/kg.

The heterogenicity of symptoms may indicate that phenol-related effects are not associated to specific regions or structures of the nervous system.

Regarding that most of the above mentioned studies were of limited quality, some of the findings were confirmed by a recently submitted 13-week study on rats (CMA, 1998b). Phenol-related effects on the neurofunction and neurobehavior were well investigated in this study on rats consisting of treatment-related reduction of body temperature (≥ 1,000 ppm, 83 mg/kg bw/day) and insignificantly altered motor activity (only females ≥ 1,000 ppm, 83 mg/kg bw/day) in most treated animals. Only few animals at the top dose (5,000 ppm, ≈ 308, and 360 mg/kg bw/day for males and females) demonstrated abnormal behaviour like hunched posture, uncoordinated movements, tremor, reduced activity, ptosis, reduced body temperature. These findings were not associated to any morphologic alteration as no lesions were detected of the peripheral and central nervous system. However, examinations to detect morphologic alterations of the nervous system were limited to staining methods with H&E and toluidine. The absence of any lesion does not necessarily mean that they are not existent, because no other specific and sensitive method was used (e.g. GFAP immunohistology, PTAH, silver impregnation techniques). For a further characterisation, extensive examinations of the central and peripheral nervous system are still necessary.

From specific studies with direct intranerval or epidural application of single or repeated high doses of phenol to monkeys, rats and cats, it was clearly shown that phenol is neurotoxic inducing inhibition of nerve conduction and/or axonal degeneration and demyelination of the spinal cord (especially in the areas of nerve roots) and distal nerves accompanied by ataxia, gait abnormalities and (hind) leg paralysis (Katz et al., 1995, Burkel and McPhee, 1970, Schaumburg et al., 1970). An inhibitory effect on the nerve conduction was confirmed by *in vitro* experiments of sections from peripheral nerves (Dodt et al., 1983). Data from these animal studies and data on the desired and undesired effects from therapeutic use were not considered for hazard classification since these injection routes are not relevant for the exposure situations of workers and consumers.

Neurotransmitter levels of several brain regions were reduced after oral 28-day administration of phenol concentrations of 19.5 mg/l (6.2 mg/kg bw/day) in mice.

No abnormal clinical sign attributable to neuronal dysfunction has been found in a two-generation study on mice with drinking water administration of phenol up to 5,000 ppm (310 mg/kg/day males, 350 mg/kg/day females) (IITRI, 1999, Ryan et al., 2001, no functional observational battery on neurofunctions and no histopathology on nervous system conducted).

Bone marrow/Hematopoietic system

A 28-day administration of phenol in the drinking water induced anaemia in mice at concentrations of 19.5 mg/l (6.2 mg/kg bw/day), a dose-dependent reduction of erythrocyte numbers was already seen at the lowest dose tested (4.7 mg/l = 1.8 mg/kg bw/day) (Hsieh et al., 1992). At a high dose of phenol (245 mg/kg bw/day) injected subcutaneously to mice, an inhibitory effect on the erythropoiesis via reduced iron incorporation during the erythrocyte maturation was recorded. The bone marrow stromal cell functions to support hemopoiesis of granulocyte/monocyte precursors was suppressed in cells from mice received intraperitoneal injections of 200 mg/kg bw/day phenol on 4 days (Gaido and Wierda, 1985). *In vitro*, a high concentration ($1 \cdot 10^{-4}$ M) of phenol was cytotoxic to stromal cells of bone marrow (Gaido and Wierda, 1984). 50 mg/kg bw/day phenol was also suppressive on the granulopoeitic stem cell population in the bone marrow of mice after subcutaneous application on 6 days (Tunek et al., 1981).

The anaemic effect seen in the mouse study (Hsieh et al., 1992) was the most sensitive effect after repeated oral administration of phenol and was suggested as the overall LOAEL for risk characterisation on the oral route. It was not confirmed by other oral studies, since haematology parameters were not examined in the mouse and rat studies of the NIH (1980). As no other repeated dose study was performed on mice, it remains unclear whether the mouse is more sensitive towards phenol toxicity than other species.

In rats exposed to chamber concentrations up to 25 ppm (0.09625 mg/l), no phenol-related effect has been observed on red blood cell parameters after 10 day inhalation period (CMA, 1998a). Minor non-significant reductions in hematocrit (-9.5%) and hemoglobin (-4.2%) concentrations were found in seven rats at 0.1 mg/l after 14 exposure days (Dalin and Kristoffersson, 1974). However examined hematology parameters were incomplete in this study and absent in other inhalation and dermal studies.

Immune system

Phenol-induced suppression of the response to T- and B-cell mitogens was observed in CD-1 mice treated on 28 days with 95.2 mg/l phenol in drinking water. T-cell dependent humoral immune response and antibody levels were reduced at phenol concentrations from 19.5 mg/l (6.2 mg/kg bw/day) (Hsieh et al., 1992). In contrast, rats exposed to phenol containing drinking water did not show any alteration of the T-cell dependent humoral response up to 5,000 ppm (301 mg/kg bw/day) (IITRI, 1999). Spleen cellularity was not affected by phenol treatment in both studies. Atrophic changes of the thymus or spleen were related to a gavage administration of phenol at doses of 12 mg/kg (1/8 female rats) and 40 mg/kg (2/8 females) on 14 days (Berman et al., 1995, Moser et al., 1995, MacPhail et al., 1995). A small appearance of the thymus and the spleen (suggestive for atrophic changes) were noted in the early death on day 14 of treatment with drinking water containing 5,000 ppm phenol (360 mg/kg bw/day) (CMA, 1998b). Chronic studies (NIH, 1980) did not confirm any major effect on the histomorphology of the immune organs (rats and mice: spleen, lymph nodes; mice; bone marrow) related to phenol. The immune system was not addressed in repeat-dose studies on the inhalation or dermal route either because examinations on testing parameters or organ tissues of the immune system were not conducted or due to the lack of any data reported hereon.

In vitro, phenol was shown to inhibit the activity of natural killer cells (Fan et al., 1989). Leukocytic chemotaxis of neutrophiles was depressed by phenol (Azuma et al., 1986).

Liver

Liver cell degeneration was evident in 1/8 female rat at 40 mg/kg bw/day phenol after 14 days of gavage administration (Berman et al., 1995, Moser et al., 1995, MacPhail et al., 1995). Increased liver enzyme levels indicated liver damage in rats exposed on 14 days to a vapour concentration of 0.1 mg/l phenol (Dalin and Kristoffersson, 1974). Studies in animals revealing liver toxicity are in line with case reports of phenol exposed workers showing enlarged liver (Merliss, 1972) or increased activities of liver transaminases in a cohort study (Shamy et al., 1994).

Lung

Purulent bronchopneumonias were related to phenol inhalation (Deichmann et al., 1944) but confidence in those findings is considered to be low. As SPF status was unknown at that time, it seems to be more likely to be induced by infectious pathogens. On the other side, a cytotoxic effect of phenol vapour was noted on lung epithelial cells *in vitro* (Zamora et al., 1983).

Kidneys

Phenol solutions directly infused into the renal circulation induced tubular toxicity at concentrations of 0.1% or higher (Coan et al., 1982). Tubular necrosis and papillary hemorrhage were seen in female rats receiving 40 mg/kg by gavage for 14 days (Berman et al., 1995, Moser et al., 1995, MacPhail et al., 1995). Also, inhalation exposure during 28 days in guinea pigs and 88 days in rabbits were reported to induce tubular degeneration along with glomerulosclerosis, interstitial inflammation and fibrosis (Deichmann et al., 1944). Chronic administration of phenol with drinking water revealed equivocal evidence of increased incidences of chronic renal inflammation (NIH, 1980).

Heart

From early studies (Deichmann et al., 1944) myocard degeneration was reported for rabbits and guinea pigs after exposure on 20 days to vapour concentrations of 0.1-0.2 mg/l. No indication on heart effects was observed in other repeated dose studies, but cardiotoxic effects were known after single exposure (see Section 4.1.2.2).

Skin

Epidermal hyperkeratosis and ulceration resulted from repeated dermal application on 18 days of aqueous phenol solutions at concentrations of 1.18-7.12% (130-783 mg/kg bw/day) to rabbits (Deichmann et al., 1950).

Overall N(L)OAEL/N(L)OAEC recommended for risk assessment procedures:

Oral administration

LOAEL 1.8 mg/kg bw/day: mouse study on subacute toxicity (Hsieh et al., 1992).

Inhalative administration

$LOAEC_{systemic}$ 0.021 mg/l: time weighted average exposure of workers (Shamy et al., 1994)
$NOAEC_{local}$ 0.09625 mg/l 14-day rat study (CMA, 1998a).

Dermal administration:

$NOAEL_{systemic}$ 1.18% (≈ 130 mg/kg bw/day) 18-day rabbit study (Deichmann et al., 1950). $NOAEL_{local}$ 2.37% (≈ 260 mg/kg bw/day) 18-day rabbit study (Deichmann et al., 1950).

Discussion

Although results from repeated dose studies on phenol-related effects are not finally conclusive regarding the overall database from earlier and recent studies, it is recommended to consider the adverse effect occurring at the lowest effect level at the most sensitive species.

The observations of elevated activities for liver enzymes (especially ALAT) and increased clotting time indicating hepatotoxicity in phenol-exposed workers allows to derive a LOAEC of 0.021 mg/l for systemic effects after chronic inhalation (Shamy et al., 1994). No adverse effects on the respiratory tract were reported in a valid 14 day-inhalation study on rats (CMA, 1998a). The highest concentration tested (0.09625 mg/l) was identified as the NOAEC for local effects on the respiratory tract.

To derive a N(L)OAEL for the oral route the drinking water study of Hsieh et al. (1992) identified the most sensitive adverse effect associated with phenol treatment. This was a significantly reduced number of erythrocytes (-32%) in mice at 1.8 mg/kg bw/day phenol representing the LOAEL. Although the NIH study (1980) was accepted with restrictions for the formal requirements on the study design, it did not include all sensitive parameters relevant in phenol toxicity. However, findings of Hsieh and his group were not confirmed by other oral studies either in mice or in rats. This is explainable in part, because there are differences in parameters examined and this target organ was not addressed. However, the mouse might be the most sensitive species with respect to hematotoxicity. However, this assumption is not fully conclusive as the chronic bioassay on B6C3F1 mice (NIH, 1980) did not give any indication on apparent hematotoxic effects which should be seen after prolonged anaemia (e.g. splenomegaly, extramedullary and medullary hematopoiesis). In addition, none of the inhalation studies gave indication on hematotoxic effects at the relatively low concentrations tested (approximately 0.1 mg/l).

Similarly, there is an inconsistency of the T-cell dependent humoral response comparing data from mouse studies (suppression from 6.2 mg/kg bw/day, Hsieh et al., 1992) to that from rat studies (no effect up to 301 mg/kg bw/day, IITRI, 1999). Again, this may be attributable to species or strain specificity, but remains unclear unless new data are generated.

The marked difference in NOAEL from the 103-weeks study of the NIH (1980) and LOAEL of the subacute toxicity study (Hsieh et al., 1992) (both studies with oral administration with the drinking water) may be attributable to the high sensitivity of testing parameters on hematoxicity, the neurofunction and the immune function in the Hsieh study as well as to the reduced testing protocols in the study from the NIH (no investigations on haematology, clinical chemistry, urine analysis, histopathology of tissues from the nervous system other than brain, and tests on neurological disorders). Therefore the NOAEL from the NIH study was not used for the risk assessment.

The overlapping of the dose ranges which estimated the LD_{50} in the acute oral toxicity and the dosages in the oral long term studies seem to be explainable by the mode of administration as a bolus uptake with the gavage, and as a continuous uptake with drinking water, respectively.

The weak data for the dermal route from early studies limit the confidence in the estimated NOAELs; they were taken in the absence of other more reliable data.

Comment

Comparing the data on the effects of phenol following repeated exposure, the findings seem to show many differences in the target organs, adverse effects and the doses at which they occur. However, this can be explained with differences in the quality and quantity of parameters tested.

There is sufficient consistency of phenol induced toxic effects on the haematopoietic system, nervous system, the kidney, the liver and skin. The myocard degeneration reported by Deichmann et al. (1944) needs further clarification. There were case reports on the occurrence of arrhythmia after single therapeutic use of phenol (Morrison et al., 1991) giving more weight of evidence that the heart is a target organ. In summary, several animal studies with subacute, and subchronic phenol administration via different routes resulted in relevant toxic effects on function and/or morphology of several organs and organ systems. Although all studies showed deficiencies with respect to the quality of the methodics and documentation or were focussed only on special aspects, the described effects can be considered as sufficiently predictive as relevant risks for human health. At least, the following effects (see **Table 4.12**) occurring at dosages below the critical dose/concentration for classification and labelling gave arguments for the classification as harmful and labelling with Xn, R 48. The doses or concentrations tested were below the level of the critical dose for classification. Under the assumption that higher doses/concentrations reaching the critical dose would have been used an aggravation of toxic effects would be expected.

Table 4.12 Summary of relevant toxic effects at or below the critical doses/concentrations which give need for R48 classification

Application route	Oral	Inhalation
Study duration	Subacute	subacute/subchronic
Critical dose for classification	≤150 mg/kg bw/day	≤ 0.75mg/l/< 0.25 mg/l
Species		
Mouse	28 days/drinking water: RBC↓ ≥1.8 mg/kg bw/day hematocrit↓ ≥33.6 mg/kg bw/day brain neuro-transmitters↓ ≥1.8 mg/kg bw/day (Hsieh et al., 1992)	
Rat	14 days, gavage: premature deaths at 120 mg/kg delayed pupil response at 120 mg/kg bw/day liver and kidney degeneration at 40 mg/kg bw/day spleen/thymus atrophy and necrosis ≥ 12 mg/kg bw/day (Berman et al., 1995; Moser et al., 1995, MacPhail et al., 1995)	14 days motor disorders and impaired function of balance regulation at 0.1 mg/l (Dalin and Kristoffersson, 1974)
Rabbit		63 exposures during 88 days: degeneration of the myocard, liver and kidneys at 0.1-0.2 mg/l (Deichmann et al., 1944)
Guinea pig		20 exposures during 28 days: unscheduled deaths, decreased activity, paralysis, degeneration of the myocard, liver and kidneys at 0.1-0.2 mg/l (Deichmann et al., 1944)

The only data from a repeat-dose dermal study in rabbits would also meet the criteria of R 48 considering tremor as a critical systemic effect that occurred at concentrations of 2.37% (260 mg/kg/day) and above which is below the guidance dose for R 48 (300 mg/kg/day for subacute toxicity studies).

Conclusion

Based on the toxic effects given in **Table 4.12** phenol has been classified as "harmful" and labelled with "Xn", R-phrases: "Harmful: danger of serious damage to health by prolonged exposure through inhalation, in contact with skin and if swallowed" (R 48/20/21/22).

4.1.2.7 Mutagenicity

4.1.2.7.1 Studies *in vitro*

Bacterial gene mutations and fungi (**Table 4.16**)

Bacterial gene mutation tests with Salmonella typhimurium were negative for doses up to 5,000 µg/plate with and without S-9 mix (Gilbert et al., 1980; Haworth et al., 1983; Glatt et al., 1989). A standard plate test and preincubation tests were conducted. There were no toxic effects up to 3,333 µg/plate with S-9 mix and up to 2,500 µg/plate without S-9 mix; for higher doses some weak toxicity was observed.

Wild et al. (1980) and Gocke et al. (1981) reported also on a negative result for the Salmonella typhimurium strain TA 98 up to 100 µmol/plate (9.4 µg/plate). When a special modified medium (ZML medium) was used instead of common Vogel-Bonner medium a weakly positive result for TA 98 was observed with a maximum effect of about 2.5-fold increase of the mutant frequency. The medium dependency could not be explained by the authors (Gocke et al., 1981).

A test with conidia of Aspergillus nidulans diploid strain 19, only done without S-9 mix, was positive (Cebrelli et al., 1987). At a dose of 15 mmol/l (1,411.6 µg/ml) genetic effects were induced; according to the authors the effects were caused by gross chromosomal aberrations. The highest tested dose of 20,000 µmol/l (1,882.2 µg/ml) was toxic (57% survival).

Mammalian cell systems (**Tables 4.17-4.26**)

Two mammalian cell gene mutation assays with V79 cells (hprt locus; only done without S-9 mix) are described in the literature (Paschin and Bahitova, 1982; Glatt et al., 1989). Only weakly positive effects were found at the highest tested doses of 250 and 500 µg/ml by Paschin and Bahitova (1982). According to Glatt et al. (1989) phenol was negative for doses up to 4,000 µmol/l (376.4 µg/ml) which was at the limit of toxicity.

Tsutsui et al. (1997) reported on positive mammalian cell gene mutation tests with SHE cells (hprt locus and Na^+/K^+ locus; only done without S-9 mix) at a dose-range of 3.0-30 µmol/l (0.28-2.82 µg/ml). No toxic effects were observed.

In two mouse lymphoma assays (Wangenheim and Bolcsfoldi, 1988; McGregor et al., 1988) similar weakly positive effects were observed with S-9 mix. Wangenheim and Bolcsfoldi (1988) reported on weakly positive result without S-9 mix whereas McGregor et al. (1988) described a

negative result without S-9 mix up to 1,800 µg/ml. The genotoxic effects were paralleled by moderate to strong cytotoxicity.

A chromosomal aberration test with CHO cells was positive with and without S-9 mix at doses from 2,000 µg/ml or from 600 µg/ml upwards, respectively (Ivett at al., 1989). Minor toxicity was observed at the top dose with and without S-9 mix. A chromosomal aberration test with SHE cells, only done without S-9 mix, was described by Tsutsui et al. (1997) as negative up to doses of 100 µmol/l (9.4 µg/ml). No toxic effects were observed.

Three *in vitro* micronucleus tests with different mammalian cells were positive without S-9 mix (Miller et al., 1995; Glatt et al., 1989; Yager et al., 1990). Also with S-9 mix, only used by Miller et al. (1995), a positive result was observed. In general, some toxicity was observed in high doses.

Doses up to 100 µmol/l (9.4 µg/ml) were negative in a test for induction of aneuploidy (hyper- and hypoploidies) with SHE cells (Tsutsui et al., 1997). The test was only performed without S-9 mix; no toxic effects were observed.

SCE tests with human lymphocytes (Morimoto et al., 1983) and CHO cells (Ivett at al., 1989) were weakly positive with S-9 mix. Without S-9 mix negative results (Glatt et al., 1989; Jansson et al., 1986), marginal/weakly positive results (Morimoto and Wolff, 1980; Ivett et al., 1989) as well as clearly positive results (Erexson et al., 1985; Khalil and Odeh, 1994; Tsutsui et al., 1997) were observed using different mammalian cell lines.

The measurement of UDS induction in SHE cells (only without S-9 mix) gave a positive result from 1.0 µmol/l (0.09 µg/ml) upwards (Tsutsui et al., 1997). No data on toxicity were given.

Garberg et al. (1988) reported on a positive result at a test for induction of DNA strand breaks in mouse lymphoma cells (L5178Y) with S-9 mix at 1,500 µmol/l (141.2 µg/ml) and 5,000 µmol/l (470.6 µg/ml). Without S-9 mix doses up to 5,000 µmol/l (470.6 µg/ml) were negative (Garberg et al., 1988; Pellack-Walker and Blumer 1986). With and without S-9 mix no toxic effects were observed.

A test on formation of DNA adducts with HL60 cells, only done without S-9 mix, was described as positive by Kolachana et al. (1993) at the only tested dose of 100 µmol/l (9.41 µg/ml). No data on toxicity were given. Binding of radiolabelled ^{14}C-phenol derived products to isolated calf thymus DNA in the presence of horseradish peroxidase and hydrogen peroxide was described by Subrahmanyam and O'Brien (1985).

Table 4.13 Overview on *in vitro* findings

Negative effects	Questionable effects	Positive effects
Mutation tests *in vitro*		
Bacterial gene mutations		Mammalian cell mutagenicity: tk locus, hprt locus, Na^+/K^+ locus
Aneuploidy		Chromosomal aberrations
		Micronuclei
		Aspergillus test (chromosomal aberrations)
Indicator tests *in vitro*		
		SCE in mammalian cells
		UDS with SHE cells
		DNA strand breaks in mammalian cells and isolated DNA
		DNA adducts in mammalian cells

4.1.2.7.2 Studies *in vivo*

Rodent bone marrow micronucleus tests with mice (**Table 4.27-4.29**)

Descriptions of different micronucleus assays with mice after single oral administration, after single intraperitoneal injection or after multiple intraperitoneal injections are available in the literature. All tests were performed with low numbers of animals: In one study 6 animals per group were used; in all other studies only groups of 3 to 5 animals per dose were investigated. All tests were conducted with polychromatic bone marrow erythrocytes. A detailed overview on the different *in vivo* micronucleus tests is given in **Tables 4.27** to **4.29**.

Table 4.14 General overview on micronucleus tests

Administration	Result (Dose in mg/kg)	Group size	Local cytotoxicity	LD_{50} (mg/kg bw)	Reference
1 · p.o.	Weakly pos. (at 265)	4	unclear	270 - 300 (see 4.1.2.2)	Ciranni et al., 1988a
	Weakly pos. (at 265)	4	drastic		Ciranni et al., 1988b
	Negative (at 250)	5	no data		Gad-El-Karim et al., 1985
	Negative (at 250)	5	no data		Gad-El-Karim et al., 1986
1 · i.p.	Positive (at 300)	6	extreme	180	McFee et al., 1991
	Positive (at 265)	4	extreme		Ciranni et al., 1988b
	Negative (up to 265)	3	no effect		Barale et al., 1990
	Weakly pos. (at 120)	3	no effect		Marrazzini et al., 1994
2 · i.p.	Negative (up to 188)	4	no data		Wild et al., 1980
3 · i.p.	Weakly pos. (at 90/ /180)	5	no effect		Shelby et al., 1993
	Weakly pos. (at 160)	5	no effect		Chen and Eastmond, 1995

Tests with single oral administration were only done with doses which correspond to the LD_{50}. In two investigations a weakly positive result was obtained; in two further tests the result was negative (see **Table 4.27**).

Ciranni et al. (1988a and 1988b) conducted two tests on the time-effect of MN-induction by 265 mg/kg bw phenol in Swiss CD-1 mice. Maximum effects were obtained at 24 h-sampling (2 or 2.5-fold). There was a drastic depression of P/N ratio in one investigation and no clear effect in the other. In both tests no data on general toxicity were given. The group of Gad-El-Karim (1985; 1986) described two investigations also on Swiss CD-1 mice after single administrations of 250 mg/kg bw. The results were clearly negative; no data on local or on general toxicity were given.

Single intraperitoneal injections of very high single doses of 265 or 300 mg/kg bw induced positive effects paralleled by extreme cytotoxicity (see **Table 4.28**).

McFee et al. (1991) reported on a positive finding after injection of 300 mg/kg bw. In two experiments the increases of micronucleated cells over the control value were 4.8-fold or 3.4-fold. Extremely cytotoxic effects were described in both experiments; data on general toxicity were not given. In a time-effect investigation Ciranni et al. (1988b) described a significant increase in the micronucleus frequency. A maximum of 5.0-fold increase was observed after injection of 265 mg/kg bw at a sampling time of 18 hours. Extremely cytotoxic effects were observed at all sampling times; no data on general toxicity were given.

Two investigations with single i.p. administration of lower doses suffer from the insufficiency of small group sizes (three animals only). Barale et al. (1990) reported on a negative result after dosing of 40 up to 160 mg/kg bw. No local cytotoxicity was induced; data on general toxicity were not given. A weak increase in the frequency of micronuclei was found by Marrazzini et al. (1994) after administration of the highest tested dose of 120 mg/kg bw. The effect was 1.7-fold over the negative control. No cytotoxic effects were induced; no data on general toxicity were given.

Multiple intraperitoneal injections of doses up to 188 mg/kg bw led to weakly positive or negative results (see **Table 4.29**).

The negative result was obtained on male and female mice (strain: NMRI) after two intraperitoneal injections of doses from 47 up to 188 mg/kg bw (Wild et al., 1980). Information on local cytotoxicity or toxic signs was not given.

A weakly positive effect was induced on male mice (strain: B6C3F1) after threefold injection of doses from 45 up to 180 mg/kg bw (Shelby et al., 1993). Two experiments were performed. A doubling of the micronucleus frequency was obtained at 180 mg/kg bw in one experiment. In the other one less than 2-fold increases were found at 90 and 180 mg/kg bw. In both experiments neither cytotoxic nor lethal effects were observed. Chen and Eastmond (1995) also reported on a weakly positive result on male mice (strain: Swiss CD-1) after threefold intraperitoneal injection of the highest tested dose of 160 mg/kg bw. No cytotoxic effects were induced; information about toxic signs was not given.

For the assessment of positive effects in micronucleus tests *in vivo* it is important to reflect that these effects are limited to high doses inducing toxic effects. Possible mechanisms for the induction of micronuclei at extremely high doses are given by hypothermia and metabolic overload. New data are available showing a direct relationship between hypothermia and induction of micronuclei in mouse bone marrow polychromatic erythrocytes at high toxic doses (see Section 4.1.2.6; Spencer et al., 2002; Dow Chemical Company, 2001). Furthermore it can be

speculated that a metabolic overload of the conjugation system, the normal pathway of biotransformation of phenol, at high doses and subsequent formation of hydroquinone and other products may also provide an explanation for the weak positive results in micronucleus tests. The induction of micronuclei at high doses seems to be based on an indirect mode-of-action with a threshold.

Rodent bone marrow chromosomal aberration test (**Table 4.30**)

Thompson and Gibson (1984) reported on negative chromosomal aberration tests in bone marrow cells of male and female rats (strain: Sprague Dawley) both after oral administration and after intraperitoneal injection of phenol. The highest tested doses corresponded to LD_{30} doses: males, p.o. 510 mg/kg bw and i.p. 180 mg/kg bw; females, p.o. 410 mg/kg bw and i.p. 110 mg/kg bw. Only 3 animals per group and only 30 metaphases per animal were analysed.

DNA strand breaks in testes (**Table 4.31**)

According to Skare and Schrotel (1984) phenol did not produce strand breaks in testicular DNA of rats both after i.p. injection of 7.9 up to 79 mg/kg bw and after five i.p. injections with 24-hour intervals from 4.0 up to 39.5 mg/kg bw. The highest tested dose in the acute studies corresponded to LD_{01} and was 36% of the LD_{50}.

Drosophila melanogaster (**Table 4.32**)

In sex-linked recessive lethal tests with Drosophila (strain: Canton-S) negative results were reported by Woodruff et al. (1985) after feeding of 2,000 ppm or after i.p. injection of 5,250 ppm. In both tests lethal effects were observed.

DNA adducts (**Table 4.33**)

Phenol did not induce DNA adducts in female Sprague-Dawley rats (bone marrow, liver, Zymbal gland; Reddy et al., 1990) and in male mice (oxidative DNA damage in bone marrow cells; Kolachana et al., 1993). According to Shufen et al. (1996) phenol induced DNA adducts after single i.p. injection of 75 mg/kg bw in Aroclor-induced SD-rats. The paper is written in Chinese and can not be adequately assessed.

Table 4.15 Overview on *in vivo* findings

Negative effects	Questionable effects	Positive effects
Mutation tests *in vivo*		
Chromosomal aberrations in rats (bone marrow)		Weak induction of micronuclei in mice at highly toxic doses (bone marrow)
Drosophila (SLRL test)		
Indicator tests *in vivo*		
DNA strand-breaks in rats (testis)		
DNA adducts in rats (bone marrow, Zymbal gland, liver) and mice (bone marrow)		

Conclusion

Phenol did no induce gene mutations in bacteria. In mammalian cell cultures positive effects were found for chromosomal aberrations, micronuclei, and gene mutations (hprt locus; Na^+/K^+ locus) in mouse lymphoma assays and in several indicator tests. A test for induction of aneuploidy was negative.

In vivo in rodents, negative results were found for chromosomal aberrations, DNA strand breaks and DNA adducts. Also Drosophila tests were negative.

Results from *in vivo* micronucleus tests were weakly positive or negative. The frequency of micronuclei is extremely low even in doses which correspond to the LD_{50}. The induction of micronuclei at high doses may be based on an indirect mode-of-action.

The EU Classification and Labelling Working Group decided in 2001 to classify phenol as a category 3 mutagen.

Based on the available evidence, it is considered that this classification still stands and that phenol should still be regarded as a somatic cell mutagen. It is noted that although the high dose positive micronuclei results being secondary to phenol-induced hypothermia is a plausible hypothesis, no definite conclusions about this mechanism can be drawn due to the limited nature of the available data (abstract form and lack of a confirmatory test showing that prevention of hypothermia by maintaining the animals body heat also prevents the induction of micronuclei).

Furthermore, it is deemed that the available *in vivo* genotoxicity data are unable to address remaining concerns about mutagenicity at the initial site of contact following inhalation or dermal exposure.

Table 4.16 *In vitro* tests: Bacteria and Aspergillus nidulans

Test system	Concentration range		Result	Toxicity	Remarks	Reference
	with S-9 mix	without S-9 mix				
Gene mutation; Salm. typh. TA 1535, TA 1537		10-100 µg/plate	Negative	No toxic effects	Standard plate test	Gilbert et al., 1980
Gene mutation; Salm. typh. TA 98, TA 100, TA 1535, TA 1537	33-3,333 µg/plate	33-2,500 µg/plate	Negative	No toxic effects	Preincubation test	Haworth et al., 1983
Gene mutation; Salm. typh. TA 97, TA 98, TA 100, TA 102, TA 104, TA 1535	20-5,000 µg/plate	100-5,000 µg/plate	Negative	At high doses	Preincubation test	Glatt et al., 1989
Gene mutation; Salm. typh. TA 98	20-100 µmol/plate (1.88 - 9.4 µg/plate)	no data	Inconclusive	No data	Negative with normal medium; weak positive with uncommon ZML medium; standard plate test	Wild et al., 1980

Table 4.16 continued overleaf

Table 4.16 continued *In vitro* tests: Bacteria and Aspergillus nidulans

Test system	Concentration range		Result	Toxicity	Remarks	Reference
	With S-9 mix	Without S-9 mix				
Gene mutation; Salm. typh. TA 98	Up to 100 µmol/plate (up to 9.4 µg/plate)	Up to 100 µmol/plate (up to 9.4 µg/plate)	Inconclusive	No data	Negative with normal medium; weak positive with uncommon ZML medium; standard plate test	Gocke et al., 1981
Aspergillus nidulans diploid strain 19	Not done	5,000-20,000 µmol/l (470.5-1,882.0 µg/ml)	Positive	Effect only at 20,000 µmol/l = 57% survival	Positive (probably gross chromosomal aberrations) only at 15 mmol/l (1411.6 µg/ml)	Cebrelli et al., 1987

Table 4.17 *In vitro* tests: Mammalian cell gene mutations

Test system	Concentration range		Result	Description of result	Reference
	with S-9 mix	without S-9 mix			
Hprt locus, V79 cells	not done	25-500 µg/ml	weakly positive	treatment: 2 hours dose (µg/ml) / MF* (x 10^{-6}) / survival of cells (%) neg.co. / 12 25 / 12 / 99 50 / 12 / 99 100 / 18 / 98 250 / 28 / 90 500 / 45 / 50	Paschin and Bahitova, 1982
Hprt locus, V79 cells	not done	up to 4,000 µmol/l (376.4 µg/ml)	negative	treatment: 24h toxicity: tested up to the limit of toxicity	Glatt et al., 1989
Hprt locus , SHE cells	not done	3.0-30 µmol/l (0.28-2.82 µg/ml)	positive	treatment: 48h dose (µg/ml) / MF* (x10^{-6}) neg.co. / < 1 0.28 / 1.3 0.94 / 2.0 2.82 / 23.0 toxicity: no toxic effects	Tsutsui et al., 1997

Table 4.17 continued overleaf

Table 4.17 continued *In vitro* tests: Mammalian cell gene mutations

Test system	Concentration range		Result	Description of result	Reference
	with S-9 mix	without S-9 mix			
Na^+/K^+ locus, SHE cells	not done	3.0-30 µmol/l (0.28-2.82 µg/ml)	positive	treatment: 48h dose (µg/ml) MF* ($x10^{-6}$) neg.co. < 1 0.28 5.6 0.94 5.6 2.82 10.1 toxicity: no toxic effects	Tsutsui et al., 1997

*MF Mutation frequency

Table 4.18 *In vitro* tests: Mouse-lymphoma assays

Test system	Concentration range		Result	Description of result	Reference
	with S-9 mix	without S-9 mix			
mouse lymphoma assay (L5178Y cells; Tk-locus)	56-445 µmol/l (5.2 - 41.8 µg/ml)	1,890-9,430 µmol/l (177.9-877.4 µg/ml)	weakly positive	weakly positive effect with and without S-9 mix With S-9 mix: doses (µg/ml) MF ($x10^{-6}$) total growth(%) neg.co. 54 5.2 72 97 10.4 141 55 20.9 149 20 31.4 133 10 41.8 178 8 Without S-9 mix: doses (µg/ml) MF ($x10^{-6}$) total growth(%) neg.co. 109 177.9 140 81 354.8 238 40 532.7 241 20 709.6 280 8 847.4 309 5	Wangenheim and Bolcsfoldi, 1988

Table 4.18 continued overleaf

Table 4.18 continued *In vitro* tests: Mouse-lymphoma assays

Test system	Concentration range		Result	Description of result	Reference
	with S-9 mix	without S-9 mix			
Mouse lymphoma assay (L5178Y cells; Tk-locus)	300-1,500 µg/ml	100-1,800 µg/ml	Weakly positive	Weakly positive effect only with S-9 mix with S-9 mix: doses MF total (µg/ml) ($x10^{-6}$) growth (%) 1.test 2.test 1.test 2.test neg.co. 28 51 300 81 14.0 600 58 147 13.5 17.5 900 45 177 12.5 15.5 1,200 43 169 9.5 14.5 1,500 57 5.5	McGregor et al., 1988

Table 4.19 *In vitro* tests: Chromosomal aberrations

Test system	Concentration range		Result	Description of result	Reference
	with S-9 mix	without S-9 mix			
chromosomal aberrations; CHO cells	2,000 – 3,000 µg/ml	600 - 800 µg/ml	positive	positive with and without S-9 mix with S-9 mix: treatment/ sampling: 2h / 2.5h dose-range (µg/ml) aberrant cells (%; excl. Gaps) neg.co. 2.0 2,000 18.0 2,500 14.0 3,000 17.0 without S-9 mix: treatment/sampling: 8h / 22.5h dose-range (µg/ml) aberrant cells (%; excl. Gaps) neg.co. 2.0 600 4.0 700 6.0 800 7.0 toxicity: no detailed data; "slight reduction in cell confluency" at the two top doses with and without S-9 mix	Ivett et al., 1989
chromosomal aberrations; SHE cells	not done	3 - 100 µmol/l (0.28 - 9.4 µg/ml)	negative	treatment/sampling: 24h/24h toxicity: no toxic effects	Tsutsui et al., 1997

Table 4.20 *In vitro* tests: Micronuclei

Test system	Concentration range		Result	Description of result	Reference
	with S-9 mix	without S-9 mix			
micronuclei, CHO cells	350 – 2,000 µg/ml	10 - 250 µg/ml	positive	positive with and without S-9 mix with S-9 mix: treatment/sampling: 3h / 48h dose micronucleated cells (%) (µg/ml) expt. A expt.B neg.co. 3.3 2.4 350 3.1 3.8 475 3.4 - 600 2.9 - 800 4.4 - 1,000 6.6 4.8 1,500 - 5.8 2,000 12.4 16.9 toxicity: at the top dose without S-9 mix: treatment/sampling: 48h / 48h dose micronucleated cells (%) (µg/ml) expt. A expt.B neg.co. 2.7 2.3 10 3.0 - 50 4.5 2.7 100 6.6 3.6 175 9.9 4.8 200 9.4 6.8 toxicity: at the two highest doses in experiment A	Miller et al., 1995
micronuclei, V79 cells	not done	4,000 µmol/l (376.4 µg/ml)	positive	treatment/sampling: 24h / 24h micronucleated cells (%) neg.co. 1.0 376.4 µg/ml 4.5 toxicity: no data	Glatt et al., 1989

Table 4.20 continued overleaf

Table 4.20 continued *In vitro* tests: Micronuclei

Test system	Concentration range		Result	Description of result	Reference
	with S-9 mix	without S-9 mix			
micronuclei, human lymphocytes	not done	50 – 5,000 µmol/l (4.7 - 470.5 µg/ml)	weakly positive	treatment/sampling: 48h / 48h dose (µg/ml) micronucleated cells (%) neg.co. 0.6 4.7 0.7 23.5 1.2 47.0 1.5 70.6 1.9 94.0 1.6 188.2 2.0 470.5 1.6 toxicity: 26% reduction of cell viability at the highest tested dose	Yager et al., 1990

Table 4.21 *In vitro* tests: Aneuploidy

Test system	Concentration range		Result	Remarks	Reference
	with S-9 mix	without S-9 mix			
aneuploidy; SHE cells	not done	10 - 100 µmol/l (0.94 - 9.4 µg/ml)	negative	treatment/sampling: 48 hours/48 hours toxicity: no toxic effects	Tsutsui et al., 1997

Table 4.22 *In vitro* tests: Sister chromatid exchanges (SCE)

Test system	Concentration range		Result	Description of result	Reference
	with S-9 mix	without S-9 mix			
human lymphocytes	3,000 µmol/l (282.3 µg/ml)	not done	weakly positive	SCE frequencies in dependence on various S-9 mix concentrations: at 10% S-9 mix concentration 14.0 SCE/cell (neg.co., 9.5 SCE/cell) toxicity: no data	Morimoto et al., 1983

Table 4.22 continued overleaf

Table 4.22 continued *In vitro* tests: Sister chromatid exchanges (SCE)

Test system	Concentration range		Result	Description of result	Reference
	with S-9 mix	without S-9 mix			
human lymphocytes	not done	8.0 – 1,000 µmol/l (0.75 - 94.11 µg/ml)	marginal positive	doses (µg/ml) SCE/cell mitotic index (%) neg.co. 7.1 0.75 6.3 100 3.76 6.9 112 18.80 7.6 115 94.11 9.8 26.5	Morimoto and Wolff, 1980
human lymphocytes	not done	5.0 – 3,000 µmol/l (0.47 - 282.3 µg/ml)	positive	doses (µg/ml) SCE/cell mitotic index (%) neg.co. 8.7 0.47 10.5 78.5 4.70 11.1 65.9 47.10 13.5 45.6 65.90 13.1 40.9 94.10 16.6 34.2 282.30 19.5 3.3	Erexson et al., 1985
human lymphocytes	not done	up to 2,000 µmol/l (up to 188.2 µg/ml)	negative	Toxicity: no data	Jansson et al., 1986
CHO cells	2,000 – 3,000 µg/ml	300 - 400 µg/ml	weakly positive	Positive with and without S-9 mix with S-9 mix: doses (µg/ml) SCE/cell neg.co. 10.4 2,000 10.4 2,500 11.6 3,000 12.7 without S-9 mix: doses (ug/ml) SCE's/cell neg.co. 10.1 300 13.3 350 14.3 400 13.9 toxicity: with S-9 mix 3,500 µg/ml is total toxic	Ivett et al., 1989

Table 4.23 *In vitro* tests: Sister chromatid exchanges (SCE)

Test system	Concentration range		Result	Description of result	Reference
	with S-9 mix	without S-9 mix			
rat bone marrow cells	not done	1.0 – 1,000 µmol/l (0.09 - 94.11 µg/ml)	positive	1. experiment: dose (µg/ml) SCE/cell mitotic index (%) neg.co. 4.1 0.09 4.5 59.0 0.94 5.8 53.7 9.41 7.2 55.5 94.11 8.7 32.0 2. experiment: dose (µg/ml) SCE/cell mitotic index (%) neg.co. 4.1 0.09 4.7 55.2 0.94 6.0 46.3 9.41 7.8 39.8 94.11 9.6 26.7	Khalil and Odeh, 1994
SHE cells	not done	10 – 3,000 µmol/l (0.94 - 282.3 µg/ml)	positive	dose (µg/ml) SCE/cell neg.co. 8.4 0.94 8.8 9.41 9.8 28.20 9.6 94.10 11.2 282.3 13.8 toxicity: no data	Tsutsui et al., 1997
V79 cells	not done	up to 1,000 µmol/l (94.1 µg/ml)	negative	toxicity: no data	Glatt et al., 1989

Table 4.24 *In vitro* tests: Unscheduled DNA synthesis (UDS)

Test system	Concentration range		Result	Remarks	Reference
	with S-9 mix	without S-9 mix			
SHE cells	not done	1.0 - 100 µmol/l (0.09 - 9.41 µg/ml)	positive	dose-dependent increase of UDS from 1.0 µmol upwards toxicity: no data	Tsutsi et al., 1997

Table 4.25 *In vitro* tests: DNA strand breaks

Test system	Concentration range		Result	Remarks	Reference
	with S-9 mix	without S-9 mix			
alkaline elution technique; mouse lymphoma cells (L5178Y)	150 – 5,000 µmol/l (14.11 - 470.6 µg/ml)	150 – 5,000 mmol/l (14.11 - 470.6 µg/ml)	positive	positive only with S-9 mix at 1,500 and 5,000 µmol/l toxicity: no toxic effects	Garberg et al., 1988
alkaline elution technique; mouse lymphoma cells (L5178Y)	not done	1,000 µmol/l (94.11 µg/ml)	negative	toxicity: no toxic effects	Pellack-Walker and Blumer, 1986

Table 4.26 *In vitro* tests: DNA adducts

Test system	Concentration range		Result	Remarks	Reference
	with S-9 mix	without S-9 mix			
phenol extraction procedure; HL60 cells (human leukaemia cell line)	not done	100 µmol (9.41 µg/ml)	positive	oxidative DNA damage toxicity: no data	Kolachana et al., 1993
liquid scintillation counting of 14C; isolated calf thymus DNA	not done	100 - 200 µmol/l (9.41 - 18.8 µg/ml)	positive	positive at both tested doses; binding in the presence of horseradish peroxidase and hydrogen peroxide	Subrahman-yam and O'Brien, 1985
chromosomal aberrations; CHO cells	2,000 – 3,000 µg/ml	600 - 800 µg/ml	positive	positive with and without S-9 mix with S-9 mix: treatment/ sampling: 2h / 2.5h dose-range (µg/ml) aberrant cells (%; excl. Gaps) neg.co. 2.0 2,000 18.0 2,500 14.0 3,000 17.0 without S-9 mix: treatment/sampling: 8h / 22.5h dose-range (µg/ml) aberrant cells (%; excl. Gaps) neg.co. 2.0 600 4.0 700 6.0 800 7.0 toxicity: no detailed data; "slight reduction in cell confluency" at the two top doses with and without S-9 mix	Ivett et al., 1989
chromosomal aberrations; SHE cells	not done	3 - 100 µmol/l (0.28 - 9.4 µg/ml)	negative	treatment/sampling: 24h / 24h toxicity: no toxic effects	Tsutsui et al., 1997

Table 4.27 *In vivo* tests: Bone marrow micronucleus tests with mice after single oral administration

Test system	Dose (mg/kg bw)	Exposure regimen	Sampling time	Result	Local cytotoxicity	General toxicity	Remarks	Reference
Swiss CD-1 mice; bone marrow erythrocytes	265	1 · p.o.	15 to 40 hours	weakly positive	unclear effect on P/N ratio	no data	time(h) MN cells (%) 0 0.20 15 0.38(s) 18 0.40(s) 24 0.50(s) 30 0.31 36 0.28 40 0.34 use of 4 pregnant females per group	Ciranni et al., 1988a
Swiss CD-1 mice; bone marrow erythrocytes	265	1 · p.o.	18 to 48 hours	weakly positive	drastic depression of P/N ratio at all sampling times (up to 0.4)	no data	time(h) MN cells (%) 0 ca. 0.15* 18 ca. 0.25* 24 ca. 0.30* 42 ca. 0.15* 48 ca. 0.25* (* estimated from columns given in a figure) 4 animals per group; gender not given	Ciranni et al., 1988b
Swiss CD-1 mice; bone marrow erythrocytes	250	1 · p.o.	30 hours	negative	no data	no data	5 males	Gad-El-Karim et al., 1985
Swiss CD-1 mice; bone marrow erythrocytes	250	1 · p.o.	30 hours	negative	no data	no data	5 males	Gad-El-Karim et al., 1986

Table 4.28 *In vivo* tests: Bone marrow micronucleus tests with mice after single i.p. administration

Test system	Dose (mg/kg bw)	Exposure regimen	Sampling time	Result	Local cytotoxicity	General toxicity	Remarks	Reference
B6C3F1 mice; bone marrow erythrocytes	300	1 · i.p.	26 hours	positive	extreme depression of P/N ratio (0.16 and 0.24)	no data	dose (mg/kg) MN cells (%) 1.expt. 2.expt. 0 0.23 0.33 300 1.10 1.14 6 males per group	McFee et al., 1991
Swiss CD-1 mice; bone marrow erythrocytes	265	1 · i.p.	18 to 48 hours	positive	extreme depression of P/N ratio ranging from 0.2 to 0.3	no data	time(h) MN cells (%) 0 ca. 0.15* 18 ca. 0.75* 24 ca. 0.45* 42 ca. 0.20* 48 ca. 0.10* (* estimated from columns given in a figure) 4 animals per group; gender not given	Ciranni et al., 1988b
Swiss CD-1 mice; bone marrow erythrocytes	40 – 160	1 · i.p.	18 hours	negative	no effect on P/N ratio	no data	3 animals per group; gender not given	Barale et al., 1990
Swiss CD-1 mice; bone marrow erythrocytes	40 – 120	1 · i.p.	18 hours	weakly positive	no effect on P/N ratio	no data	dose (mg/kg) MN cells (%) 0 0.163 40 0.186 80 0.215 120 0.282(s) 3 males	Marrazzini et al., 1994

Table 4.29 *In vivo* tests: Bone marrow micronucleus tests with mice after multiple i.p. administration

Test system	Dose (mg/kg bw)	Exposure regimen	Sampling Time	Result	Local cytotoxicity	General toxicity	Remarks	Reference
NMRI mice; bone marrow erythrocytes	47 – 188	2 · i.p. at 24-hour interval	6 hours after last treatment	negative	no data	no data	2 males and 2 females per group	Wild et al., 1980 (see also Gocke et al., 1981)
B6C3F1 mice; bone marrow erythrocytes	45 – 180	3 · i.p. at 24-hour intervals	24 hours after last treatment	weakly positive	no effects on P/N ratio	no lethal effects	dose MN cells (%) 1.expt. 2.expt. 0 0.24 0.26 45 0.24 0.29 90 0.24 0.40(s) 180 0.53(s) 0.43(s) 5 males per group	Shelby et al., 1993
Swiss CD-1 mice; bone marrow erythrocytes	50 – 160	3 · i.p. at 24-hour intervals	24 hours after last treatment	weakly positive	no effect on P/N ratio	no data	according to a figure an increased frequency was obtained at 3 · 160 mg/kg; no details; no statistics; the authors conclude a weak to moderate; 5 males per group	Chen and Eastmond,, 1995

Table 4.30 *In vivo* tests: Rodent bone marrow chromosomal aberration test

Test system	Dose (mg/kg bw)	Exposure regimen	Sampling time	Result	Local cytotoxicity	General toxicity	Remarks	Reference
Sprague-Dawley rats; bone marrow cells	450 - 510 (males)	1 · p.o.	20 hours	negative	no clear effect	LD_{30}= 510 mg/kg	only 30 mitoses / animal were scored	Thompson and Gibson, 1984
	300 - 410 (females)	1 · p.o.	20 hours	negative	no clear effect	LD_{30}= 410 mg/kg	3 males and 3 female per group	
	80 - 180 (males)	1 · i.p.	20 hours	negative	effect at the top dose	LD_{30}= 180 mg/kg		
	72 - 110 (females)	1 · i.p.	20 hours	negative	effect at the top dose	LD_{30}= 110 mg/kg		

Table 4.31 *In vivo* tests: DNA strand breaks in testes

Test system	Dose (mg/kg bw)	Exposure regimen	Sampling Time	Result	General toxicity	Remarks	Reference
DNA strand breaks; Sprague-Dawley rats	7.9 – 79	1 · i.p.	2, 6 and 24 hours	negative	97 mg/kg = LD01	tested organ: testis	Skare and Schrotel, 1984
	4.0 - 39.5	5 · i.p. with 24-hour intervals	2 hours after last injection	negative		one animal for each dose level and time point alkaline elution/ fluorometric assay	

Table 4.32 *In vivo* tests: Drosophila melanogaster

Test system	Exposure	Result	General toxicity	Reference
Sex-linked recessive lethal test; Canton-S males	Feeding 2,000 ppm (diet) for 3 days	Negative	30% mortality	Woodruff et al., 1985
	1 · injection of 5,250 ppm 24 - 48 hours before mating	Negative	6% mortality	

Table 4.33 *In vivo* tests: DNA adducts

Test system	Dose (mg/kg bw)	Exposure regimen	Sampling time	Result	General toxicity	Remarks	Reference
32P-postlabeling; Sprague-Dawley rats	75	4 · p.o. with 24-hour intervals	24 hours after last dosing	negative	no data	Tested organs: bone marrow, zymbal gland, liver 4 females	Reddy et al., 1990
phenol extraction; B6C3F1 mice	75	1 · i.p.	1 h	negative	no data	no oxidative DNA damage in bone marrow cells 3 males	Kolachana et al., 1993

4.1.2.8 Carcinogenicity

– In 103-weeks cancer studies on F344 rats and B6C3F1 mice with oral administration of 2,500 and 5,000 ppm phenol in the drinking water (≈ 200 and 450 mg/kg bw/day for rats and 281 and 375 mg/kg bw/day for mice), phenol was not carcinogenic for both sexes. The purity of the test substance was reported to be > 98% for one of three batches used. The final body weight gain was reduced in high dose rats and both dose groups in mice. Water consume was reduced in both dose groups in rats (-10 and -20%) and in both dose groups in mice (-25 and –40-50%). There was no effect on food consumption and mortality. No treatment-related effects of the incidences of inflammatory, degenerative and hyperplastic lesions were seen in treated rats and mice. The incidence of leukaemia or lymphomas, pheochromocytomas, and c-cell carcinomas was significantly increased in male rats that received 2,500 ppm phenol (see below). Increases in tumour incidence were only seen in the low dose group, no such effect could be observed in the high dose group. Thus, an association with administration of phenol was not established for this rat strain. In mice, no tumour induction can be associated with the administration of phenol (NIH, 1980).

Table 4.34 Tumours in male rats (NIH, 1980)

Tumours in male rats	Control group	2,500 ppm Phenol	5,000 ppm Phenol
Leukaemia or malignant lymphoma	18/50	31/50	25/50
Pheochromocytomas	13/50	22/50	9/50
C-cell adenomas	4/50	2/50	0/50
C-cell carcinomas	0/50	5/49	1/50

- Medium-term dermal treatment of phenol in FVB/N mice or its transgenic mouse line TG.AC carrying a v-Ha-ras gene revealed no increase of skin tumours but inhibition of hair growth and chronic skin irritation. Three mg phenol was applied twice weekly on the clipped dorsal skin for 20 weeks (Spalding et al., 1993, Tennant et al., 1995). In a promoter-initiator model, dermal application of phenol resulted in an increased number of skin tumours (4 papillomas and 1 squamous carcinoma/20 females) after initiation with DMBA in ICH/Ha Swiss mice (Van Duuren et al., 1968). Another early tumour-promotion study (Boutwell and Bosch, 1959) demonstrated strong tumour-promoting activity of phenol in young adult albino mice (Sutter and Holtzman strains). Groups of 23 mice received a pre-treatment with the 75 μg dimethylbenzanthracene (DMBA) in a benzene solution followed by twice weekly skin applications of 10% solution of phenol in benzol (no data on benzene concentration). Control groups received DMBA alone or phenol without initiation treatment. During the first 6 weeks of phenol treatment, skin wounds and hyperplasia was seen in many mice. Animals demonstrated hair loss and inhibition of hair growth in the treated skin area. At week 13 after initiation, 95% of phenol-treated mice developed papillomas and 73% had carcinomas. DMBA-only treatment resulted in papillomas in 4% of the mice at 42 weeks. Phenol alone induced papillomas in 36% of treated mice after 72 weeks and a single fibrosarcoma appeared at week 58. Similar frequencies of skin tumours were found in a second experiment at phenol concentration of 10% with or without DMBA initiation, but a lesser concentration of phenol (5%) was found to have a moderate promoting action. Only one out of 30 female mice developed a papilloma after treatment with 5% phenol without initiation. No other toxic lesions were seen at this concentration. A co-carcinogenic potency was not found when phenol and benzo(a)pyrene were co-applied on mouse skin (Van Duuren et al., 1971).

Cell proliferation study

- Neither the thickness nor the labelling indices for cell proliferation after incorporation of a single post-treatment BrdU injection were significantly increased in the mucosa of the glandular stomach and esophagus of five male F344 rats given phenol at a concentration of 2% in the drinking water for 4 weeks compared to control rats (Kawabe et al., 1994).

4.1.2.8.1 Studies in humans

- In a case-control study on 57 male cases of respiratory tumours (Kauppinen et al., 1986), defined as cancers originating in organs in direct contact with chemical agents, such as the tongue, mouth, pharynx, nose, sinuses, larynx, epiglottis, trachea and lung approximately 90% were of the lung and trachea. Three control subjects for each case (171 men without respiratory cancer) were selected from a same cohort of 3,805 men who had worked for at least one year in the particleboard, plywood, sawmill, or formaldehyde glue industries between 1944 and 1965 and followed up until 1981. The comparison of exposures was carried out according to work histories and job exposure matrices for each plant. The relative risks for exposure to phenol, adjusted for smoking, was increased (OD 4.0, 12 cases, $p < 0.05$, without provision for any latent period and OD 2.9, 7 cases, $p < 0.05$ with provision of a latent period of ten years). The relative risks for phenol in wood dust were only increased without provision for any latent period (OD 4.1, 9 cases, $p < 0.05$, adjusted for smoking). The relative risks for exposure did not increase with duration of exposure to phenol, but increased with duration of exposure to phenol in wood dust. The authors noted that the OD of phenol was confounded by exposure to pesticides. When workers exposed to phenol and pesticides were excluded, the OD ratios decreased to a non-significant level.

Classification and labelling

Using the EU-criteria on carcinogenic potential, there is no need for classification and labelling neither on further testing.

Summary and conclusion

Oral long term studies on rats and mice revealed no effect of phenol on tumour induction. A medium-term study on a transgenic mouse model did not give any indication on treatment-related proliferative responses. Phenol was shown to act as a promoter in skin cancer bioassays in mice. A weak carcinogenic effect was observed after long-term skin application of a 10% solution of phenol in benzene (without initiation), but was considered less relevant. The test solution was strongly irritative, and contained the carcinogen benzene. However, there is some concern on the basis of weakly positive *in vivo* mutagenicity data and from the phenol metabolite hydroquinone classified as a suspected carcinogen (Category 3). This concern is considered to be of minor significance, as long term studies revealed no relevant indication for carcinogenicity. However, in conclusion, phenol is considered not to be a carcinogen in animals.

There are no data revealing an association of phenol exposure to increased tumour rates in humans. No firm conclusion on risk levels could be drawn from a case-control study on respiratory cancer of workers exposed to phenol.

4.1.2.9 Toxicity for reproduction

4.1.2.9.1 Studies in animals

Fertility impairment

Phenol was investigated for impairment of reproductive performance and fertility in a two-generation (drinking water) reproductive toxicity study complying with GLP standards (IITRI, 1999; Ryan et al., 2001) which was supplemented with additional immunotoxicity screening and investigation of hematotoxicity and of clinical pathology in males (see Section 4.1.2.6). Phenol (purity not indicated) was administered continuously via drinking water at concentrations of 0, 200, 1,000 and 5,000 ppm (calculated to mean daily uptake of 14.7/20.0, 70.9/93.0 and 301.0/320.5 mg/kg bw/day in males/females, respectively) to groups of 30 male and female Sprague-Dawley rats (P0 parental generation) during a period of 10 weeks prior to mating, mating (2 week period), gestation and lactation until sacrifice. P0 sires were then assigned to further investigation of immunology, haematology and clinical biochemistry. At weaning, on p.n. day 22, selected offspring (at least 1 pup/sex/litter) was taken to produce the next generation and was continued on phenol in drinking water at the same dose levels as their parents (calculated to mean daily uptake of 13.5/20.9, 69.8/93.8 and 319.1/379.4 mg/kg bw/day in F1 parental males/females, respectively) during a period of 11 weeks prior to mating, mating (2-week period), gestation and lactation. F2 offspring was not intentionally exposed to the test substance. F1 sires were sacrificed after mating, and F1 dams and all their pups (F2 generation) were sacrificed following weaning (at p.n. day 22). The offspring of both generations (F1/F2) had been randomly culled to 4/sex/litter at p.n. day 4.

Parental animals were examined for their mating and reproductive performances. The animals were checked daily for mortality and once/weekly for clinical signs. Food and water consumption was recorded once/weekly. Body weights of P0/F1 parental animals were recorded

once/weekly and for dams during gestation on g.d. days 0, 7, 14 and 20. Both dams and offspring were weighed on p.n. days 0, 4, 7, 14 and 21, and average pup weights were calculated for each litter and each dose group. Besides body weight also the weight gains were calculated for all animals except for the pups during lactation. Offspring survival was calculated based on the number alive on a given day subtracted from the number alive on the previous day. All pups were subjected to gross external evaluation on the day of birth. In addition, the selected P0 offspring (F1 generation) was checked for vaginal opening (females during p.n. days 28-45) and preputial separation (males during p.n. days 35-55).

At least 20 rats/sex/group from the P0 and F1 generations were assessed by gross pathology at necropsy (including weight determination of several organs), and organs of the male/female reproductive system of the high dose groups and of the controls were subjected to histopathological examination.

Estrous cycle data were evaluated for P0 and F1 females over a three-week period prior to mating and throughout the following mating period until evidence of mating appeared. In addition, the estrous stage of each female was determined on two to four days prior to and on the day of necropsy.

Sperm motility, sperm morphology and epididymal sperm counts in the P0 and F1 generation was assessed in at least 20 males in the control and in the high dose groups. Homogenisation resistant testicular spermatids in the P0 and F1 generation were assessed in at least 20 males in the control and in the high dose groups at the day of collection, and those of the mid dose group F1 males from frozen specimen.

There were no substance-related mortalities in male/female parental animals or in the dams during the period of gestation and lactation. Three out of 26 female pups (F1 generation) died shortly after weaning; these deaths appeared to be associated with reduced acclimation to the test substance in the drinking water, since these animals were not drinking the water. Clinical signs consisted of discoloured or wet inguinal fur and redness around the nose or eyes and were observed at slightly higher incidences in the test substance-treated groups than in the control group.

Mean water consumption was statistically significantly decreased in the high dose group male sires of the P0 and the F1 generation throughout the study (pre and post-mating). Mean food consumption was statistically significantly reduced in the high dose group male sires of the P0 generation throughout the study (pre and post-mating). Mean body weights were statistically significantly reduced in the high dose group male sires of the P0 generation during pre-mating from three weeks onwards and during post-mating and in those of the F1 generation throughout the study. A similar response pattern was observed for female animals. Mean water consumption was statistically significantly decreased in the high dose group females of the P0 and the F1 generation throughout the study (pre-mating, gestation, lactation and post-lactation). Mean food consumption was statistically significantly reduced in the high dose group females of the P0 and the F1 generation during the first weeks of pre-mating and for the P0 females also during lactation. Mean body weights were statistically significantly reduced ($p \leq 0.05$) in the high dose group females of the P0 and the F1 generation throughout the study (pre-mating, gestation, lactation and post-lactation) with signs of body weight loss during lactation. No such effects were revealed in animals at the lower drinking water concentration levels during this study. The overall effects on body weight at the 5,000 ppm drinking water concentrations were considered to result from the reduced water uptake at that concentration level which itself was considered to come from flavour aversion to the test substance in the drinking water.

No treatment-related necropsy findings were recorded. At sacrifice organ pathology of males and females of the P0 and F1 generation of the high dose groups revealed some increased organ-to body weight ratios (brain, kidney, liver, testes, epididymides) which were considered secondary effects related to significantly reduced body weights. No treatment-related lesions were detected from histopathological evaluation in any of the organs examined (kidneys, spleen, liver, and thymus). A significant decrease in absolute prostate weight (no dose-related trend) was noted for all three test-substance treated groups in the F1 generation, but not in the P 0 generation. Significant reductions in absolute and relative uterus weights (no dose-related trend) were noted across all three treated groups in the F1, but not in the P0 generation. No adverse histopathological changes were observed in these organs. Microscopic examination of the other reproductive organs including accessory sex organs failed to indicate any treatment-related lesions.

Evaluation of the estrous cycle data during the 21-day evaluation period revealed that the mean frequency of estrous (3.8 to 4.7 days) was similar across all groups for both generations and was unaffected by treatment with the test substance.

Testicular sperm count and production rate was unaffected in the P0 generation. In the F1 generation statistically significantly increases in testicular sperm count and production rate were noted in the high dose group compared to the controls, whereas no differences in testicular count was noted in the mid dose group. The observed changes in the high dose group were presumed to be associated with reduced absolute testis weight secondary to reduced body weight, rather than to indicate a true, respectively substance-related effect. Sperm motility and morphology were unaffected by treatment across both generations.

No adverse effects were observed on reproductive capacity or capability. The average length of gestation was similar across all groups with approximately 22 to 22.5 days for both generations. For the P0 generation the mating index (sperm positive/group) was 97% in the control, and 100, 97, and 97% in the 200, 1,000, and 5,000 ppm groups; for the F1 generation the mating index was 100% in the control, and 96, 100, and 100% in the low, mid, and high dose groups. For the P0 generation the percentage successful mating (parturition/sperm positive) was 93% in the control, low, mid and high dose group. For the F1 generation the percentage successful mating was 84% in the control, and 92, 92, and 87% in the 200, 1,000 and 5,000 ppm groups.

The average number of live births/litter and deaths/litter on postnatal day 0 was similar for all groups and across both generations. However, survival of the high dose (5,000 ppm) offspring was adversely affected in both generations in the presence of overt maternal toxicity as indicated by reduced maternal body weight and body weight loss. In the high dose group percent F1 offspring survival was statistically significantly reduced on p.n. day 4, and after culling was lower up to p.n. day 21 than in the concomitant control, low and mid dose groups. F2 offspring survival was statistically significantly reduced in the high dose group on p.n. day 4 as well as after culling up to p.n. day 21. Average offspring survival (percentage) was comparable throughout the pre-weaning phase of the study for control, low and mid dose groups for both generations. The average litter body weights of the offspring of both generations were statistically significantly reduced at postnatal day 0 and up to weaning at p.n. day 21 in the high dose (5,000 ppm) treated groups. The initial body weight reduction of about 5 to 7% on p.n. day 0 increased during the postnatal period and at weaning amounted to about 28 to 30% in comparison to the controls. No such body weight effects in the offspring were revealed for the lower drinking water concentration levels. As for adult animals indicated above, flavour aversion to the test substance was considered to be a factor responsible for the increasing magnitude of the body weight response observed in the pups of the 5,000 ppm groups during pre-weaning, since offspring begins drinking water postnatally between days 7 and 14. Furthermore, the

flavour aversion is reflected in the decreased water consumption of these pups persisting into adulthood and resulting in growth retardation as indicated by lower body weights of these animals. Evaluation of developmental landmarks of sexual maturation revealed a 3-day delay in vaginal opening and preputial separation in the post-weaning offspring of the high dose (5,000 ppm) group, whereas no such delay was revealed for the low and mid dose groups. Since vaginal opening and preputial separation are correlated with body weight, the delayed sexual maturation in the high dose offspring was considered to result from growth retardation.

The reports from an early study of Heller and Purcell (1938) are insufficient and are considered not to be valid for further assessment due to missing or absolutely inadequate documentation of methods, data and results (e.g. no data on animal maintenance, breeding habits, concurrent control groups, methods used to evaluate the animals for reproductive impairment and/or maternal toxicity etc.). In that study, where rats (unspecified strain and number of animals used) had been exposed to phenol (not further specified) throughout their life cycle via drinking water, missing evidence of any impairment of reproduction on 3 generations at levels of up to 5,000 ppm phenol in drinking water is restricted to reported results like “growth normal”, “general appearance good” or “reproduction without noticeable interference”. Likewise the reported results from higher phenol concentrations in drinking water (up to 12,000 ppm) are insufficient for any further assessment.

Likewise, any fertility related results reported from the 13 week study of the cancer studies on F344 rats and B6C3F1 mice (NIH, 1980) have not been considered for the assessment, since detailed data were not available from the report.

Summary and conclusion

Phenol was investigated for impairment of reproductive performance and fertility in a valid two-generation (drinking water) reproductive toxicity study. At the highest tested drinking water concentrations of 5,000 ppm, which led to reduced water intake and consequently decreased body weight and body weight gain in the animals, no impairment of reproductive capability and fertility was revealed for both sexes. However, litter survival and offspring body weights were reduced during the period of lactation/pre-weaning in the 5,000 ppm groups across both generations, with the effects on litter survival more pronounced in the F2 generation. Furthermore, signs of impaired offspring development were observed during the study in P0 progeny (reduced birth weight, impaired pre- and post-weaning body weight gain associated with delay in physical development and sexual maturation) and in F1 progeny (reduced birth weight, impaired pre-weaning body weight gain), however at a dose level that clearly indicated systemic toxicity in their dams and in the parental animals. From the findings of reduced water intake, body weight and organ weight impairment in the P0 and F1 animals at 5,000 ppm a NOAEL for general, systemic toxicity of 1,000 ppm according to a mean uptake of about 70 mg phenol/kg bw for males and of about 93 mg phenol/kg bw for females can be derived from this study, indicating that the observed impairment of development at the higher concentration levels may be considered to be secondary to the overall reduced state of health of these animals.

Developmental toxicity

In a recent oral developmental toxicity study (Argus Research Laboratories, Inc., Protocol Number 916-011, Final Report 1997) phenol (purity: 90% USP) was administered as aqueous solution at total daily dosages of 60, 120 and 360 mg/kg body weight during days 6 to 15 of gestation to groups of 25 Sprague Dawley rats per group. Reverse osmosis membrane processed water was used as vehicle. Dosages of 0 (vehicle), 20, 40 and 120 mg test solution/kg body

weight were administered via gavage three times daily at a volume of 10 ml/kg body weight. Dams were observed for viability at least twice each day. They were observed for clinical observations after the second daily dosage and once daily during the post-dosage period (from g.d. 16 - 20). Body weights were recorded on g.d. 0 and daily during the dosage and post-dosage period. Feed consumption was recorded on g.d. 0, 6, 9, 12, 16, 18 and 20. At sacrifice on g.d. 20 gross necropsy was performed, and numbers of corpora lutea, implantations, live and dead fetuses and early and late resorption were recorded for each dam. Fetuses were weighed, sexed and examined for gross external alterations. Approximately one-half of the fetuses of each litter were examined for either visceral or for skeletal alterations. One rat at the 360 mg/kg dosage group was found dead on g.d. 11, yet, clinical observations had been normal up to the day of death and there were no abnormal necropsy findings. The 15 conceptuses also appeared normal for their developmental age. Clinical observations in terms of excess salivation and respiratory distress (tachypnea) were found to be significantly increased ($p < 0.01$) in dams at the high (360 mg/kg) dosage group. At necropsy no treatment related findings were observed in dams of either dosage group. Mean maternal body weight was statistically significantly lower in the 360 mg/kg dosage group during the entire dosage and post-dosage period. At this dosage level, mean maternal body weight gain was reduced to 39.8 $\pm$ 9.5 g in comparison to 64.0 $\pm$ 10.7 g in the control group for the period of administration. This effect persisted and was not compensated for, since mean maternal body weight gain was calculated to be statistically significantly lower ($p < 0.05$) further on for the period of day 6 up to the day of sacrifice (117.8 $\pm$ 18.4 g in comparison to 140.6 $\pm$ 16.7 g in the control group). Effects on maternal body weight were observed at the 120 mg/kg dosage level, with statistically significantly reduced mean maternal body weight gain ($p < 0.01$) of 56.8 $\pm$ 10.8 g in comparison to the 64.0 $\pm$ 10.7 g in the control group during the period of administration but not later. Food consumption of the dams was revealed to be somewhat lower during the period of administration in terms of 18% less average feed intake in comparison to the control group for the 360 mg/kg, respectively 7% less average food intake in the 120 mg/kg dosage groups. No effects on body weight or on food consumption were observed at the 60 mg/kg dosage group.

At termination the respective pregnancy rates were found to be 95.8, 100 and 95.8% in the dosed groups and 92% in the control group. The litter averages for corpora lutea, implantations, litter size, live fetuses, early and late resorption, percent resorbed conceptuses and percent male fetuses and the number of dams with any resorption were similar among the groups and did not significantly differ. Average fetal body weight was slightly but statistically significantly ($p < 0.05$) reduced for 5.8% at the 360 mg/kg dosage groups. Fetal body weights were not reduced for dosages up to and including 120 mg/kg/day. A total of 369, 378, 348, and 365 live fetuses were examined for morphological alterations for the 0, 60, 120, and 360 dosage groups, respectively. There were no increases in fetal gross external, soft tissue and skeletal malformations or variations. The only finding was that average number of ossification sites per fetus per litter in metatarsals was significantly ($p < 0.05$) reduced in the 360 mg/kg/day dosage group in comparison to the control group. This effect is generally considered to be a reversible delay in development associated with reduced fetal growth.

From the results of this study a NOAEL/maternal toxicity of 60 mg/kg body weight/day, based on reduced maternal weight gain during the period of treatment at the next higher dosage level, and a NOAEL/developmental toxicity of 120 mg/kg body weight/day based on indications of fetal growth retardation at the next higher dosage level can be derived.

Also, in two NTP teratology studies phenol had been evaluated for maternal and developmental toxicity in timed-pregnant CD-1 mice and CD rats.

In the study with Swiss albino (CD-1) mice (Jones-Price et al., 1983c) phenol was administered (in distilled water) at doses of 0, 70, 140, and 280 mg/kg bw by gavage in a volume of 10 ml/kg bw daily during the period of major organogenesis (gestational days 6 - 15).

Based on the results from a preceding preliminary study with pregnant females the dose of 280 mg/kg bw was included as a "high" dose in the main study which was expected to produce statistically significant signs of maternal and/or fetal toxicity, while allowing ≥ 90% maternal survival. 22-29 pregnancies had been confirmed per group. Dams were monitored for weight gain and clinical signs of toxicity during the investigation. At sacrifice (gestational day 17), maternal liver weight, gravid uterine weight as well as the numbers of implantations, resorption, late fetal deaths and live fetuses were recorded for each dam. Live fetuses (214-308 per group) were examined for weight, sex, and gross morphological abnormalities. Visceral and skeletal examinations were also performed. With the experimental conditions of this study distinct maternal toxicity was observed at the high dose level (280 mg/kg bw) including 11% mortality, reduced body weight and reduced weight gain as well as clinical signs of toxicity (e.g. tremor, ataxia). The respective pregnancy rates at termination were found to be 84%, 84% and 71% in the dosed groups and 83% in the control group. No dose related changes were noted for prenatal mortality or the incidence of morphological abnormalities in any of the dosed groups, except for an apparent increase in cleft palate at the highest dose level, a malformation for which the CD-1 mouse is predisposed under conditions of maternal stress. At daily doses of 280 mg phenol/kg bw mean gravid uterine weight as well as average fetal body weight per litter was statistically significantly reduced.

In the study with CD rats (Jones-Price et al., 1983b) phenol was administered (in distilled water) at doses of 0, 30, 60, 120 mg/kg bw daily by gavage in a volume of 5 ml/kg bw during the period of major organogenesis (gestational days 6-15). Twenty to 22 pregnancies had been confirmed per group. Dams were monitored for weight gain and clinical signs of toxicity during the investigation. Evaluation of maternal and developmental endpoints (of 268-293 live fetuses per group) were the same as for the study with CD-1 mice, however they were evaluated at termination on gestational day 20. All phenol-treated dams survived until sacrifice. Pregnancy rates at termination were high (95-100%) and comparable across all groups. Prenatal viability was 100% in every group, and there was no evidence for an increased incidence of morphological abnormalities (malformations and/or variations) in the fetuses from the phenol-treated dams. A slight but statistically significant increase in the proportion of litters with resorption sites was revealed for the low- and for the mid-dose group, however not for the high-dose group. In the high-dose group average fetal body weight per litter was slightly but statistically significantly reduced to 93% in comparison to that from the control group. However, interpretation of the data and the results of this study are not possible due to significant pitfalls during this investigation. Weight loss (≥ 5g in a 24-hour period) in dams was observed across all treated groups between g.d. 6 to 13, and it is noted in the protocol that not before g.d. 13 it was recognised that several cages had been without any food supply at all. Further, the study was performed in a replicate manner and also inadequate documentation of the assignment of the animals to the respective groups was noted in the protocol, which made further clarifications impossible. Thus, the results of this study are of limited significance and therefore will not be considered for risk characterisation purposes.

In a recent validation study of an integrated bioassay on different aspects of toxicity, phenol was assessed together with 9 other compounds for the screening of developmental toxicity (Narotsky and Kavlock, 1995). In this study 15-20 pregnant Fischer-344 rats received phenol (in water) at doses of 0, 40, and 53.3 mg/kg bw daily by gavage on gestational days 6-19. The "high" dose level, selected to produce some overt maternal toxicity, was reported to come from results of a

companion repeated dose (14 days) toxicity study on non-pregnant females. The "low" dose level was established to 75% of the "high" dose level. For these two dose levels there were no significant effects on maternal body weight gain. It was reported that phenol was associated clinically with altered respiration (dyspnea, rales and vocalisation). Since similar problems were also observed in this study in animals treated with other compounds with occasional deaths immediately after dosing, inadequate treatment might be a factor to be considered. As for the experiments with phenol, one out of 15 pregnant females resorbed the entire litter at the "low" dose level and two out of 16 did so at the "high" dose level, from which in summary a (not further indicated) marginally significant increase in prenatal loss in the "high" dose group was derived by the authors. All three of these dams however suffered from severe respiratory syndrome. For an additional high-dose female, also with severe respiratory syndrome, excessive perinatal mortality was reported, with two out of the four survivors exhibiting malformations (kinked tails). All developmental effects reported were limited to these four litters only and may have been secondary to severe impairment of their dams. In contrast to this, no effects on pup body weights on postnatal days 1 or 6 were observed. With regard to this and in the view of the specifically restricted developmental effects in these experiments the results of this study are not considered for risk characterisation. The data from this study can at the most be taken as a certain confirmation of the results from the teratology study on CD rats indicating a NOAEL for developmental toxicity of about 60 mg/kg bw/day.

Summary and conclusion

Phenol was evaluated for maternal and developmental toxicity in teratology studies with rats and mice with the oral route (gavage) of administration.

In the mice study effects of impairment of development (reduced average fetal body weight, cleft palate) were identified at dosages of 280 mg/kg bw/day that also led to clear-cut signs of maternal toxicity. A NOAEL/developmental toxicity of 140 mg/kg bw/day and a NOAEL/maternal toxicity of 140 mg/kg bw/day can be derived from the study with mice.

In the well-performed ARGUS rat teratology study effects of fetal growth retardation (slightly lower average fetal body weight, indications of slight ossification delay) were identified at a dose level of 360 mg/kg bw/day that also led to clear-cut signs of maternal toxicity. No such developmental effects were detected at dosages of 120 mg/kg bw/day, which however had been revealed to impair maternal body weight gain. A NOAEL/developmental toxicity of 120 mg/kg bw/day and a NOAEL/maternal toxicity of 60 mg/kg bw/day can be derived from the study.

For the evaluation of the substance specific potential to adversely affect prenatal as well as later development by pre-/peri-/postnatal exposure of the conceptus also the data generated from the 2-generation rat study have to be taken into consideration. With this study (continuous exposure of the conceptus during the gestational and lactational period) phenol was also found to induce signs of prenatal growth retardation in terms of slightly lower pup birth weights and to impair peri-postnatal viability of the offspring. Also impairment of postnatal growth (lower body weight gain, delay in morphological development and sexual maturation) had been observed. These effects were induced at drinking water concentrations of 5,000 ppm according to a calculated mean daily intake of 320 mg/kg body weight of their dams, which had also led to clear-cut signs of systemic toxicity in the parental animals. No effects on the performance of dams or of their offspring were identified at the next lower tested drinking water concentration of 1,000 ppm according to a calculated mean daily intake of 93 mg/kg body weight for the dams. A NOAEL/developmental toxicity of 93 mg/kg bw/day and a NOAEL/maternal toxicity of 93 mg/kg bw/day can be derived from the study.

From the assessment of the data from the teratology studies with mice and rats phenol does not seem to have any specific embryotoxic or teratogenic properties.

From the overall assessment of the available data it appears that exposure to phenol during the period of gestation and lactation can induce some growth retardation to the fetus and impair postnatal viability and growth. However, the observed effects were predominant at exposures that also were toxic to the dams. Thus, signs of slight fetal growth retardation are not considered indicative for a specific fetotoxic effect of phenol.

Since substance administration during the conventional teratology studies covers only the period of organogenesis and since across studies the observed effects in particular concerned fetal growth and peri-postnatal performance, it appears appropriate to base risk characterisation for developmental effects on the data obtained from the 2 generation study (IITRI, 1999; Ryan et al., 2001). Thus, the NOAEL for developmental toxicity is 93 mg/kg bw/day.

Other information

Phenol was also investigated *in vitro* in a rat whole embryo culture system (Chapman et al., 1994). Embryos of selected developmental stages (8-10 somites) were incubated with various concentrations of phenol in the culture medium with or without a rat hepatic S9 bioactivating system over a period of 30 hours. In the absence of S9 mix phenol concentrations of up to 1,600 µM did not reveal any statistically significant effects on the evaluated parameters of dysmorphogenesis or growth and development. In the presence of S9 mix (from Aroclor 1,254-induced animals) *in vitro* growth and development of the embryos was concentration-dependent and significantly affected with phenol concentrations as low as 10 µM. The study further reports that within a variety of other inducing agents the S9 mix of phenobarbital-induced rats exhibited the greatest phenol bioactivating activity. Furthermore the embryotoxic and dysmorphogenic activities of the phenol metabolites hydroquinone, benzoquinone, catechol, and t,t-muconaldehyde were also investigated during this study. Each of these chemicals elicited significant embryotoxic/dysmorphogenic effects already without any bioactivating system. T,t-muconaldehyde appeared to be the most potent of these four metabolites in terms of 100% embryoletality at concentrations as low as 50 µM in the culture medium.

4.1.2.9.2 Studies in humans

No data available.

Summary and conclusions of toxicity for reproduction

No data on reproductive toxicity in humans are available.

Phenol was investigated for impairment of reproductive performance and fertility in a two-generation (drinking water) reproductive toxicity study in rats. At the highest tested concentration level, according to a mean daily uptake of 300 to 320 mg phenol/kg body weight, which led to reduced water intake and consequently decreased body weight and body weight gain including organ weight impairment in the animals, no adverse effects on reproductive capability and fertility were revealed for either sex across the two generations. Furthermore, sperm parameters and estrous cyclicity had not been affected by phenol treatment. Any effects as revealed during this study were confined to the observation of impaired offspring viability and body weight gain during the pre-weaning period for the 5,000 ppm treated groups for both

generations. No such effects had been revealed for the lower tested dosage levels. From the evaluation of this study no adverse effects on reproductive capability and fertility could be revealed up to and including the highest dosages tested (5,000 ppm in drinking water according approximately 301 (males) respectively 320 (females) mg phenol/kg bw/day. Thus it can be concluded for fertility that this endpoint has been adequately examined.

Phenol was evaluated for developmental toxicity in studies with mice and rats. From these studies there are no indications for an embryotoxic or teratogenic potential of phenol. When pregnant rats or mice had been exposed to phenol during gestation (and lactation) indications of prenatal growth retardation and impaired peri-postnatal viability and postnatal growth had been revealed. These effects had been induced at exposure levels that obviously induced systemic toxic effects in the dams and therefore are considered to be secondary and not an indication for a specific fetotoxic potential of phenol. From the overall evaluation of the available studies, for risk characterisation of reproductive toxicity with respect to development a NOAEL/developmental toxicity for phenol of 93 mg/kg body weight is recommended. This NOAEL/developmental toxicity is based on the observations upon offspring performance and development from the 2-generation study.

There are no animal studies with the dermal or the inhalatory route of administration available.

From the assessment of the available animal studies phenol was not identified to possess any specific properties adverse to reproduction. Therefore, there is no need for classification and labelling.

4.1.3 Risk characterisation

4.1.3.1 General aspects

Phenol is well absorbed via gastrointestinal and respiratory tract and the dermal route. Concerning the oral route a high absorption was measured in rats, sheep and pigs with 90, 85, and 84% of the orally administered phenol dose of 25 mg/kg bw after 8 hours. Volunteers exposed to phenol concentrations of 6-20 mg/m^3 via inhalation absorbed 60 to 88% of the substance. After dermal application of phenol to rats, 40% of the applied dose was excreted in the urine by 4 hours, 70% by 12 hours and the excretion was essentially complete (with 75%) by 24 hours. Distribution of phenol in body tissues occurs rapidly. Phenol is metabolised to sulfate and glucuronide conjugates. Excretion via urine is the main elimination pathway of phenol metabolites in humans and animals for the different exposure routes. The ratio of sulfate/glucuronide conjugates excreted in urine is dose-dependent with a capacity-limited sulfatation at high dosages in rats and mice. Cats showed a poor glucuronidation of phenol, only conjugation with sulfate occurred. Small amounts of conjugated hydroquinone were only detected in the metabolic profiles for humans and rats. Metabolism predominantly occurs in liver, gut and kidneys. For risk assessment purposes the rates of oral and inhalation absorption are assumed to be 100%, whereas for dermal exposure the rate was set to 80%.

Signs and symptoms of acute toxicity of phenol in humans and experimental animals are similar regardless of the route of administration. Acute doses of phenol can produce symptoms of toxicity within minutes of administration thus a rapid absorption occurs. Oral toxicity of phenol in humans leading to death is reported for doses as low as 140-290 mg/kg bw. Absorption from spilling phenolic solutions on the skin of humans seems to be very rapid, and death resulted from collapse within 30 minutes to several hours. Death has resulted from absorption of phenol

through a skin area of 64 inch², too. For animals, oral LD_{50} values of 340 mg/kg bw are reported (rats), of approximately 300 mg/kg bw (mice), and of less than 620 mg/kg bw (rabbits). A dermal LD_{50} value of 660-707 mg/kg bw was determined for female rats. LC_{50} values are not available; however, rats are reported to tolerate phenol concentrations as high as 236 ppm (900 mg/m³) for 8 hours, resulting in ocular and nasal irritation, loss of co-ordination, tremors, and prostration. Based on the frequent reports on human experience with occupational exposure to phenol in earlier times phenol is classified as "toxic" and labelled with "R 23/24/25 (Toxic by inhalation, in contact with skin and if swallowed)".

Initial skin contact with phenol produces a white wrinkled discoloration with no experience of pain due to the local anaesthetic properties of phenol. Phenol causes severe chemical burns; occasionally skin necrosis is seen with solutions as dilute as 1%. Eye irritation in rabbits caused by a 5% aqueous phenolic solution was irreversible after an observation period of 7 days. Thus, local irritation caused by phenolic solutions cannot be assessed properly. Based on the corrosive properties phenol is labelled with the R-phrase "R 34, causes burns".

Phenol did not cause any signs of skin sensitisation in tests with guinea pigs (modified Buehler Test) and mice (Mouse Ear Swelling Assay), and there is no evidence of allergic contact dermatitis in humans.

Long-term exposure to phenol has shown effects on the nervous system and liver (in humans and animals), and on hematopoietic and immune system, kidneys, and skin (animals).

Limited data are available on chronic effects of phenol in humans from oral, dermal or inhalation exposure indicating reduced spontaneous activity, muscle weakness, pain and disordered cognitive capacities. In animals dysfunctions of the nervous system including tremor, convulsions, loss of co-ordination, paralysis, reduced motor and spontaneous activity, and reduced body temperature have been reported.

In phenol-exposed workers elevated activities for serum transaminases (especially ALAT) and increased clotting time were observed at a concentration of 0.021 mg/l indicating hepatotoxicity after chronic inhalation.

Repeated dose studies in animals have reported unscheduled deaths after inhalation (0.1-0.2 mg/l, hamster), dermal (783 mg/kg bw/day, rabbit) or gavage (120 mg/kg bw/day, rat) exposure to phenol, but no treatment-related mortalities have been seen after long-term exposure of phenol within the drinking water at dosages up to 450 mg/kg bw/day in rats and 375 mg/kg bw/day in mice. In some studies, mortalities were associated with growth retardation or respiratory distress.

Anaemia and suppressive effects on erythropoietic and granulopoeitic stem cells and bone marrow stromal cells were found in studies on mice, whereas no data are available for other species. Application of phenol in drinking water was shown to induce T- and B-cell suppressive effects (reduced lymphocyte proliferation response to mitogens, antibody levels and T-cell dependent humoral immunity) in mice at low dosages (6.2 mg/kg bw and above), however, no effect on T-cell dependent humoral response was found in rats. Atrophic changes of thymus or spleen were occasionally seen in rats repeatedly exposed to phenol by the oral route. Cancer studies on mice and rats indicated no histomorphologic alterations of immune organs.

In line with case reports on phenol exposed workers, liver damage has also been reported in rats repeatedly exposed to phenol by the inhalation and oral route. Enlarged liver, elevated levels of liver enzymes and, in animals only, liver cell degeneration was observed. Necrosis of renal tubules and papillary hemorrhage have been reported in rats after repeated oral administration of

phenol. Studies in animals of limited reliance related myocard degeneration and inflammatory responses of lung and kidneys to subchronic inhalation exposure to phenol. In rabbits, prolonged dermal exposure to phenol at concentrations of 1.18% and above (130 mg/kg bw/day) induced epidermal hyperkeratosis and ulceration. Based on all findings classification as "harmful" and labelling with the R-phrases R 48/20/21/22 "Danger of serious damage to health by prolonged exposure through inhalation, in contact with skin and if swallowed" has been agreed.

The following overall N(L)OAELs/NOAECs are recommended for risk assessment purposes. Oral administration: LOAEL of 1.8 mg/kg/day from the mouse study on subacute toxicity (Hsieh et al., 1992). Inhalative administration: NOAEC of 0.0963 mg/l for local effects from the 14-day rat study (CMA, 1998a), whereas a LOAEC of 0.021 mg/l for systemic effects was derived from a time weighted average exposure of workers (Shamy et al., 1994). Dermal administration: A NOAEL for systemic effects of 1.18% (≈ 130 mg/kg bw/day) was derived from the 18-day rabbit study (Deichmann et al., 1950), whereas the NOAEL for local effects was 2.37% (≈ 260 mg/kg bw/day) 1in the same study.

Phenol is positive with respect to various genetic effects in mammalian cell cultures. In general, relatively weak effects are induced. *In vivo*, phenol is a weak inducer of micronuclei in mouse bone marrow cells; the effect is bound to high doses which are equivalent to or near to the maximum tolerable dose. The induction of micronuclei at high doses may be based on an indirect mode-of-action (hypothermia). Phenol is classified by the EU C&L working group as a mutagen category 3 and labelled with R 68 "Possible risks of irreversible effects".

Oral long term studies in rats and mice revealed no effect of phenol on tumour induction. A medium-term study in a transgenic mouse model did not give any indication on treatment-related proliferative responses. Phenol was shown to act as a promoter in skin cancer bioassays in mice. A weak carcinogenic effect was observed after long-term skin application of a 10% solution of phenol in benzene (without initiation), but was considered less relevant. The test solution was strongly irritative, and it contained the carcinogen benzene. However, there is some concern on the basis of positive *in vivo* mutagenicity data and from the phenol metabolite hydroquinone classified as a suspected carcinogen (Category 3). This concern is considered to be of minor significance, as long term studies revealed no relevant indication for carcinogenicity. However, in conclusion, phenol is considered not to be carcinogenic in animals.

There are no data revealing an association of phenol exposure to increased tumour rates in humans. No firm conclusion on risk levels could be drawn from a case-control study on respiratory cancer of workers exposed to phenol.

No data are available on reproductive toxicity of phenol in humans. Phenol was investigated for impairment of reproductive performance and fertility in a two-generation (drinking water) reproductive toxicity study in rats. No adverse effects on reproductive capability and fertility were revealed for either sex across two generations up to and including the highest dosages tested (5,000 ppm, according to 300 (males) and 320 (females) mg/kg bw/day). No effects on sperm parameters or on estrous cyclicity were revealed. Effects observed during this study were confined to the observation of impaired offspring viability and offspring growth delay during the pre-weaning period for the groups of the highest tested concentration level. No substance specific embryotoxic or teratogenic potential was revealed for phenol in studies with mice and rats. Also, no indications for a substance-related specific fetotoxic potential are obtained from the overall assessment of the available data. Based on the results of the above-mentioned 2-generation study a NOAEL/developmental toxicity of 93 mg/kg bw/day is recommended for risk characterisation. From the evaluation of the available data base on animal investigations there is at present no indication that phenol is a reproductive toxicant.

4.1.3.2 Workers

4.1.3.2.1 Introductory remarks

Phenol is solid at 20°C with a melting point of 40.9°C. It is soluble in water and organic solvents. The vapour pressure of phenol at 20°C lies at 0.2 hPa. Approximately 65% of the produced phenol is processed further as a chemical intermediate for example, to bisphenol A, caprolactam, salicylic acid, diphenyl ether, alkyl phenols, nitrophenols and other chemicals. 30% is used to manufacture phenol formaldehyde resins and a small but non-quantifiable part serves as a component in cosmetics and medical preparations.

The occupational exposure scenarios have been described and discussed in Section 4.1.1.2. Exposure to phenol is to be expected during the handling of pure phenol and phenolic resins. The routes to be considered in connection with the workplace are inhalation against phenol vapour (especially during the hardening process of phenolic resins at elevated temperatures (≤ 180°C)), and dermal contact with the solid substance and its formulations. For workers the inhalation exposure levels as reported in **Table 4.5** are taken forward to risk characterisation. Dermal exposure is assessed with the EASE model or based on literature results (see **Table 4.6**).

The toxicological data of phenol are described and discussed in Section 4.1.2. Risk estimations are based on human and animal data. The threshold levels from the hazard assessment part of the report are taken forward to occupational risk assessment. The corrosive properties and the serious systemic toxicity might be addressed as the most prominent effects phenol.

Absorption of phenol via different routes of exposure

Phenol is well absorbed via gastrointestinal and respiratory tract and the dermal route as described in Section 4.1.2.1. Concerning the oral route a high absorption was measured in rats, sheep and pigs with 90, 85, and 84% of the orally administered phenol dose of 25 mg/kg bw after 8 hours (Kao et al., 1979). Volunteers exposed to phenol concentrations of 6-20 mg/m^3 via inhalation absorbed 60 to 88% of the substance (dermal absorption was excluded). After dermal application of phenol, 40% of the applied dose was excreted in the urine by 4 hours, 70% by 12 hours and the excretion was essentially complete by 24 hours.

For risk assessment purposes, for oral uptake and inhalation an absorption percentage of 100%, for dermal contact of 80% is taken forward.

Occupational exposure and internal body burden

In **Table 4.35** the exposure levels are summarised and the route-specific and total internal body burden are identified. For dermal contact, phenol exposure levels for corrosive and non-corrosive preparations are differentiated. For non-corrosive preparations, but not for the corrosive ones, daily exposure is anticipated to occur. It should be recognised, that the dermal exposure levels in scenarios 2, 3a and 3b for the non-corrosive preparations are assumed to be higher than for the corrosive ones. That means that risk assessment for both acute and repeated dose toxicity is based on the same higher dermal exposure values.

In addition to the shift average values in **Table 4.35** two short-term exposure values are available. The short-term concentration of 17.8 mg/m³ (5 minutes) is accounted for risk characterisation of local effects following acute inhalation (**Table 4.37**). The short-term value of

7.6 mg/m³ (< 1 hour) for scenario 3 does not really differ from the corresponding shift-average value and thus is not taken forward to risk characterisation.

Table 4.35 Phenol exposure levels which are relevant for occupational risk assessment and internal body burden

Exposure scenario	Inhalation shift average (mg/m³)	Dermal contact shift average (mg/p/d),	Internal body burden (mg/p/d)		
			Inhalation(1)	Dermal(2)	Combined
1.Production and further processing	3.3 daily	21 corrosive not daily	33	17 corrosive not daily	50 only for acute toxicity
2.Formulation of phenolic resins	20 daily	21 corrosive not daily	200	72 not corrosive daily	272 most critical activity in Sc. 2 daily for all endpoints
		90 not corrosive daily			
3a.Use of phenolic resins (no spray techniques)	5 daily	3 corrosive not daily	50 daily	10 not corrosive daily	60 most critical activity in Sc. 3a daily for all endpoints
		13 not corrosive daily			
3b.Use of phenolic resins (spraying techniques)		75 corrosive not daily		240 not corrosive daily	290 most critical activity in Sc. 3b for all endpoints
		300 not corrosive daily			

1) Based on the assumption of 100% inhalative absorption; breathing volume of 10 m³ per shift
2) Based on the assumption of 80% dermal absorption

Default values for physiological parameters

Body weight, rat	250 g
Body weight, worker	70 kg
Respiratory rate, rat at rest	0.8 l/min/kg
Respiratory rate, worker at rest	0.2 l/min/kg
Respiratory volume of worker during 8 hours at rest	6.7 m^3
Respiratory volume of worker during 8 hours of light activity	10 m^3

Calculation of MOS values

MOS values are calculated as quotient of experimental NOAEL (or LOAEL) from animal studies or human case reports and workplace exposure levels. If the route of application in animal or human studies is different from the actual occupational exposure, the dose units of the experimental and exposure data have to be adapted prior to MOS calculation. As result of this adaptation a "starting point" for the MOS calculation is identified.

The exposure routes considered in occupational risk assessment are inhalation and dermal contact. The MOS values for exposure by each route are considered separately. The combined MOS-value is calculated as quotient of the internal NAEL (i.e. the external NOAEL multiplied with the percentage of absorption) and the total internal body burden.

With respect to the possible outcome of an assessment for combined risks, interest focuses on scenarios with **conclusion (ii)** at both exposure routes. Based on theoretical considerations, combined exposure will not increase the most critical route-specific risk component more than twice.

Evaluation of MOS values

Risk assessment based on MOS values implies the identification of a minimal MOS as decision mark between **conclusion (ii)** and **(iii)**. The following procedure to identify the minimal MOS is developed in order to get consistent conclusions for different chemicals: Substance-specific adjustment factors, which may vary depending on data availability and the specific toxicological endpoint to be evaluated, are used for the extrapolation of studies in animals to the worker population (e.g. adaptation of scenarios, route-to-route extrapolation, interspecies extrapolation and duration adjustment). The uncertainties in the specific calculations are weighed by expert judgement and expressed as an additional "uncertainty factor". The multiplicative combination of these different factors and the uncertainty factor yield the minimal MOS value.

If the MOS value for a certain exposure scenario is below the minimal MOS, the corresponding risk situation is considered to be of concern. A MOS value higher than the minimal MOS indicates no concern.

In a parallel procedure, which gives identical but more direct results, the toxicological starting point carried forward to risk characterisation may be divided by the endpoint-specific assessment factors. As a result, an exposure level is identified which, by direct comparison with the occupational exposure levels, may serve as trigger for decisions. In the context of this risk assessment report it will be called "critical exposure level". Concern will be expressed for scenarios above this trigger value.

Interspecies differences

Species differences might exist concerning the susceptibility for phenol toxicity. However no information on the relative sensitivity of humans is available. There is no mechanistic argument to suggest that findings are restricted to animals and should not be transferred to humans. For the purpose of occupational risk assessment, scaling on the basis of metabolic rate is used as a default assumption for interspecies extrapolation.

For interspecies extrapolation of oral or dermal data metabolic rate scaling results in lower effective dose levels in mg per kg bodyweight for humans compared to experimental animals. For mice the scaling factor is 7, for rats 4 (for calculation see NO_NL, 1999). A value of 2.4 is applied for rabbits.

For inhalation the principle of metabolic rate scaling implies that a specific inhalation exposure level (in mg/m^3) is toxicologically equivalent in experimental animals and humans. However, attention must be paid to the fact that a sound extrapolation requires that exposure conditions in the different species are directly comparable. For example, rats are thought to be at rest under study conditions, the corresponding human breathing volume at rest in 8 hours is 6.7 m^3 (0.2 l/min/kg · 60 min/h · 70 kg). Workers, however, are assumed to breathe 10 m^3 during a normal working day under conditions of light activity. Thus to maintain toxicological equivalence, the experimental air concentrations need to be corrected with a factor of 1.5 to reveal the corresponding occupational exposure levels.

Duration adjustment

For chemical substances it is usually expected that the specified effect concentrations decrease with increasing duration of application. Available human and experimental data for phenol are difficult to interpret in terms of duration dependency of adverse effects. If necessary, considerations on duration adjustment are outlined in the endpoint-specific risk assessment sections.

Uncertainty considerations

The adjustment factors outlined above serve to adapt studies in animals to humans. They rely mainly upon general knowledge in physiology or toxicity. From a statistical point of view the individual parameters have to be understood as point estimates belonging to probability density functions. The intention is to take each factor from a point near the maximum of its distribution. The multiplicative combination of all factors is therefore supposed to result in a central tendency point estimate, addressing a situation which is likely to occur. However, the actual risks may either be less or more pronounced than estimated.

In practice an additional uncertainty factor is defined for each toxicological endpoint. It is used to modify the initial data in terms of precaution. This factor takes into account several aspects, which by their nature are not easy to quantify, as for instance the reliability of the data base, the biological relevance of the observed effects, the slope of the dose-response curve or the variability of the human population. By definition uncertainty factors have to be based on expert judgement. To give some orientation it is proposed to use an uncertainty factor of 5 for the evaluation of repeated inhalative toxicity based on a subacute oral study (BAU, 1994). Depending on the available data base, the uncertainty factor may be higher or lower than 5. For instance, to assess the acute inhalative toxicity of phenol only an uncertainty factor of 1 is used.

Intraspecies variability

There are no substance-specific data which might permit quantification of possible differences in sensitivity among workers. A specific intraspecies extrapolation factor is not used for evaluation of MOS values. To a certain extent, the aspect of human variability will be covered by uncertainty considerations introduced to the risk evaluation.

4.1.3.2.2 Occupational risk assessment

Acute toxicity

Systemic effects (inhalation)

In an acute 8-hour inhalation study rats were exposed to 900 mg/m³ phenol. This air concentration caused severe co-ordination disturbances and tremor but was not lethal (Flickinger, 1976). Additional information originates from a 14-day-inhalation study (see Section "Local effects by inhalation (RDT)"). Rats were exposed to phenol vapour up to a concentration of 96 mg/m^3. No adverse effects were observed in the respiratory tract or in any other organ system. There is another less valid 14-day inhalation study (Dalin and Kristoffersson, 1974) revealing adverse effects (e.g. clinical signs of motor disorders and increased serum liver enzymes) at the tested phenol concentration of 100 mg/m³.

The assessment of acute systemic inhalation toxicity of phenol is mainly based upon the results of an epidemiological study (Shamy et al., 1994). For a more detailed discussion of the results of this study see Section 4.1.2.6 and "repeated dose toxicity" in Section 4.1.3.2.2. It is reported that a time-weighted phenol exposure of about 21 mg/m³ resulted in changes of haematological and clinical chemistry parameters, some of them indicating some degree of hepatotoxicity. Analysis of the blood was performed at the end of the shift of the last working day of the week. It is not reported whether the biochemical changes already occurred at the beginning of the long-term period of exposure. It might be speculated that the LOAEL following one day of exposure is somewhat higher than the reported level of 21 mg/m³. Not being able to propose more specific adjustment factors, it is recommended to take this level of 21 mg/m³ as starting point of acute risk characterisation in combination with a minimal MOS of 1. Recognising the borderline character of the decision, **conclusion (iii)** is reached for Scenario 2 (formulation of phenolic resins) with the exposure level of 20 mg/m³. The typical exposure level for Scenario 2 is lower than the reasonable worst case of 20 mg/m³ (see occupational exposure assessment) and does not lead to concern.

Conclusion (iii).

Systemic effects (dermal)

For oral uptake, a lethal human dose is reported as 140 mg/kg.

Dermal contact to liquid or solid phenol causes severe acute symptoms of local and systemic toxicity in humans and animals. Death has occurred in humans which have been exposed by skin contact. Absorption from spilling phenolic solutions on the skin of humans seems to be rapid. In one case death has occurred within 30 minutes after dermal contact. Kania (1981) reports, that death occurred from absorption of phenol through a skin area of 64 inch^2.

For animals a dermal LD_{50} value of 660-707 mg/kg bw was determined for female rats (Corning and Hayes, 1970). Other information results from a dermal rabbit study with repeated dermal application. Signs of systemic intoxications including lethality were found at 650 and 780 mg/kg/day. At 390 mg/kg/day phenol produced tremors. The NOAEL for clinical effects was 130 mg/kg/day. The study design did not contain any laboratory or post-mortem investigations. As a possible starting point for MOS calculation the human dose that corresponds to the dermal NOAEL of 130 mg/kg/day is identified as 9,100 mg/person/day (130 mg/kg/day · 70 kg). In evaluation of MOS values for acute exposure the following aspects have to be considered: (a) metabolic rate scaling from rabbits to humans yields a factor of 2.4,

(b) an uncertainty factor of 5 is proposed because of the substantial uncertainty of the NOAEL and accounting for some degree of interspecies differences. Altogether the minimal MOS is calculated to be 12 (2.4 · 5). The according critical exposure level is 758 mg/person (9,100/12).

As outlined above, there is some human evidence of liver toxicity correlated with inhalatory exposure of workers to 21 mg/m³ of phenol (Shamy et al., 1994). For the assessment of acute inhalation toxicity the level of 21 mg/m³ was taken as starting point in combination with a minimal MOS of 1. The inhalation data may be used for dermal risk assessment as well: assuming a breathing volume of 10 m³, the effective phenol concentration of 21 mg/m³ is converted into the internal dose of 210 mg/person. Based on the assumption of 80% dermal absorption the external starting point for dermal risk characterisation is 263 mg/person.

The critical acute exposure level of 758 mg/person (based on the dermal rabbit study) is only 3 times greater than the corresponding level of 263 mg/person (based on the human evidence by inhalation). Both data bases have their substantial limitations for risk assessment. For phenol a similar high percentage of absorption is known across all relevant routes of exposure. In using the Shamy data, a species extrapolation is not necessary. Thus, it is proposed to preferentially base the assessment of acute dermal toxicity on the human evidence by inhalation (study of Shamy et al., 1994).

Against that background of considerations for acute dermal toxicity **conclusion (iii)** is only reached for Scenario 3b (use of phenolic resins, spraying techniques).

Conclusion (iii).

Combined exposure

Combined exposure (dermal contact, inhalation) is expressed as the total internal body burden (see **Table 4.36**). The scenario-specific MOS values and the minimal MOS rely upon the same rationale as outlined in the previous section on acute dermal toxicity. For combined exposure **conclusion (iii)** is reached for Scenarios 2 and 3b. For Scenario 2 this conclusion is mainly based on inhalation exposure; for Scenario 3b the most prominent risk factor is dermal contact.

Conclusion (iii).

Table 4.36 MOS values for acute toxicity of phenol, systemic effects

	Inhalation	Dermal	Combined
Starting point for MOS calculation	21 mg/m³	263 mg/p/d	210 mg/p/d
Minimal MOS	1	1	1
Critical exposure level	21 mg/m³	263 mg/p/d	210 mg/p/d

Table 4.36 continued overleaf

Table 4.36 continued MOS values for acute toxicity of phenol, systemic effects

	Inhalation			Dermal			Combined		
Scenario number, area of production and use	Exposure (mg/m^3)	MOS	Conclusion	Exposure (mg/p)	MOS	Conclusion	Internal body burden (mg/p)	MOS	Conclusion
1. Production and further processing	3.3	6	ii	21	13	ii	50	4.2	ii
2. Formulation of phenolic resins	20	1	iii	90	3	ii	272	0.8	iii(1)
3a. Use of phenolic resins (no spray techniques)	5	4	ii	13	20	ii	60	3.5	ii
3b. Use of phenolic resins (spraying techniques)				300	0.9	iii	290	0.7	iii (1)

1) Conclusion (iii) already results from dermal or inhalative exposure, therefore no specific concern for the combined exposure is indicated

Irritation/Corrosivity

Acute inhalation

On the background of the corrosive properties of phenol local effects in the respiratory tract following inhalation are expected. One information comes from an 8-hour inhalation study in rats where 900 mg/m^3 phenol caused ocular and nasal irritation. From human case reports the following effects are reported: dyspnea, cough, cyanosis, and pulmonary oedema. For more precise characterisation of possible local effects a 14-day inhalation study was performed which is described in detail in section "Local effects by inhalation (RDT)" (CMA, 1998a).

The NOAEC of 96 mg/m^3 is taken as starting point for the assessment of inhalative local effects. The following assessment factors are applied for the identification of the minimal MOS:

- physiological differences between humans at rest and workers account for a factor of 1.5
- study duration was 6 hours daily, to correct for occupational exposure of 8 hours, a factor of 1.3 will be used
- because the NOAEC derives from a 14-day inhalation study, it already includes precautionary aspects with respect to local effects after singular exposure. Therefore no uncertainty factor is included.

Thus the corresponding critical exposure level calculates to 48 mg/m^3 (96 $mg/m^3/2$). The MOS values are reported in **Table 4.37**. This evaluation is not contradictory to the results of the Shamy study, because there was no reporting of respiratory irritation in exposed workers. The question might arise whether the known local anaesthetic effect of phenol influences the human perception of respiratory irritation. Referring to this no data is available; however, it might be speculated, that the influence of that specific effect might be low for relatively low doses or concentrations.

There is no concern with respect to local tissue damage after singular exposure. An additional risk component, however, may result from stimulation of the trigeminus nerve (sensory irritation) which is described in the following section on "Sensory irritation".

Conclusion (ii).

Sensory irritation

Sensory irritation is reported from animal data for phenol. A test, made with Swiss OF1 mice showed a RD_{50}-value of 630 mg/m^3 (166 ppm), 65 mg/m^3 (17 ppm) appeared to be an uncomfortable but tolerable concentration, minimal or no effect was detected at a concentration of 8 mg/m^3 (2 ppm). Alarie introduced the air concentration of $0.03 \cdot RD_{50}$ as prediction of an exposure level with a minimal or low degree of sensory irritation in humans, which was confirmed by other authors (Alarie 1981, Bos et al., 1992, Schaper 1993). The according air concentration for phenol calculates to 19 mg/m^3 (630 mg/m^3 · 0.03). Analysis of experimental and studies in humans on sensory irritation mainly is based on the relationship between RD_{50} values in animals and human thresholds for sensory irritation (and not on the corresponding relationship for minimal experimental effects). For that reason it is preferred to start risk assessment with the general approach ($0.03 \cdot RD_{50}$) instead of using lower experimental effect levels for which there is no specific experience as to adequate adjustment factors.

In workers the stinging and burning sensation caused by stimulation of the trigeminus nerve which is closely connected to respiratory depression is generally perceived within few minutes after exposure. Thus stimulation of the trigeminus nerve, unlike other effects, does not depend significantly on exposure duration. The main trigger for effects seems to be the air concentration of the substance. Risk assessment therefore does not correct for exposure duration and short term values are also included in MOS calculation.

The exposure level of about 19 mg/m^3 is chosen as starting point concerning respiratory depression. In this range of exposure a relevant effect is not anticipated to occur in humans. This evaluation is not contradictory to the Shamy study, because there was no reporting of stinging and burning sensations of exposed workers. This clinical type of effect should have been recognised and reported. For evaluation of the resulting MOS values no further aspects have to be taken into account, an uncertainty factor does not seem necessary. The corresponding minimal MOS is considered to be 1.

The highest identified inhalative exposure values are described for the short-term concentration of scenario 1 with an exposure value of 17.8 and Scenario 2 (formulation of phenolic resins) with an exposure value of 20 (see **Table 4.37**), which both reveal a borderline risk situation. Based on the combined interpretation of the RD_{50} data and human experience **conclusion (ii)** is applied for these occupational exposure scenarios with respect to sensory irritation of phenol.

Conclusion (ii).

Single dermal contact

Phenol has extreme corrosive properties on the skin. Therefore studies in animals on relevant skin irritation/corrosion tests are not available. In a rat study which was conducted in order to assess skin decontamination procedures, moderate to severe chemical burns were observed after a 1-minute uncovered application of undiluted (molten) phenol.

Initial skin contact of humans with phenol produces a white wrinkled discoloration with the affected area turning brown and subsequently becoming gangrenous. Ten percent solutions

regularly produce corrosion, and occasionally skin necrosis is seen with solutions as dilute as 1%. Phenol has local anaesthetic properties; therefore the afflicted persons described no experience of pain after dermal contact with phenol.

The formulations handled at the workplace contain up to 15% phenol. For the purpose of risk assessment it is assumed that skin contact with corrosive solutions will cause severe lesions. It is realised that control measures exist for phenol, which should be able to reduce skin exposure, if complied with. However, since a warning effect by local pain is not expected and single exposures might lead to irreversible damage at the skin, concern is expressed for all scenarios in which phenol or its corrosive preparations are handled.

For those phenol preparations which are classified and labelled as irritating to the skin, **conclusion (ii)** is proposed on the grounds that control measures exist which can minimise exposure and risk of irritation, thereby reducing concern. However, these controls must be implemented and complied with to reduce the risk of skin irritation.

Conclusion (iii).

Contact to the eyes

Due to the extreme corrosive properties phenol has the potential to cause serious damage to the eyes in humans and test animals. Eye irritation in rabbits caused by a 5% aqueous phenolic solution was irreversible after an observation period of 7 days.

The formulations handled at the workplace contain up to 15% phenol. For the purpose of risk assessment it is assumed that eye contact with this solutions will cause severe lesions. Because of its local anaesthetic properties, the pain following contact with the corrosive substance may be diminished leading to a weak effect of warning and possibly to more intensive local damage of the eye. In order to make risk managers aware of this problem, **conclusion (iii)** is proposed for corrosivity following contact to the eyes.

For those phenol preparations which are classified and labelled as irritating to the eyes, **conclusion (ii)** is proposed on the grounds that control measures exist which can minimise exposure and risk of irritation, thereby reducing concern. However, these controls must be implemented and complied with to reduce the risk of irritation to the eyes.

Conclusion (iii).

Sensitisation

Dermal

Phenol did not cause any signs of skin sensitisation in tests conducted with guinea pigs (modified Buehler Test, Itoh 1982) and mice (Mouse Ear Swelling Assay, Descotes 1988). Likewise there is no evidence of allergic contact dermatitis in humans. Therefore, there is no concern with respect to skin sensitisation at the workplace.

Conclusion (ii).

Inhalation

No information on respiratory sensitisation is available. Phenol is not suspected to be a potent respiratory sensitiser in humans according to the fact that during all the years of use no notice of

specific case reports has been given. There is no concern with respect to respiratory sensitisation at the workplace.

Conclusion (ii).

Repeated dose toxicity

Local effects by inhalation (RDT)

By experience, there is a potential of local effects in the respiratory tract following chronic inhalation of a corrosive substance. For phenol, however, the weight of evidence is weak. Ocular and nasal irritation is reported in rats following a single inhalation exposure to 900 mg/m³.

A 14-day rat inhalation study, specially designed to examine local effects on the respiratory tract, is available (CMA, 1998a). Fisher 344 rats (20 animals/sex/group) were administered by nose-only exposures to phenol vapour 5 days/week, 6 hours/day at target concentrations of 0, 1.9, 19 and 96 mg/m^3. No adverse effects were seen in the respiratory tract or in any other organ system until the highest tested value of 96 mg/m^3 phenol. Thus this value of 96 mg/m^3 represents the best value available for local effects by inhalation after repeated exposure. This value is used as starting point for MOS calculation.

The question to what extent the effect or threshold level would drop below 96 mg/m^3 if the duration of the study would be extended is difficult to decide. Application of a default factor for duration adjustment seems to be inappropriate because the corresponding LOAEL is not known (the 14-day LOAEL might be somewhere between 100 and 900 mg/m³).

Some additional guidance might result from the Shamy study already used for the assessment of systemic toxicity. In that study there is no report on local effects in the respiratory tract. Although there were no specific investigations, substantial local effects should have been recognised and reported by occupational physicians. The question might rise whether the known local anaesthetic effect of phenol influences the human perception of respiratory irritation. Referring to this no data is available; however, it might be speculated, that the influence of that specific effect might be low for relatively low doses or concentrations.

Combined evaluation of experimental data and human experience, yet underlining the absence of histological changes in the rat inhalation study at 96 mg/m^3, may support the conclusion that long-term exposure to about 20 mg/m³ should not result in substantial local effects in the respiratory tract and should not be considered of concern. This evaluation of the experimental and human data, in combination with the experimental starting point of 96 mg/m³, is equivalent to a minimal MOS of about 4 for local effects by repeated inhalation.

With reference to the MOS values (see **Table 4.37**) there is no concern for local respiratory effects of phenol after repeated inhalation. As consequence **conclusion (ii)** is applied.

Conclusion (ii).

Table 4.37 MOS values for local effects of phenol after acute and repeated inhalation

		Repeated dose toxicity, local		Acute toxicity/ Irritation		Sensory irritation	
Starting point for MOS calculation		96 mg/m³				19 mg/m³	
Minimal MOS		4		2		1	
Critical exposure level		24 mg/m³		48 mg/m³		19 mg/m³	
Scenario number, area of production and use	**Exposure (mg/m³)**	**MOS**	**Conclusion**	**MOS**	**Conclusion**	**MOS**	**Conclusion**
1. Production and further processing	3.3	29	ii	29	ii	5.8	ii
	17.8 (short-term)			5	ii	1.1	ii
2. Formulation of phenolic resins	20	4.8	ii	4.8	ii	1	ii
3. Use of phenolic resins	5	19	ii	19	ii	3.8	ii

Local effects by dermal contact (RDT)

One dermal rabbit study with repeated dermal application is available, which is described in detail in Section 4.1.2.6. Local effects were observed at > 390 mg/kg bw (3.56% phenol in aqueous solution) with epidermal hyperkeratosis and ulceration.

For phenol four dermal exposure scenarios were defined (**Table 4.6**). For all of these scenarios there are subscenarios with dermal exposure towards the corrosive solid or towards corrosive formulations. Single dermal contact was considered to be of concern (**conclusion (iii)**) because the warning effect normally related to the corrosivity of substances might be reduced because of the local anaesthetic property of phenol. While it is assumed that single contacts to the corrosive material might occur, it is considered probable, that the isolated experience of skin corrosion at a specific workplace results in the avoidance of daily repeated skin contact.

For those phenol preparations which are classified and labelled as irritating to the skin, for acute skin irritation **conclusion (ii)** was proposed on the grounds that control measures exist which can minimise exposure and risk of irritation, thereby reducing concern. However, these controls must be implemented and complied with to reduce the risk of skin irritation for both acute and repeated dermal exposure. Based on these considerations as to the control of risk for acute irritation to the skin, no additional concern is recognised for local effects for scenarios for which repeated dermal exposure is considered possible.

Conclusion (ii).

Systemic effects by inhalation (RDT)

The assessment of repeated dose toxicity of phenol (systemic effects by inhalation) relies on human and experimental evidence. The quality and reliability of the human and experimental database is rather limited thus resulting in substantial uncertainties of risk assessment.

The most reliable experimental dataset is the 14-day inhalation study on phenol (CMA, 1998a). Nose-only exposures up to 96 mg/m³ did not result in systemic adverse effects. There is another less valid 14-day inhalation study (Dalin and Kristoffersson, 1974) revealing adverse effects (e.g. clinical signs of motor disorders and increased serum liver enzymes) at the tested phenol concentration of 100 mg/m³. The validity of the latter inhalation study is rather limited because there is no reporting of the strain of rats, no data on number of animals and no information on the exposure duration per day.

Special emphasis is given to the results of a human study especially revealing elevated serum levels of liver enzymes and increased clotting time in workers occupationally exposed to a time-weighted phenol concentration of 21 mg/m³ (Shamy et al., 1994). According to the authors 20 workers were exposed to phenol alone. The mean duration of exposure is reported to be about 13 years. It is reported that blood samples were collected at the end of the shift of the last working day of the week.

The importance of the Shamy study is somewhat limited by specific insufficiencies: The original paper does not discuss the significant, but small changes of the clinical chemistry and haematology parameters in terms of pathological implications. Additionally, the report does not allow for an evaluation of the quality of the reported exposure data. There is no information on possible variations of exposure schedules within the time period of about 13 years of exposure. There are no individual exposure data. There is no information, whether sampling occurred regularly and whether there were different biochemical effects at the beginning and the end of the 13-year exposure period.

The reason of still giving some confidence to the result of this human study is the evidence of elevated urinary phenol concentrations in phenol-exposed workers. It is considered valuable to compare the external exposure (a time-weighted average exposure of 21 mg/m³) with the internal phenol exposure (a mean value of about 68 mg phenol/ g creatinine). Further validated data from literature support a correlation between a time-weighted workplace exposure of about 20 mg/m³ of phenol and a urinary phenol excretion of 250-400 mg/g creatinine (DFG, 1990). Against the background of this reference data the reported level of urinary phenol excretion in the Shamy study should be caused by an exposure level clearly lower than the reported 21 mg/m³, or, vice versa, the exposure level of 21 mg/m³ should have resulted in an at least 3-times higher phenol excretion. The report of Shamy et al. does not allow for an assessment of the relative reliability of the external or internal phenol exposure data. Nevertheless, the possibility cannot be excluded, that relevant external phenol exposure to the workers was somewhat lower than reported, in that case implying a systemic toxic potency of phenol higher than reported. However, that sort of consideration cannot be weighted against the possibility of additional exposure of the workers in the Shamy study to other toxic chemicals.

At first sight studies in humans and animals seem to be somewhat contradictory. Whereas human evidence indicates biochemical effects near exposure levels of about 20 mg/m³, the experimental data (14-day inhalation studies) seem to document a somewhat lower toxic potency of phenol in rats. This impression of substantial potency differences between humans and rats is getting weaker when introducing necessary extrapolation factors to adjust the experimental results gained in the 14-day inhalation studies to the chronic exposure situation of workers (assessment factors accounting for exposure schedules and breathing rates, additional dermal uptake via the vapour phase, LOAEC to NOAEC extrapolation for the Dalin and Kristoffersson study, possibly a small duration adjustment factor).

In conclusion, the LOAEC (workers) of 21 mg/m³ is taken forward to risk characterisation. For calculation of the minimal MOS an assessment factor of 3 for an LOAEC/NOAEC extrapolation

and a further uncertainty factor of perhaps 2, especially accounting for the uncertainties of the study-specific exposure level leading to the biochemical changes reported, is proposed. Overall, based on the starting point of the LOAEC of 21 mg/m³, a minimal MOS of about 6 is proposed. Based on the limited reliability of the worker study, this minimal MOS may not be interpreted as a strict line for reaching conclusions. The corresponding critical exposure level calculates to about 4 mg/m³ (21 mg/m³/6).

With reference to **Table 4.38** there is concern for repeated dose toxicity (inhalation, systemic effects) for all three workplace exposure scenarios. The concern is clear-cut for formulation of phenolic resins (see Scenario 2). For the exposure Scenarios 1 and 3 any conclusion proves to be a borderline decision. With reference to the overall interpretation of the data, putting special emphasis to the limited epidemiological results reported by Shamy et al., **conclusion (iii)** is proposed for Scenarios 1 and 3 as well. It is acknowledged that available toxicity data on phenol do not allow a reliable assessment of repeated dose toxicity (inhalation, systemic effects) for the exposure range below 20 mg/m³.

Conclusion (iii).

Table 4.38 MOS values for inhalative repeated dose toxicity of phenol, systemic effects

	Inhalation		
Starting point for MOS calculation	21 mg/m³		
Minimal MOS	6		
Critical exposure level	4 mg/m³		
Scenario number, area of production and use	**Exposure (mg/m³)**	**MOS**	**Conclusion**
1. Production and further processing	3.3	6	iii
2. Formulation of phenolic resins	20	1	iii
3. Use of phenolic resins	5	4	iii

Systemic effects by dermal contact (RDT)

One dermal rabbit study with repeated dermal application is available (Deichmann et al., 1950). In this study phenol was applied over a period of 18 days on the skin of rabbits in daily amounts of 130, 260, 390, 520, 650, and 780 mg/kg bw phenol. Signs of systemic intoxication (which are not further described in detail) were found at 650 and 780 mg/kg/day. At ≥ 260 mg/kg/day phenol produced tremors. At the lowest dermal dose of 130 mg/kg/day no clinical signs of intoxication were observed. The study design did not contain any laboratory or post-mortem investigations.

As a possible starting point for MOS calculation the human dose that corresponds to the dermal NOAEL of 130 mg/kg/day is identified as 9,100 mg/person/day (130 mg/kg/day · 70 kg). In evaluation of MOS values the following aspects have to be considered: (a) metabolic rate scaling from rabbits to humans yields a factor of 2.4, (b) duration adjustment from a subacute to a chronic study design should be accounted for with a factor of 6, (c) an uncertainty factor of 10 is proposed because of the substantial uncertainty of the NOAEL and accounting for some degree

of intraspecies differences. Altogether the minimal MOS is calculated to be 144 (2.4 · 6 · 10). The according critical exposure level is 63 mg/person/day (9,100/144).

Because of the substantial limitation of the relevance of the dermal NOAEL from the rabbit study, for dermal risk assessment it is proposed to additionally account for the worker experience for the inhalatory route.

As outlined in the section on systemic effects by inhalation (RDT), the LOAEC for workers is 21 mg/m³. Assuming a breathing volume of 10 m³, the phenol concentration of 21 mg/m³ is converted into the internal dose of 210 mg/person/day. Because of the assumption of 80% absorption by the dermal route, the dose of 263 mg/person/day is taken as external starting point for systemic dermal risk assessment. For calculation of the minimal MOS an assessment factor of 3 for an LOAEC/NOAEC extrapolation and a further uncertainty factor of about 2, especially accounting for the uncertainties of the study-specific exposure level leading to the reported biochemical changes, is proposed. Overall, based on the starting point of the LOAEC of 263 mg/person/day, a minimal MOS of about 6 is proposed. Based on the limited reliability of the worker study, this minimal MOS may not be interpreted as a strict line for reaching conclusions. The corresponding critical exposure level calculates to about 44 mg/person/day (263 mg/person/day divided by 6).

The quality of dermal risk assessment for phenol is substantially limited by the low reliability of both the dermal rabbit study and the human experience by inhalation. It is proposed to use both lines of argumentation. The overall implication is similar for both routes of extrapolation: The critical dermal exposure levels calculated range from 44 mg/person/day (human evidence by inhalation) to 63 mg/person/day (dermal rabbit study). Against the background of the various adjustment factors that have been used, the difference between both ways of extrapolation is rather low. For the purposes of risk assessment, the lower value of 44 mg/person/day, which is supported by both lines of argumentation, is used.

For non-corrosive preparations of phenol repeated dermal exposure levels for Scenarios 2, 3a and 3b (see **Table 4.39**) have been calculated. For the activities described by Scenario 1 a daily dermal exposure is not assumed. For systemic effects by repeated dermal contact, concern is expressed for Scenario 2 (formulation of phenolic resins) and 3b (use of phenolic resins using spraying techniques).

Conclusion (iii).

Table 4.39 MOS values for dermal repeated dose toxicity of phenol, systemic effects

	Dermal contact		
Starting point for MOS calculation	263 mg/p/d		
Minimal MOS	6		
Critical exposure level	44 mg/p/d		
Scenario number, area of production and use	**Exposure (mg/p/d)**	**MOS**	**Conclusion**
1. Production and further processing	No daily exposure!	-	-
2. Formulation of phenolic resins	90	3	iii

Table 4.39 continued overleaf

Table 4.39 continued MOS values for dermal repeated dose toxicity of phenol, systemic effects

	Dermal contact		
Scenario number, area of production and use	**Exposure (mg/p/d)**	**MOS**	**Conclusion**
3a. Use of phenolic resins (no spray techniques)	13	20	ii
3b. Use of phenolic resins (spraying techniques)	300	0.9	iii

Systemic effects by combined exposure (RTD)

For all three occupational scenarios concern has already been expressed for systemic effects following chronic inhalation of phenol. For Scenarios 2 and 3b (spraying techniques) in addition there is a relevant contribution to total systemic health risks by dermal exposure. Overall, **conclusion (iii)** is reached for all occupational scenarios for systemic effects by combined exposure.

Conclusion (iii).

Mutagenicity

Phenol is positive with respect to various genetic effects in mammalian cell cultures. In general, relatively weak effects are induced. *In vivo*, phenol is a weak inducer of micronuclei in mouse bone marrow cells; the effect is bound to high doses which are equivalent to or near to the maximum tolerable dose. The frequency of micronuclei is extremely low even in doses which correspond to the LD_{50}. The induction of micronuclei at high doses may be based on an indirect mode-of-action.

Taking into account that the frequency of micronuclei is extremely low even in doses which correspond to the LD_{50} and the occupational exposure levels are low in comparison to that high experimental exposure levels a substantial mutagenic risk for workers is not anticipated to occur. Recognising the classification as a mutagen category 3, but putting emphasis on semi quantitative potency considerations, it is proposed to reach no concern.

Conclusion (ii).

Carcinogenicity

There are no data revealing an association of phenol exposure to increased tumour rates in humans.

Oral long term studies on rats and mice showed no effect of phenol on tumour induction. Concentrations of 2,500 and 5,000 ppm phenol in the drinking water (200 and 450 mg/kg/day for rats and 281 and 375 mg/kg/day for mice) during a time period of 103 weeks revealed no carcinogenic effect for both sexes.

Phenol was shown to act as a promoter in skin cancer bioassays in mice. A weak carcinogenic effect was observed after long-term skin application of a 10% solution of phenol in benzene (without initiation). This effect was considered to be less relevant, because this solution contained the carcinogen benzene and had strong irritative properties.

In conclusion phenol is considered not to be a carcinogen in animals. Being aware of the discussion on the mutagenic potential of phenol, but emphasising the experimental results on carcinogenicity, it is proposed to reach "no concern" for workers for carcinogenicity.

Conclusion (ii).

Reproductive toxicity

Fertility impairment and developmental toxicity

No data on reproductive toxicity in humans are available.

Phenol was investigated in a two-generation rat study for impairment of reproductive performance and fertility (IITRI, 1999; see Section 4.1.2.9). At the highest tested concentration level of 5,000 ppm, according to a mean daily uptake of 300 to 320 mg/kg/day phenol, the water intake of the animals was reduced and consequently body weight and body weight gain in the animals were decreased.

However, the observed effects were predominant at exposures that were also toxic to the dams. Thus, signs of slight fetal growth retardation are not considered indicative for a specific fetotoxic effect of phenol.

From the overall assessment of the available animal studies phenol was not identified to possess any specific properties adverse to reproduction. Thus, for fertility impairment and developmental toxicity, **conclusion (ii)** is drawn.

Conclusion (ii).

4.1.3.2.3 Summary of conclusions for the occupational risk assessment of phenol

As result of the occupational risk assessment for phenol, concern is raised for specified toxicological endpoints (**Table 4.40**). **Table 4.41** summarises the occupational exposure scenarios with concern for phenol. **Tables 4.42** and **4.43** try to visualise the risk profile of phenol for inhalation and dermal contact. The risk situations (defined by exposure scenario and the critical exposure level for a specific toxicological endpoint) are arranged in such a way, that the "high risk" situations principally are located in the left upper corner of the table, whereas the "low" risk situations are located in the lower right area of the table. This type of table may help to reach consistent conclusions for different endpoints and scenarios.

Table 4.40 Endpoint-specific overall conclusions

Toxicological endpoints		Concern for at least one scenario
Acute toxicity (systemic effects)	inhalation	iii
	dermal	iii
	combined	iii (1)
Irritation/ Corrosivity	dermal (single contact)	iii
	eye	iii
	acute respiratory tract	
	sensory irritation	
Sensitisation	skin	
	respiratory	
Repeated dose toxicity	inhalation, local	
	inhalation, systemic	iii
	dermal, local	
	dermal, systemic	iii
	combined, systemic	iii (1)
Mutagenicity		
Carcinogenicity	inhalation	
	dermal	
	combined	
Fertility impairment	inhalation	
	dermal	
	combined	
Developmental toxicity	inhalation	
	dermal	
	combined	

1) Conclusion (iii) already results from inhalative and dermal exposure therefore; no specific concern for the combined exposure scenario is indicated
2) Blank fields: conclusion (ii)

The risk profile of phenol is mainly characterised by the following risk components:

- Single contact (skin, eye) and corrosivity
- Systemic effects by repeated inhalation
- Systemic effects by repeated dermal contact

Special emphasis should be given to the corrosive effect of phenol and its corrosive preparations following dermal contact and contact to the eye. Because of its local anaesthetic properties, the pain following contact with the corrosive substance may be diminished leading to a weak effect of warning and possibly to more intensive local damage of the skin and eye. In order to make risk managers aware of this problem, **conclusion (iii)** is proposed for corrosivity following dermal contact and contact to the eyes for all scenarios.

Putting special emphasis on the human experience reported by Shamy et al. (1994) a critical inhalation exposure level near 4 mg/m³ was proposed. The confidence in this critical exposure level is rather limited because of uncertainties both of the underlying exposure assessment and of the pathological interpretation of the reported significant changes of clinical chemistry and haematology parameters. The overall interpretation of data still supported to express concern for all exposure scenarios with repeated inhalation. But it is clearly recognised, that there was the alternative of either reaching a conclusion on concern based on the weak evidence of information on phenol potency at low doses (as finally proposed) or of expressing the need for further experimental data on the dose response relationship of phenol (as not proposed).

In the past, dermal contact to liquid or solid phenol caused severe acute symptoms of systemic toxicity in humans. Unfortunately there are no valid data in order to describe a threshold level for acute and repeated dermal toxicity. Route-to-route extrapolation of the results of the Shamy et al. study (1994) resulted in concern for Scenario 2 (formulation of phenolic resins) and Scenario 3b (use of phenolic resins, spraying techniques) relating to systemic toxicity especially following repeated dermal contact (daily dermal exposure is assumed for non-corrosive preparations).

Last but not least it should be addressed that inhalation exposure to a corrosive material principally is anticipated to result in respiratory tract irritation. However, the available evidence indicates that the necessary inhalation exposure levels to trigger substantial local effects in the respiratory tract are greater than the identified RWC exposure levels.

The standard approach of assessing occupational exposure is to cluster similar occupational activities and to describe the reasonable worst case for the integrated scenario. For the inhalation exposure level of Scenario 2 (formulation of phenolic resins) both the reasonable worst case and the typical value was established. Conclusions on concern are based on the reasonable worst case. The typical value of Scenario 2 with respect to inhalation exposure is similar to Scenario 1 (for details see occupational exposure assessment).

In view of the outcome of the risk characterisation, i.e. the exposures associated with **conclusion (iii)** and the actual national occupational exposure limits, it is recommended to conclude on the necessity to reconsider these values.

Table 4.41 Summary of exposure scenarios with concern for phenol

Scenarios	Acute toxicity systemic		Irritation, corrosivity		Repeated dose toxicity, systemic	
	Inhalation	Dermal	Eyes	Skin	Inhalation	Dermal
1. Production and further processing			iii		iii	
2. Formulation of phenolic resins	iii		iii		iii	iii
3a. Use of phenolic resins (no spray techniques)			iii		iii	
3b. Use of phenolic resins (spraying techniques)		iii				iii

a) Blank fields: conclusion (ii)
b) Conclusion (iii) already results from inhalative and dermal exposure therefore no specific concern for the combined exposure scenario is indicated

Table 4.42 Ranking of the critical exposure levels for phenol with respect to inhalative exposure at the workplace

Scenario	Exposure level in mg/m³	Repeated dose toxicity, systemic	Acute toxicity, systemic	Acute inhalation/ sensory irritation	Repeated dose toxicity, local	Acute toxicity, local
		Critical exposure level in mg/m³				
		4	21	19	24	48
2. Formulation of phenolic resins	20	iii	iii			
3. Use of phenolic resins	5	iii				
1. Production and further processing	3.3	iii				
	short term: 17.8					

a) Blank fields: conclusion (ii)

Table 4.43 Ranking of the critical exposure levels for phenol with respect to dermal exposure at the workplace

Scenario	Exposure level in mg/p/d	Repeated dose toxicity, systemic	Acute toxicity, systemic
		Critical exposure level in mg/p/d	
		44	263
3b. Use of phenolic resins (spraying techniques)	300	iii	iii
2. Formulation of phenolic resins	90	iii	
1. Production and further processing	21		
3a. Use of phenolic resins (no spray techniques)	13		

a) Blank fields: conclusion (ii)

4.1.3.3 Consumers

4.1.3.3.1 Consumer exposure

Chronic exposure by use of phenol-containing consumer products may occur via the inhalation and dermal route.

During the application of floor waxes/polishes, and disinfectants consumers may be exposed via inhalation to maximum average concentrations of about 4 mg/m^3 (10 minutes) with possible peak values of 12.7 mg/m^3 and 10.2 mg/m^3, respectively. The average concentration after use of floor waxes was calculated to be 1.1 mg/m^3. This concentration will be used in the risk characterisation of chronic exposure. Yearly average dose rates were estimated up to 0.48 mg/kg bw/day for female adults and 0.7 mg/kg bw/day 10-year-old children, respectively.

Dermal exposure of the consumer via cosmetics (soap, shampoo) is assumed to be in the order of about 0.02 mg/kg bw/day. The dermal exposure from use of phenol containing floor waxes and disinfectants can account to 0.44 mg/kg bw/event and 0.9 mg/kg w/event.

4.1.3.3.2 Acute toxicity

Acute intoxication of humans with phenol is reported frequently. Lethal oral dose for humans is reported to be 140-290 mg/kg body weight. For animals, oral LD_{50} values of 340 mg/kg bw are reported for rats, of approximately 300 mg/kg bw for mice, and of less than 620 mg/kg bw for rabbits. A dermal LD_{50} value of 660-707 mg/kg bw was determined for female rats. Following the exposure assessment, consumers are not expected to be exposed to phenol in the range of hazardous doses which can be derived from acute oral or dermal toxicity figures. Therefore, the substance is of no concern for the consumer in relation to acute oral or dermal toxicity.

However, an inhalation exposure may be of concern. LC_{50} values are not available but rats are reported to tolerate phenol concentrations as high as 900 mg/m³ for 8 hours, resulting in ocular and nasal irritation, loss of co-ordination, tremors, and prostration. Following the exposure assessment there may be an acute inhalation exposure to phenol during the application of floor waxes with a maximum average concentration of about 4 mg/m³ (10 minutes) and a possible peak concentration of 12.7 mg/m^3. Because vapours penetrate the skin surface with absorption efficiency approximately equal to that for inhalation it is impossible to differentiate whether possible detrimental health effects are related to dermal or inhalatory exposure. However, taking into account all assumptions being applied in the exposure estimation (short duration time, model scenario, worst case conditions) and the weakness of the information from the study by Shamy et al. (1994) on phenol-exposed workers (see Section 4.1.2.6) and the nature and severity of effects, it is concluded there should be no concern for consumers with respect to acute inhalation.

Conclusion (ii).

4.1.3.3.3 Irritation/Corrosivity

Corrosivity is the main effect at the site of contact. Skin and eyes can be severely affected when coming into contact depending on substance concentration (even a 1% phenolic solution is reported to have caused skin necrosis). Based on the reported data, phenol is classified as "C, corrosive" and labelled "R34, causes burns".

Due to the long time human experience with phenol and aware of the fact that data on the acute toxicology of phenol mostly base on occasional events with humans or experiments with human volunteers, the US National Institute for Occupational Safety and Health (NIOSH) in 1976 set a limit value of 1% phenol in solutions used or handled occupationally. All solutions containing more than 1% of phenol have to be handled with extreme care.

According to the EU Cosmetics Directive 76/768/EEC and amendments the use of phenol and its alkali salts in soaps and shampoos is permitted in concentrations up to 1%; such products must be labelled "contains phenol".[6]

Following the exposure assessment, consumers are expected to be dermally exposed to phenol containing products. Given the levels of the substance contained in consumer products (up to 2.5%) it can not be excluded that skin irritation will occur despite the short application times (10 minutes).

[6] According to the amendments of the Cosmetics Directive 76/768/EEC by Directive 2005/80/EC of November 21, 2005, phenol is listed in Annex II (List of substances which must not form a part of the composition of cosmetic products).

Conclusion (iii).

4.1.3.3.4 Sensitisation

There is no evidence for skin sensitising properties of phenol by animal tests as well as by human experience

Conclusion (ii).

4.1.3.3.5 Repeated dose toxicity

Long-term exposure to phenol has shown effects on the nervous system and liver (in humans and animals), and on hematopoietic and immune system, kidneys, and skin (animals).

Limited data available on chronic effects of phenol in humans from oral, dermal or inhalation exposure indicated reduced spontaneous activity, muscle weakness, pain and disordered cognitive capacities. Animal studies after repeated administration by these routes have also reported dysfunctions of the nervous system including tremor, convulsions, loss of co-ordination, paralysis, reduced motor and spontaneous activity, and reduced body temperature.

Repeated dose studies on animals have reported unscheduled deaths after inhalation (100-200 mg/m^3, hamster), dermal (783 mg/kg bw/day, rabbit) or gavage (120 mg/kg bw/day, rat) exposure to phenol, but no treatment-related mortalities were seen after long-term exposure of phenol within the drinking water at dosages up to 450 mg/kg bw/day in rats and 375 mg/kg bw/day in mice. In some studies, mortalities were associated to growth retardation or respiratory distress.

Anaemia and suppressive effects on the erythropoietic and granulopoeitic stem cells and bone marrow stromal cells were found in studies on mice, whereas no data are available for other species. Application of phenol in drinking water was shown to induce T- and B-cell suppressive effects (reduced lymphocyte proliferation response to mitogens, antibody levels and T-cell dependent humoral immunity) in mice at low dosages (6.2 mg/kg bw and above), however, no effect on T-cell dependent humoral response was found for rats. Atrophic changes of thymus or spleen were occasionally seen in rats repeatedly exposed to phenol by the oral route. No histomorphologic alterations of immune organs were seen in cancer studies on mice and rats.

In phenol-exposed workers elevated activities for serum aminotransferases and increased clotting time were observed at a concentration of 0.021 mg/l indicating hepatotoxicity after chronic inhalation. Liver damage has also been reported in rats repeatedly exposed to phenol by the inhalation and oral route. Enlarged liver, elevated levels of liver enzymes and, in animals only, liver cell degeneration was observed. Necrosis of renal tubules and papillary hemorrhage has been reported for the rat after repeated oral administration of phenol.

In rabbits, prolonged dermal exposure to phenol at concentrations of 1.18% and above (130 mg/kg bw/day) induced epidermal hyperkeratosis and ulceration.

The following N(L)OAEL/C values derived for systemic toxic effects will be used for the risk assessment:

Oral administration

LOAEL of 1.8 mg/kg bw/day for hematotoxic and immunotoxic effects from the subacute mouse study (Hsieh, 1992),

Inhalation and dermal administration

LOAEC systemic of 21 mg/m^3 for hepatotoxic effects from the time weighted exposure of workers (Shamy et al., 1994).

For the decision on the appropriateness of MOS, the following aspects have been considered and taken into account:

- overall confidence in the database.

The data taken into account for performing the risk characterisation have been evaluated with regard to their reliability, relevance and completeness according to Section 3.2 of the TGD. The data were published in peer reviewed journals or submitted to the Competent Authority in private reports being adequately detailed and in accordance with internationally recognised guidelines and to GLP.

The findings of all studies are not contradictory so that the judgement can be based on the database (see Section 4.1.2.6).

There are no reasons to assume limited confidence.

- uncertainty arising from the variability in the experimental data.

Oral studies

The results from repeated dose studies on phenol-related effects are not finally conclusive regarding the overall database from earlier and recent studies. To derive a N(L)OAEL for the oral route the adverse effects occurring at the lowest effect level at the most sensitive species are considered to be appropriate. The significantly reduced number of erythrocytes (-32%) in mice at 1.8 mg/kg bw/day observed in the drinking water study of Hsieh et al. (1992) is considered to represent the LOAEL with oral phenol treatment. Although the NIH study (1980) was accepted with restrictions for the formal requirements on the study design, it did not include all sensitive parameters relevant in phenol toxicity.

The findings of Hsieh and his group were not confirmed by other oral studies either in mice or in rats. This is explainable in part, because there are differences in parameters examined. However, the mouse might be the most sensitive species with respect to hematotoxicity though this assumption is not fully conclusive with the chronic bioassay on B6C3F1 mice (NIH, 1980) which did not give any indication on apparent hematotoxic effects which should be seen after prolonged anaemia (e.g. splenomegaly, extramedullary and medullary hematopoiesis). In addition, none of the inhalation studies gave indication on hematotoxic effects.

Similarly, there is an inconsistency of the T-cell dependent humoral response comparing data from mouse studies (suppression from 6.2 mg/kg bw/day, Hsieh et al., 1992) to that from rat studies (no effect up to 301 mg/kg bw/day, CMA, 1999). This may be attributed to species or strain specificity, too.

The marked difference in NOAEL from the 103-weeks study of the NIH (1980) and LOAEL of the subacute toxicity study (Hsieh et al., 1992) (both studies with oral administration with the

drinking water) may be attributable to the high sensitivity of testing parameters on hematoxicity, the neurofunction and the immune function in the Hsieh study as compared to the reduced testing protocols in the NIH study. Therefore the NOAEL from the 103-weeks study was considered to be not relevant for the risk assessment.

Inhalation studies

The observations of elevated activities for serum aminotransferases (especially ALAT) and increased clotting time indicating hepatotoxicity in phenol-exposed workers allow to derive a LOAEL of 21 mg/m³ for systemic effects after chronic inhalation (Shamy et al., 1994). No adverse effects on the respiratory tract were reported in a valid 14 day-inhalation study on rats (CMA, 1998a). No remarkable differences between control and exposed animals for clinical observation, body weights, food consumption, clinical pathology, organ weights and macroscopic and microscopic post-mortem examinations, at termination and recovery were seen at phenol concentrations up to 96.3 mg/m³.

A 14 day-inhalation with phenol concentration of 100 mg/m³ on rats induced clinical signs of motor disorders with impaired function of the balance regulation (Dalin and Kristoffersson, 1974). Increased serum liver enzymes (LDH, ASAT, ALAT, GLDH) were indicative of liver damage. The study was incomplete with respect to parameters of haematology and clinical chemistry (no data on necropsy, organ weights and histopathology).

Further subchronic inhalation studies were performed in rats, rabbits, and guinea pigs at vapour concentrations of 100-200 mg/m³. Rats showed no pathological lesions. The changes seen in the rabbits and guinea pigs were considered of low reliability because purulent bronchopneumonia may also indicate a primary infectious disease. Moreover, the study is of limited validity because of the absence of data on phenol purity, growth, haematology, clinical chemistry, organ weights and a list of organs examined microscopically.

Dermal studies

Phenol absorption after repeated dermal applications on 18 days at concentrations of 1.18-7.12% aqueous phenol solutions produced tremors (≥ 2.37%) as well as epidermal hyperkeratosis and ulceration in rabbits at concentrations > 3.56%. Signs of systemic intoxication were described at concentrations of 5.93 and 7.12% (Deichmann et al., 1950). The NOAEL for systemic toxic effects was 1.18% (130 mg/kg bw/day). The study design did not contain any laboratory or post-mortem investigations (see Section 4.1.2.6). Because of this substantial limitation of the relevance of the dermal NOAEL from the rabbit study, for dermal risk assessment it is proposed to adjust the worker experience for the inhalation route.

As outlined in Section 4.1.2.6 on systemic effects by inhalation, the LOAEC for workers is 21 mg/m³. Assuming a breathing volume of 10 m³ (see Section 4.1.3.2.2) and 100% absorption, the phenol concentration of 21 mg/m³ is converted into an internal dose of 210 mg/person corresponding to 3.5 mg/kg bw/day. This value is proposed to be taken for dermal risk assessment.

Taking into account the variability in the experimental data and the limited validity of some studies there is concern which has to be expressed in the magnitude of the MOS.

Intra- and interspecies variation

Comparing the effect levels for effects on the hematopoietic and immune system mice seem to be more sensitive than rats (LOAEL mice 1.8 mg/kg bw/day versus NOAEL rats > 300 mg/kg bw/day).

Data on kinetics of the substance do not allow to calculate the intraspecies and interspecies variability by applying modern approaches. However, the available data give no hint on a particular high variability in kinetics. The variability of the data on the toxicodynamics has been described above and has been considered not to justify an increased MOS. For establishing the MOS for an oral exposure (see Section 4.1.3.4), the LOAEL of the most sensitive species (drinking water study on mice) has been applied, whereas for inhalation and dermal exposure, the LOAEC from phenol-exposed workers has been used. In using the Shamy data considerations on interspecies variations are not necessary.

The nature and severity of the effect

The effects described in mice as "low observed adverse effect" is anaemia and suppressive effects on the erythropoietic and granulopoeitic stem cells, and bone marrow stromal cells. These effects are considered to be serious health effects. The changes in biochemical parameters resulting from occupational exposure to phenol are considered as indications of liver toxicity.

Therefore there is concern, which has to be expressed in the magnitude of the MOS.

Differences in exposure (route, duration, frequency and pattern)

Following the exposure assessment, application of floor waxes, polishes, and disinfectants may lead to a chronic exposure of consumers via inhalation. The systemic LOAEC used for the discussion of the MOS regarding these applications is derived from observations on phenol-exposed workers.

The application of phenol containing waxes and cleaners will lead to a dermal exposure of consumers. In addition, the consumer may be exposed dermally to phenol via cosmetics. Because of the limitation of the relevance of the dermal NOAEL from the rabbit study the dermal risk assessment will also be based on the systemic LOAEL derived from observations on phenol-exposed workers.

There are no reasons to assume a special concern from the available toxicokinetic information (concerning different routes absorption was set with 100% for inhalation and 80% for dermal route, respectively).

The human population to which the quantitative and/or qualitative information on exposure applies

Following the exposure scenario there is no reason to assume a special risk for elderly. There may be concern on people suffering from special diseases like anaemia and for children, which has to be expressed in the magnitude of the MOS.

Other factors

There are no other factors known requiring a peculiar margin of safety.

MOS for oral exposure scenario

Relevant oral exposure of the consumer has not to be assumed.

MOS for inhalation exposure scenario

During application of floor waxes the consumer may be exposed to an average concentration of 4 mg/m^3 (for 10 minutes). After application consumers may be exposed to phenol from floor waxes to a concentration of 1.1 mg/m^3 (see Section 4.1.1.3).

Local effects

No adverse effects were seen in the respiratory tract of rats until the highest tested value of 96 mg/m³ phenol (CMA, 1998a). This value is used to conclude on local effects by inhalation after repeated exposure (see Section 4.1.3.2).

The margin of safety between the

estimated exposure of	1.1 mg/m³
and the	
NOAEC (local) of	96 mg/m³

is considered to be sufficient. Thus, there is no concern for local respiratory effects of phenol after repeated inhalation.

Conclusion (ii).

Systemic effects

As LOAEC for systemic effects the value of 21 mg/m³ from observations on phenol-exposed workers is used.

The margin of safety between the

estimated exposure of	1.1 mg/m³
and the	
LOAEC (human) of	21 mg/m³

is considered to be not sufficient.

This conclusion is based on observations that inhalation of phenol by workers leads to increased activities of ALAT and ASAT in the blood indicating hepatotoxicity. On the other hand, taking into account the limitations of this study (in regard to lacking data on individual exposure, ranges of exposure height, and daily exposure duration as well as on recording time points and duration) and the uncertainties inherent in the exposure estimation (worst case conditions) this scenario may be considered as a border-line case.

Conclusion (iii).

MOS for dermal exposure scenarios

Systemic effects

The dermal exposure from use of phenol containing waxes and disinfectants can account 0.44 mg/kg bw/event and 0.9 mg/kg bw/event, respectively. Assuming a dermal absorption of 80% the internal exposure from disinfectants may be 0.72 mg/kg bw/event.

The margin of safety between the

exposure level of	0.72 mg/kg bw
and the	
converted human LOAEL (dermal) of	~ 3.5 mg/kg bw/day

is judged to be not sufficient taking into account a frequent exposure and that the MOS consideration is based on a LOAEL and the limitations of the human LOAEC used for the route-to-route extrapolation.

Conclusion (iii).

- The calculation of the dermal exposure of consumers due to cosmetics leads to an external exposure of about 0.02 mg/kg bw/day which corresponds to an internal exposure of 0.016 mg/kg bw/day.

The margin of safety between the

estimated exposure level of	0.016 mg/kg bw/day
and the	
converted human LOAEL (dermal) of	~3.5 mg/kg bw/day

is judged to be sufficient even taking into account that the MOS consideration is based on a LOAEL and the limitations of the human LOAEC used for the route-to-route extrapolation.

Conclusion (ii).

- The calculation of a combined dermal exposure for consumers (use of cosmetics and phenol containing disinfectants) leads to an external exposure of about 0.9 mg/kg bw/day which corresponds to an internal exposure of 0.72 mg/kg bw/day.

The margin of safety between the

calculated exposure level (internal) of	0.72 mg/kg bw/day
and the	
converted human LOAEL (dermal) of ~	3.5 mg/kg bw/day

is judged to be not sufficient taking into account that the MOS consideration is based on a LOAEL and the limitations of the human LOAEC used for the route-to-route extrapolation.

Conclusion (iii).

Local effects

The calculation of a combined dermal exposure for consumers (use of cosmetics and phenol containing disinfectants) leads to an exposure of about 0.9 mg/kg bw/day.

Local effects were observed in the rabbit study with repeated dermal application at > 390 mg/kg bw (3.56% phenol) with epidermal hyperkeratosis and ulceration. As NOAEL for local effects 260 mg/kg bw/day (2.37%) was derived from this study (Deichmann et al., 1950).

The margin of safety between the

exposure level of	0.9 mg/kg bw/day
and the	
NOAEL (dermal) of	260 mg/kg bw/day

is considered to be sufficient.

Conclusion (ii).

4.1.3.3.6 Genotoxicity

Phenol is positive with respect to various genetic effects in mammalian cell cultures. In general, relatively weak effects are induced. *In vivo*, phenol is a weak inducer of micronuclei in mouse bone marrow cells; the effect is bound to high doses which are equivalent to or near to the maximum tolerable dose.

Phenol is classified as category 3 mutagen and labelled "R 68, possible risks of irreversible effects". However, taking into account that the *in vivo* effects occurred at high doses and the low exposure values a risk for consumers with respect to this endpoint is not expected.

Conclusion (ii).

4.1.3.3.7 Carcinogenicity

Oral long term studies on rats and mice revealed no effects of phenol on tumour induction. A medium-term study on transgenic mice did not give any indication on treatment-related proliferative responses. Phenol was shown to act as a promoter in skin cancer bioassays in mice. A weak carcinogenic effect was observed after long-term skin application of a 10% solution of phenol in benzene (without initiation). However, it is considered less relevant because the test solution contained the carcinogen benzene. A possible concern due to positive *in vivo* mutagenicity data is considered to be of minor significance, as long term studies revealed no relevant indication for carcinogenicity.

There are no data revealing an association of phenol exposure to increased tumour rates in humans. No firm conclusion on risk levels could be drawn from a case-control study on respiratory cancer of workers exposed to phenol.

Conclusion (ii).

4.1.3.3.8 Reproductive toxicity

No data are available on reproductive toxicity of phenol in humans. Phenol was investigated for impairment of reproductive performance and fertility in a two-generation (drinking water) reproductive toxicity study in rats. No adverse effects on reproductive capability and fertility were revealed for either sex across two generations up to and including the highest dosages tested (5,000 ppm, according to 300 and 320 mg/kg bw/day for males and females, respectively).

No effects on sperm parameters or on estrous cyclicity were revealed. Effects observed during this study were confined to the observation of impaired offspring viability and offspring growth delay during the pre-weaning period for the groups of the highest tested concentration level. No substance specific embryotoxic or teratogenic potential was revealed for phenol in studies with mice and rats. Also, no indications for a substance-related specific fetotoxic potential are obtained from the overall assessment of the available data. Based on the results of the 2-generation study a NOAEL/developmental toxicity of 93 mg/kg bw/day is used for risk characterisation.

For the decision on the appropriateness of MOS, the following aspects regarding the critical effects as well as exposure have been considered and taken into account:

Overall confidence in the database

The data taken into account for performing the risk characterisation have been evaluated with regard to their reliability, relevance and completeness according to Section 3.2 of the TGD. The data were published in peer reviewed journals or submitted to the Competent Authority in private reports being adequately detailed and in accordance with internationally recognised guidelines and to GLP.

The findings of all studies are not contradictory so that the judgement can be based on the database (see Section 4.1.2.9).

There are no reasons to assume limited confidence.

Uncertainty arising from the variability in the experimental data

No special concerns have to be raised from this point.

Intra- and interspecies variation

There are no indications to limit the findings to a single species.

The nature and severity of the effect

Marginal influences on reproduction have been observed. At the highest tested drinking water concentration of 5,000 ppm litter survival and offspring body weights were reduced during the period of lactation/pre-weaning. Fetotoxicity is only present at maternal toxic doses.

Dose-response-relationship

The mentioned effects were observed at the highest dose, leading to systemic toxicity.

There is no reason to assume concern which has to be expressed in an increased MOS taking into account the exposure level.

Differences in exposure (route, duration, frequency and pattern)

Following the exposure assessment, the consumer may be exposed to phenol via inhalation and the dermal route, whereas oral exposure is assumed of minor importance. The NOAEL used for the discussion of the MOS regarding these exposure scenarios are derived from a 2-generation drinking water study on rats. The daily dose rate of inhalation (0.7 mg/kg bw/day for children)

and the estimated dermal body burden (about 20 µg/kg bw/day) are compared with the NOAEL from a 2-generation drinking water study.

There are no reasons to assume that special concern can be derived from this procedure nor from the available toxicokinetic information (concerning different routes absorption was set with 100% for inhalation and 80% for dermal route, respectively).

MOS for the inhalation exposure scenario

During application of floor waxes the consumer may be exposed to an average concentration of 4 mg/m^3 (for 10 minutes) which results in a daily dose of about 0.06 mg/kg bw/day. After application consumers may be exposed to phenol from floor waxes to a concentration of 1.1 mg/m^3 which corresponds to a daily dose rate of 0.48 mg/kg bw/day for adults and of 0.7 mg/kg bw/day for children (see Section 4.1.1.3).

Fertility

The results from the 2-generation study gave no indication for an impairment of fertility (see Section 4.1.2.9). Therefore, fertility is not considered to be a relevant endpoint.

Conclusion (ii).

Reduction measures beyond those which are being applied already.

Developmental toxicity

The calculation of the inhalation exposure of children due to floor waxes leads to a daily exposure of 0.7 mg/kg bw/day. The margin of safety between the

estimated exposure level of	0.7 mg/kg bw/day
and the	
NOAEL of	93 mg/kg bw/day

is judged to be sufficient. Thus, the substance is of no concern.

Conclusion (ii).

MOS for the dermal exposure scenario

Fertility

The results from the 2-generation study gave no indication for an impairment of fertility.

Thus, fertility is not considered to be of concern in relation to dermal exposure via cosmetics and uptake from use of phenol containing waxes and disinfectants.

Conclusion (ii).

Developmental toxicity

The calculation of the dermal exposure of consumers due to cosmetics and from phenol containing disinfectants leads to an exposure of about 0.9 mg/kg bw/day.

The margin of safety between the

estimated exposure level of	0.9 mg/kg bw/day
and the	
NOAEL of	93 mg/kg bw/day

is judged to be sufficient taking into account the rate and the extent of dermal absorption (80%). Thus, the substance is of no concern.

Conclusion (ii).

4.1.3.4 Humans exposed via the environment

Indirect exposure via the environment is calculated using data for oral intake via plant shoot and drinking water. Following the local scenario data (at a point source) an intake of a total daily dose of 0.0464 mg/kg bw/day is calculated with a fraction of the $DOSE_{plant\ shoot}$ of 91%. Following the data for the regional scenario, the total daily dose is smaller ($1.5 \cdot 10^{-4}$ mg/kg bw/day) with the main contributions of the $DOSE_{drw}$ and $DOSE_{plant\ shoot}$ with fractions of 46% and 41%, respectively.

4.1.3.4.1 Repeated dose toxicity-oral intake

A NOAEL for oral administration has not been established; an oral LOAEL of 1.8 mg/kg bw/day was derived from the subacute mouse study (Hsieh, 1992) (see Section 4.1.2.6 and 4.1.3.3). The estimated total body burden with an assumed absorption of 100% is compared to that oral LOAEL.

MOS for the exposure scenario: humans exposed via the environment

Local scenario

The calculated internal dose for local exposure is 0.0464 mg/kg bw/day. The margin of safety between the

estimated exposure level of	0.0464 mg/kg bw/day
and the	
oral LOAEL of	1.8 mg/kg bw/day

is judged to be not sufficient, even if special considerations on intra- and interspecies variation, nature and severity of the effects and possible human populations at risk are taken into consideration.

Conclusion (iii).

Regional scenario

The total calculated internal dose for regional exposure is $1.5 \cdot 10^{-4}$ mg/kg bw/day. The margin of safety between the

estimated exposure level of	$1.5 \cdot 10^{-4}$ mg/kg bw/day
and the	
oral LOAEL of	1.8 mg/kg bw/day

is judged to be sufficient. Thus, the substance is of no concern in relation to indirect exposure via the environment.

Conclusion (ii).

4.1.3.4.2 Repeated dose toxicity - inhalation exposure

Local scenario

Following the local scenario data a concentration of 0.018 mg/m^3 phenol in the air is calculated (see **Table 4.9**). The NOAEC for local effects at the respiratory tract in the 14-day rat inhalation study (CMA, 1998a) was 96.3 mg/m³, whereas a LOAEC of 21 mg/m³ for systemic effects was derived from a time weighted average exposure of workers (Shamy et al., 1994).

Comparison indirect exposure - Local scenario/local effects / NOAEC:

Indirect exposure (local)	0.018 mg/m3
and	
NOAEC	96.3 mg/m3

The margin of safety expressed by the magnitude between the calculated exposure and the NOAEC is high for local effects.

Conclusion (ii).

Comparison indirect exposure - Local scenario/systemic effects/LOAEC:

Indirect exposure (local)	0.018 mg/m³
and	
LOAEC (human)	21 mg/m³

The margin of safety expressed by the magnitude between the calculated exposure and the LOAEC for systemic effects is considered to be sufficient.

Conclusion (ii).

Regional scenario

Taking into account the even smaller air concentration in the regional scenario ($2.6 \cdot 10^{-5}$ mg/m^3) there is also no concern

Conclusion (ii).

4.1.3.4.3 Reproductive toxicity

Phenol was investigated for impairment of reproductive performance and fertility in a two-generation (drinking water) reproductive toxicity study in rats. No adverse effects on reproductive capability and fertility were revealed for either sex across two generations. No substance specific embryotoxic or teratogenic potential was revealed for phenol in studies with mice and rats. Also, no indications for a substance-related specific fetotoxic potential are obtained from the overall assessment of the available data. A NOAEL/developmental toxicity of 93 mg/kg bw/day is used for risk characterisation, which is based on the 2-generation study (see Sections 4.1.2.9 and 4.1.3.3).

Fertility

The results from the two-generation study gave no indication for an impairment of fertility. Therefore, fertility is not considered to be a relevant endpoint for indirect exposure via the environment.

Conclusion (ii).

4.1.3.4.4 Developmental toxicity

MOS for the exposure scenario: humans exposed via the environment

Local scenario

The total calculated internal dose for local exposure is 0.0464 mg/kg bw/day. The margin of safety between the

exposure level of	0.0464 mg/kg bw/day
and the	
NOAEL of	93 mg/kg bw/day

is judged to be sufficient. Thus, the substance is of no concern in relation to indirect exposure via the environment.

Conclusion (ii).

Regional scenario

The total calculated internal dose for regional exposure is $1.5 \cdot 10^{-4}$ mg/kg bw/day. The margin of safety between the

exposure level of	$1.5 \cdot 10^{-4}$ mg/kg bw/day
and the	
NOAEL of	93 mg/kg bw/day

is judged to be sufficient. Thus, the substance is of no concern in relation to indirect exposure via the environment.

Conclusion (ii).

4.1.3.5 Combined exposure

It is possible for an individual to receive exposure to phenol at work, from consumer products and indirectly via the environment.

The highest occupational exposure may occur during the formulation of phenolic resins (via inhalation and dermal contact) resulting in a body burden of about 4 mg/kg bw/day (see **Table 4.35**). The combined dermal exposure of consumers to phenol (cosmetics and consumer products - disinfectants) is estimated to amount up to 0.9 mg/kg bw/day. The highest levels that would be received indirectly from environmental sources (local scenario, plant shoot) of 0.046 mg/kg bw/day are comparably low against the burdens by other routes.

The margin of safety between combined exposure levels in the range of 1 to 5 mg/kg bw/day and the converted human LOAEL of ~ 3.5 mg/kg bw/day is judged to be not sufficient taking into account the use of a LOAEL and limitations of the human LOAEC used for the route-to-route extrapolation.

Taken together, the **conclusion (iii)** reached for workers as well for consumers applies also to combined exposure.

Conclusion (iii).

4.2 HUMAN HEALTH (PHYSICO-CHEMICAL PROPERTIES)

4.2.1 Exposure assessment

4.2.1.1 Occupational exposure

See Sections 4.1.1.1 and 4.1.1.2.

4.2.2 Effects assessment: Hazard identification and Dose (concentration) - response (effect) assessment

4.2.2.1 Explosivity

Phenol is not explosive.

4.2.2.2 Flammability

Phenol is not highly flammable. The flash point amounts to 82°C (CHEMSAFE), according to DIN 51 794 the ignition temperature is in the region of 595°C (CHEMSAFE).

4.2.2.3 Oxidising potential

Due to its chemical structure, phenol is not expected to possess any oxidising properties.

4.2.3 Risk characterisation

4.2.3.1 Workers

According to information provided by the manufacturer, ignitable mixtures may form with air. The lower explosion limit in air amounts to 1.3% by volume at 1,013 hPa. This corresponds to a concentration of 50 g phenol/m^3. Comparison of the measured maximum phenol concentrations at the workplace of 19 or 42 mg/m^3 (see Section 4.2.1.1) with the lower explosion limit of 50 g/m^3 produces a factor of 2,630 and 1,190 respectively. A risk is excluded.

In the case of leakage from a closed system, phenol concentrations above the lower explosion limit cannot be excluded. A risk is not to be expected if the notices relating to fire and explosion protection (keep away from ignition sources, no smoking) are observed.

5 RESULTS

5.1 ENVIRONMENT

5.1.1 General information

Phenol is released into the environment during production and processing. Based on the exposure data submitted by the industry and the exposure estimates based on the "default values" according to the TGD, where actual data were missing, releases of approximately 124 tonnes/annum into the hydrosphere and approximately 535 tonnes/annum into the atmosphere are estimated for Europe.

In relation to the releases of phenol as a result of industrial production and processing, the diffuse releases of phenol into the environment are considerably higher and represent the main source of phenol in the environment. The following figures refer to the territory of the EU. As a result of human metabolism, approximately 2,096 tonnes/annum of phenol is released into the hydrosphere and approximately 6 tonnes/annum into the soil via the spreading of sewage sludge. Furthermore, releases into the atmosphere are to be expected due to the photochemical degradation of benzene, vehicle exhaust fumes and a very wide range of combustion processes. The resultant releases into the atmosphere were calculated at approximately 96,830 tonnes/annum. In spite of the high release quantities, no substantial transport from the atmosphere into other environmental compartments is expected due to fast photochemical degradation of phenol (half-life = 42 minutes).

Taking into consideration all point sources and diffuse emissions, a regional background concentration of phenol in the hydrosphere of 2.41 µg/l is calculated. For the atmosphere, a regional PEC of 0.026 µg/m^3 results for phenol and in natural soil a regional background concentration of 0.59 µg/kg is estimated. Local exposure of the environment as a result of production and industrial use of phenol in the chemical industry had been estimated to be significantly below the concentrations resulting from unintentional releases. No unacceptable risks for the environment had been identified for the production and industrial use of phenol.

For some sites where no actual release data could be obtained a risk to the microorganism population of the biological WWTP and therefore a concern for the proper function of the waste water purification system have to be expected.

The results and conclusions drawn from the risk characterisation for phenol are summarised below:

5.1.2 Waste-water treatment plants

Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

This conclusion applies to the industrial WWTP at 8 out of 32 sites. For all these sites the $Clocal_{eff}$ is based on default values and could possibly be lowered by site-specific and traceable exposure data. However, it is not expected to obtain exposure data for all these sites with reasonable efforts and time expenditure. In addition, the concern cannot be removed by testing due to the result from an available respiration inhibition test with industrial sludge.

5.1.3 Unintentional release

Conclusion (i) There is need for further information and/or testing.

In the case of the release of phenol as a product of human metabolism, water concentrations of 22.57 µg/l results for direct discharges of municipal waste water into a receiving stream and 5.1 µg/l for indirect discharges into the receiving stream via municipal WWTPs (see Section 3.1.3.4). With regard to Europe it is assumed that approximately 70% of the population release their waste water into the receiving stream via municipal WWTPs and that 30% discharge directly into a receiving stream.

Taking into consideration the $PNEC_{aqua}$ of 7.7 µg/l, a PEC/PNEC ratio > 1 results for the direct discharges of phenol as a product of human metabolism without purification of the municipal waste water in a biological treatment plant. This emission path is not the subject of this risk assessment, but further investigations, i.e. measurement of the phenol content in the influent of municipal WWTPs or in untreated municipal waste water and/or monitoring of the phenol content in streams of direct discharges should be considered by the responsible authorities.

It was not possible to provide an estimation of exposure for the aquatic environment with regard to the areas relating to the coking, gasification and liquefaction of coal, refineries and pulp manufacture.

Phenol may enter the soil as a result of the spreading of liquid manure from livestock farming. For the spread of liquid manure derived from livestock farming over agricultural areas it is not possible to estimate a total release to soil.

It was not possible to estimate the exposure to the aquatic and terrestrial environment from landfills without landfill leachate collecting system.

5.1.4 Aquatic environment

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

5.1.5 Atmosphere

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

5.1.6 Terrestrial compartment

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

5.1.7 Secondary poisoning

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

5.2 HUMAN HEALTH

5.2.1 Human Health (toxicity)

5.2.1.1 Workers

Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

For phenol risk assessment, three occupational exposure scenarios are defined: production and further processing (Scenario 1), formulation of phenolic resins (Scenario 2) and use of phenolic resins, the latter being divided in a subscenario without (3a) and with spraying techniques (3b).

For all dermal exposure scenarios corrosivity following skin contact and contact to the eyes gives reason for concern. It is known, that sensation of pain due to local exposure to phenol may be diminished possibly leading to less awareness and thus higher degrees of local damage. Special emphasis should be given by risk managers to all dermal exposure scenarios (Scenario 1, 2 and 3) when deciding on the possible need for further risk reduction measures.

For all scenarios concern is expressed with respect to systemic toxicity following repeated inhalation. No concern is reached for respiratory tract irritation. In addition, for Scenarios 2 and 3b, concern is expressed for systemic toxicity following repeated dermal exposure. With respect to acute toxicity, concern is indicated for Scenario 2 (only for inhalation) and for scenario 3b (only for dermal contact).

5.2.1.2 Consumers

Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

Dermal exposure of consumers via disinfectants leads to **conclusion (iii)** because of systemic repeated dose toxicity and possible skin irritation.

In addition application of floor waxes leads to concern with respect to systemic repeated dose toxicity by inhalation.

5.2.1.3 Humans exposed via the environment

Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

There is concern for local indirect exposure via plant shoot.

5.2.2 Human health (risk from physico-chemical properties)

There are no significant risks from physico-chemical properties

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

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ABBREVIATIONS

ADI	Acceptable Daily Intake
AF	Assessment Factor
ASTM	American Society for Testing and Materials
ATP	Adaptation to Technical Progress
AUC	Area Under The Curve
B	Bioaccumulation
BBA	Biologische Bundesanstalt für Land- und Forstwirtschaft
BCF	Bioconcentration Factor
BMC	Benchmark Concentration
BMD	Benchmark Dose
BMF	Biomagnification Factor
BOD	Biochemical Oxygen Demand
bw	body weight / *Bw*, *bw*
C	Corrosive (Symbols and indications of danger for dangerous substances and preparations according to Annex II of Directive 67/548/EEC)
CA	Chromosome Aberration
CA	Competent Authority
CAS	Chemical Abstract Services
CEC	Commission of the European Communities
CEN	European Standards Organisation / European Committee for Normalisation
CEPE	European Committee for Paints and Inks
CMR	Carcinogenic, Mutagenic and toxic to Reproduction
CNS	Central Nervous System
COD	Chemical Oxygen Demand
CSTEE	Scientific Committee for Toxicity, Ecotoxicity and the Environment (DG SANCO)
CT_{50}	Clearance Time, elimination or depuration expressed as half-life
d.wt	dry weight / dw
dfi	daily food intake
DG	Directorate General
DIN	Deutsche Industrie Norm (German norm)
DNA	DeoxyriboNucleic Acid
DOC	Dissolved Organic Carbon
DT50	Degradation half-life or period required for 50 percent dissipation / degradation
DT90	Period required for 90 percent dissipation / degradation
E	Explosive (Symbols and indications of danger for dangerous substances and preparations according to Annex II of Directive 67/548/EEC)
EASE	Estimation and Assessment of Substance Exposure Physico-chemical properties [Model]

EbC50	Effect Concentration measured as 50% reduction in biomass growth in algae tests
EC	European Communities
EC10	Effect Concentration measured as 10% effect
EC50	median Effect Concentration
ECB	European Chemicals Bureau
ECETOC	European Centre for Ecotoxicology and Toxicology of Chemicals
ECVAM	European Centre for the Validation of Alternative Methods
EDC	Endocrine Disrupting Chemical
EEC	European Economic Communities
EINECS	European Inventory of Existing Commercial Chemical Substances
ELINCS	European List of New Chemical Substances
EN	European Norm
EPA	Environmental Protection Agency (USA)
ErC50	Effect Concentration measured as 50% reduction in growth rate in algae tests
ESD	Emission Scenario Document
EU	European Union
EUSES	European Union System for the Evaluation of Substances [software tool in support of the Technical Guidance Document on risk assessment]
F(+)	(Highly) flammable (Symbols and indications of danger for dangerous substances and preparations according to Annex II of Directive 67/548/EEC)
FAO	Food and Agriculture Organisation of the United Nations
FELS	Fish Early Life Stage
foc	Organic carbon factor (compartment depending)
GLP	Good Laboratory Practice
HEDSET	EC/OECD Harmonised Electronic Data Set (for data collection of existing substances)
HELCOM	Helsinki Commission -Baltic Marine Environment Protection Commission
HPLC	High Pressure Liquid Chromatography
HPVC	High Production Volume Chemical (> 1000 tonnes/annum)
IARC	International Agency for Research on Cancer
IC	Industrial Category
IC50	median Immobilisation Concentration or median Inhibitory Concentration
ILO	International Labour Organisation
IPCS	International Programme on Chemical Safety
ISO	International Organisation for Standardisation
IUCLID	International Uniform Chemical Information Database (existing substances)
IUPAC	International Union for Pure and Applied Chemistry
JEFCA	Joint FAO/WHO Expert Committee on Food Additives
JMPR	Joint FAO/WHO Meeting on Pesticide Residues

Koc	organic carbon normalised distribution coefficient
Kow	octanol/water partition coefficient
Kp	solids-water partition coefficient
L(E)C50	median Lethal (Effect) Concentration
LAEL	Lowest Adverse Effect Level
LC50	median Lethal Concentration
LD50	median Lethal Dose
LEV	Local Exhaust Ventilation
LLNA	Local Lymph Node Assay
LOAEL	Lowest Observed Adverse Effect Level
LOEC	Lowest Observed Effect Concentration
LOED	Lowest Observed Effect Dose
LOEL	Lowest Observed Effect Level
MAC	Maximum Allowable Concentration
MATC	Maximum Acceptable Toxic Concentration
MC	Main Category
MITI	Ministry of International Trade and Industry, Japan
MOE	Margin of Exposure
MOS	Margin of Safety
MW	Molecular Weight
N	Dangerous for the environment (Symbols and indications of danger for dangerous substances and preparations according to Annex II of Directive 67/548/EEC
NAEL	No Adverse Effect Level
NOAEL	No Observed Adverse Effect Level
NOEL	No Observed Effect Level
NOEC	No Observed Effect Concentration
NTP	National Toxicology Program (USA)
O	Oxidising (Symbols and indications of danger for dangerous substances and preparations according to Annex II of Directive 67/548/EEC)
OC	Organic Carbon content
OECD	Organisation for Economic Cooperation and Development
OEL	Occupational Exposure Limit
OJ	Official Journal
OSPAR	Oslo and Paris Convention for the protection of the marine environment of the Northeast Atlantic
P	Persistent
PBT	Persistent, Bioaccumulative and Toxic
PBPK	Physiologically Based PharmacoKinetic modelling

PBTK	Physiologically Based ToxicoKinetic modelling
PEC	Predicted Environmental Concentration
pH	logarithm (to the base 10) (of the hydrogen ion concentration $\{H^+\}$
pKa	logarithm (to the base 10) of the acid dissociation constant
pKb	logarithm (to the base 10) of the base dissociation constant
PNEC	Predicted No Effect Concentration
POP	Persistent Organic Pollutant
PPE	Personal Protective Equipment
QSAR	(Quantitative) Structure-Activity Relationship
R phrases	Risk phrases according to Annex III of Directive 67/548/EEC
RAR	Risk Assessment Report
RC	Risk Characterisation
RfC	Reference Concentration
RfD	Reference Dose
RNA	RiboNucleic Acid
RPE	Respiratory Protective Equipment
RWC	Reasonable Worst-Case
S phrases	Safety phrases according to Annex IV of Directive 67/548/EEC
SAR	Structure-Activity Relationships
SBR	Standardised birth ratio
SCE	Sister Chromatic Exchange
SCHER	Scientific Committee on Health and Envionment Risks
SDS	Safety Data Sheet
SETAC	Society of Environmental Toxicology And Chemistry
SNIF	Summary Notification Interchange Format (new substances)
SSD	Species Sensitivity Distribution
STP	Sewage Treatment Plant
T(+)	(Very) Toxic (Symbols and indications of danger for dangerous substances and preparations according to Annex II of Directive 67/548/EEC)
TDI	Tolerable Daily Intake
TG	Test Guideline
TGD	Technical Guidance Document
TNsG	Technical Notes for Guidance (for Biocides)
TNO	The Netherlands Organisation for Applied Scientific Research
ThOD	Theoritical Oxygen Demand
UC	Use Category
UDS	Unscheduled DNA Synthesis
UN	United Nations

UNEP	United Nations Environment Programme
US EPA	Environmental Protection Agency, USA
UV	Ultraviolet Region of Spectrum
UVCB	Unknown or Variable composition, Complex reaction products of Biological material
vB	very Bioaccumulative
VOC	Volatile Organic Compound
vP	very Persistent
vPvB	very Persistent and very Bioaccumulative
v/v	volume per volume ratio
w/w	weight per weight ratio
WHO	World Health Organisation
WWTP	Waste Water Treatment Plant
Xn	Harmful (Symbols and indications of danger for dangerous substances and preparations according to Annex II of Directive 67/548/EEC)
Xi	Irritant (Symbols and indications of danger for dangerous substances and preparations according to Annex II of Directive 67/548/EEC)

Appendix A Distribution and Fate Calculation (Simple Treat Calculation)

Distribution and Fate

$d := Tag$

Substance: Phenol CAS.Nr.: 108-95-2

melting point:	$MP := 313.9 \cdot K$
vapour pressure:	$VP := 20 \cdot Pa$
water solubility:	$SOL := 84000 \cdot mg \cdot l^{-1}$
part. coefficient octanol/water:	$LOGP_{OW} := 1.47$
moleculare weight:	$MOLW := 0.094 \cdot kg \cdot mol^{-1}$
gas constant:	$R := 8.3143 \cdot J \cdot (mol \cdot (K))^{-1}$
temperature:	$T := 293 \cdot K$
conc. of suspended matter in the river:	$SUSP_{water} := 15 \cdot mg \cdot l^{-1}$
density of the solid phase:	$RHO_{solid} := 2500 \cdot kg \cdot m^{-3}$
volume fraction water in susp. matter:	$Fwater_{susp} := 0.9$
volume fraction solids in susp.matter:	$Fsolid_{susp} := 0.1$
volume fraction of water in sediment:	$Fwater_{sed} := 0.8$
volume fraction of solids in sediment:	$Fsolid_{sed} := 0.2$
volume fraction of air in soil:	$Fair_{soil} := 0.2$
volume fraction of water in soil:	$Fwater_{soil} := 0.2$
volume fraction of solids in soil:	$Fsolid_{soil} := 0.6$
aerobic fraction of the sediment comp.:	$Faer_{sed} := 0.1$
product of CONjunge and $SURF_{air}$:	$product := 10^{-4} \cdot Pa$

distribution air/water: Henry-constant

$$HENRY := \frac{VP \cdot MOLW}{SOL} \qquad HENRY = 0.022 \cdot Pa \cdot m^3 \cdot mol^{-1}$$

$$\log\left(\frac{HENRY}{Pa \cdot m^3 \cdot mol^{-1}}\right) = -1.65$$

$$K_{air\_water} := \frac{HENRY}{R \cdot T} \qquad K_{air\_water} = 9.187 \cdot 10^{-6}$$

solid/water-partition ceefficient Kp_{comp} and total compartment/water-partition coefficient K_{comp_water}

$a := 0.57$ (a,b from chapter 4.3.4, table 4)

$b := 1.08$

$K_{OC} := 10^{a \cdot LOGP_{OW} + b} \cdot l \cdot kg^{-1}$ $K_{OC} = 82.775 \cdot l \cdot kg^{-1}$

Suspended matter

$Kp_{susp} := 0.1 \cdot K_{OC}$ $Kp_{susp} = 8.278 \cdot l \cdot kg^{-1}$

$K_{susp\_water} := Fwater_{susp} + Fsolid_{susp} \cdot Kp_{susp} \cdot RHO_{solid}$ $K_{susp\_water} = 2.969$

factor for the calculation of $Clocal_{water}$:

$faktor := 1 + Kp_{susp} \cdot SUSP_{water}$ $faktor = 1$

Sediment

$Kp_{sed} := 0.1 \cdot K_{OC}$ $Kp_{sed} = 8.278 \cdot l \cdot kg^{-1}$

$K_{sed\_water} := Fwater_{sed} + Fsolid_{sed} \cdot Kp_{sed} \cdot RHO_{solid}$ $K_{sed\_water} = 4.939$

Soil

$Kp_{soil} := 0.02 \cdot K_{OC}$ $Kp_{soil} = 1.656 \cdot l \cdot kg^{-1}$

$K_{soil\_water} := Fair_{soil} \cdot K_{air\_water} + Fwater_{soil} + Fsolid_{soil} \cdot Kp_{soil} \cdot RHO_{solid}$

$K_{soil\_water} = 2.683$

Sludge

$K_{p\_sludge} := 0.37 \cdot K_{OC}$ $K_{p\_sludge} = 30.627 \cdot l \cdot kg^{-1}$

Elimination in STPs

rate constant in STP: k =1 h^{-1} elimination P = f (k, logpow, logH) =87.4 %

fraction directed to surface water $Fstp_{water}$ =12.6 %

biodegradation in different compartments

surface water

$kbio_{water} := 4.7 \cdot 10^{-2} \cdot d^{-1}$ (cTGD, table 5)

$kbio_{water} := 0.05 \cdot d^{-1}$ (using experimental value for $kbio_{water}$)

soil

$DT50bio_{soil} := 30 \cdot d$ $kbio_{soil} := \frac{\ln(2)}{DT50bio_{soil}}$ $kbio_{soil} = 0.023 \cdot d^{-1}$ (cTGD, table 6)

$kbio_{soil} := 0.1 \cdot d^{-1}$ (using experimental value for $kbio_{soil}$)

sediment

$kbio_{sed} := \frac{\ln(2)}{DT50bio_{soil}} \cdot Faer_{sed}$ $kbio_{sed} = 2.31 \cdot 10^{-3} \cdot d^{-1}$

$kbio_{sed} := kbio_{soil} \cdot Faer_{sed}$ $kbio_{sed} = 0.01 \cdot d^{-1}$ (using experimental value for $kbio_{soil}$)

degradation in surface waters

$khydr_{water} := 1.1 \cdot 10^{-10} \cdot d^{-1}$

$kphoto_{water} := 3.6 \cdot 10^{-4} \cdot d^{-1}$ (mean experimental value)

$kdeg_{water} := khydr_{water} + kphoto_{water} + kbio_{water}$

$kdeg_{water} = 0.05 \cdot d^{-1}$

Atmosphere

calculation of CONjunge * SURFaer for the OPS-model

$VPL := \frac{VP}{\exp\left[6.79 \cdot \left(1 - \frac{MP}{285 \cdot K}\right)\right]}$ $VP := wenn(MP > 285 \cdot K, VPL, VP)$ $VP = 39.816 \cdot Pa$

$Fass_{aer} := \frac{product}{VP + product}$

$Fass_{aer} = 2.512 \cdot 10^{-6}$

degradation in the atmosphere

$kdeg_{air}$ =1 h^{-1} (see RAR)

SimpleTreat 3.0 (debugged version, 7 Feb 97)

input

Characterization of the chemical

Name compound = Phenol **CAS 108-95-2**

Physico-chemical properties			
Molecular weight =	94,11	[1E+02] g mol^{-1}	0,0941 kg mol^{-1}
K_{ow} =	29.51	[1E+03] (-)	29.51 (-)
Vapour pressure =	2,00E+01	[1E+00] Pa	20 Pa
Solubility =	8,40E+04	[1E+02] mg L^{-1}	892,57 mol m^{-3}
K_a =		[1E-20] (-)	1E-20 (-)
K_b =		[1E-20] (-)	1E-20 (-)
Henry constant (H) =		[2E-02] Pa m^3 mol^{-1}	0,022 Pa m^3 mol^{-1}
K_p (raw sewage) =		[9E+00] L kg_{dwt}^{-1}	8,853 L kg_{dwt}^{-1}
K_p (activated sludge) =		[1E+01] L kg_{dwt}^{-1}	10,92 L kg_{dwt}^{-1}

Biodegradation in activated sludge
Temperature dependence (y/n) [n] (-) n
Method 1: estimated from OECD/EU standardized biodegradability tests (USES 2.0)
Assumption: degradation according to first order kinetics with respect to the concentration in the aqueous phase of activated sludge, implying that the chemical adsorbed to solids is not available for biodegradation.
The following values are recommended:
Readily biodegradable, fulfilling 10 d window criterion: range is 1 to 3 hr^{-1} (TGD-EU: 1 hr^{-1})
Readily biodegradable, not fulfilling 10 d window criterion: range is 0.3 to 1 hr^{-1} (TGD-EU: 0.3 hr^{-1})
Inherently biodegradable in MITI II and within 10 d in the Zahn-Wellens (window = 3 d): range is 0.1 to 0.3 hr^{-1}
Inherently biodegradable: range is 0 .01 to 0.1 hr^{-1} (TGD-EU: 0.1 hr^{-1}) k biodeg1 =1[0]hr^{-1} 0,0003 s^{-1} ,T water =15C

output of SimpleTreat 3.0 (debugged version, 7 Feb 97) **report of Phenol** **including primary sedimentation**	
Elimination in the primary settler volatilization via primary sludge	 0,0 0,3
total	0,3%
Elimination in the aerator stripping biodegradation	 0,0 87,1
total	87,1%
Elimination in the solids liquid separator volatilization via surplus sludge	 0,0 0,0
total	0,0%
Total elimination from waste water Total emission via effluent	87,4% 12,6%------V 12,62% diss. 0,00% ass.
100,0	100,0%

Appendix B $Clocal_{air}$ calculation for Table 3.12

Atmosphere (OPS-model)

Calculation of Clocal $_{air}$ and PEC local $_{air}$

substance: phenol CAS-Nr.: 108-95-2

stage of life cycle: processing at Pc12

$d := 86400 \cdot s$

$a := 365 \cdot d$

$mg := 1 \cdot 10^{-6} \cdot kg$

tonnage for specific scenario: $TONNAGE := 200000 \cdot tonne \cdot a^{-1}$

release factor (TGD default): $f_{emission} := 0.001$

fraction of main source (one site): $Fmainsource := 1$

days of use per year (TGD default): $Temission := 300 \cdot d \cdot a^{-1}$

release during life cycle to air: $RELEASE := TONNAGE \cdot f_{emission}$

$RELEASE = 200 \cdot tonne \cdot a^{-1}$

local emission during episode to air: $Elocal_{air} := \frac{Fmainsource \cdot RELEASE}{Temission}$

$Elocal_{air} = 666.667 \cdot kg \cdot d^{-1}$

concentration in air at source strength of 1kg/d: $Cstd_{air} := 2.78 \cdot 10^{-4} \cdot mg \cdot m^{-3} \cdot kg^{-1} \cdot d$

fraction of the emission to air from STP (SIMPLETREAT): $Fstp_{air} := 0.0 \cdot \%$

local emission rate to water during emission episode: $Elocal_{water} := 66.67 \cdot kg \cdot d^{-1}$

local emission to air from STP during emission episode: $Estp_{air} := Fstp_{air} \cdot Elocal_{water}$

$Estp_{air} = 0 \cdot kg \cdot d^{-1}$

local concentation in air during emission episode: $Clocal_{air} := wenn\left(Elocal_{air} > Estp_{air}, Elocal_{air} \cdot Cstd_{air}, Estp_{air} \cdot Cstd_{air}\right)$

$Clocal_{air} = 0.185 \cdot mg \cdot m^{-3}$

annual average concentration in air, 100m from point source: $Clocal_{air\_ann} := Clocal_{air} \cdot \frac{Temission}{365 \cdot d \cdot a^{-1}}$

$Clocal_{air\_ann} = 0.152 \cdot mg \cdot m^{-3}$

regional concentration in air: $PECregional_{air} := 0.000026 \cdot mg \cdot m^{-3}$

annual average predicted environmental concentration in air: $PEClocal_{air\_ann} := Clocal_{air\_ann} + PECregional_{air}$

$PEClocal_{air\_ann} = 0.152 \cdot mg \cdot m^{-3}$

Calculation of the deposition rate

standard deposition flux of aerosol-bound compounds at a source strength of 1kg/d

$$DEPstd_{aer} := 1 \cdot 10^{-2} \cdot mg \cdot m^{-2} \cdot d^{-1} \cdot kg^{-1} \cdot d$$

fraction of the chemical bound to aerosol (see: Distribution and Fate)

$$Fass_{aer} := 2.512 \cdot 10^{-6}$$

deposition flux of gaseous compounds as a function of Henry`s Law coefficient,at a source strength of 1kg/d

logH<-2	5*10 $^{-4}$ mg*m^{-2}*d^{-1}
-2<logH<2	4*10^{-4} mg*m^{-2}*d^{-1}
logH>2	3*10^{-4} mg*m^{-2}*d^{-1}

$$DEPstd_{gas} := 4 \cdot 10^{-4} \cdot mg \cdot m^{-2} \cdot d^{-1} \cdot kg^{-1} \cdot d$$

total deposition flux during emission episode

$$DEPtotal := \left(Elocal_{air} + Estp_{air}\right) \cdot \left[Fass_{aer} \cdot DEPstd_{aer} + \left(1 - Fass_{aer}\right) \cdot DEPstd_{gas}\right]$$

$$DEPtotal = 0.267 \, mg \cdot m^{-2} \cdot d^{-1}$$

annual average total depostion flux

$$DEPtotal_{ann} := DEPtotal \cdot \frac{Temission}{365 \cdot d \cdot a^{-1}}$$

$$DEPtotal_{ann} = 0.219 \, mg \cdot m^{-2} \cdot d^{-1}$$

Atmosphere (OPS-model)

Calculation of Clocal $_{air}$ and PEC local $_{air}$

substance: phenol CAS-Nr.: 108-95-2

stage of life cycle: processing at Pc4

$d := 86400 \cdot s$

$a := 365 \cdot d$

$mg := 1 \cdot 10^{-6} \cdot kg$

tonnage for specific scenario: $TONNAGE := 116631 \cdot tonne \cdot a^{-1}$

release factor (TGD default): $f_{emission} := 0.0000000103$

fraction of main source (one site): $Fmainsource := 1$

days of use per year (TGD default): $Temission := 300 \cdot d \cdot a^{-1}$

release during life cycle to air: $RELEASE := TONNAGE \cdot f_{emission}$

$RELEASE = 1.201 \cdot 10^{-3} \ tonne \cdot a^{-1}$

local emission during episode to air: $Elocal_{air} := \frac{Fmainsource \cdot RELEASE}{Temission}$

$Elocal_{air} = 4.004 \cdot 10^{-3} \ kg \cdot d^{-1}$

concentration in air at source strength of 1kg/d: $Cstd_{air} := 2.78 \cdot 10^{-4} \cdot mg \cdot m^{-3} \cdot kg^{-1} \cdot d$

fraction of the emission to air from STP (SIMPLETREAT): $Fstp_{air} := 0.0 \cdot \%$

local emission rate to water during emission episode: $Elocal_{water} := 0.283 \cdot kg \cdot d^{-1}$

local emission to air from STP during emission episode: $Estp_{air} := Fstp_{air} \cdot Elocal_{water}$

$Estp_{air} = 0 \ kg \cdot d^{-1}$

local concentation in air during emission episode: $Clocal_{air} := wenn\left(Elocal_{air} > Estp_{air}, Elocal_{air} \cdot Cstd_{air}, Estp_{air} \cdot Cstd_{air}\right)$

$Clocal_{air} = 1.113 \cdot 10^{-6} \ mg \cdot m^{-3}$

annual average concentration in air, 100m from point source: $Clocal_{air\_ann} := Clocal_{air} \cdot \frac{Temission}{365 \cdot d \cdot a^{-1}}$

$Clocal_{air\_ann} = 9.15 \cdot 10^{-7} \ mg \cdot m^{-3}$

regional concentration in air: $PECregional_{air} := 0.000026 mg \cdot m^{-3}$

annual average predicted environmental concentration in air: $PEClocal_{air\_ann} := Clocal_{air\_ann} + PECregional_{air}$

$PEClocal_{air\_ann} = 2.691 \cdot 10^{-5} \ mg \cdot m^{-3}$

Calculation of the deposition rate

standard deposition flux of aerosol-bound compounds at a source strength of 1kg/d

$$DEPstd_{aer} := 1 \cdot 10^{-2} \cdot mg \cdot m^{-2} \cdot d^{-1} \cdot kg^{-1} \cdot d$$

fraction of the chemical bound to aerosol (see: Distribution and Fate)

$$Fass_{aer} := 2.512 \cdot 10^{-6}$$

deposition flux of gaseous compounds as a function of Henry`s Law coefficient,at a source strength of 1kg/d

logH<-2	5*10 $^{-4}$ mg*m^{-2}*d^{-1}
-2<logH<2	4*10^{-4} mg*m^{-2}*d^{-1}
logH>2	3*10^{-4} mg*m^{-2}*d^{-1}

$$DEPstd_{gas} := 4 \cdot 10^{-4} \cdot mg \cdot m^{-2} \cdot d^{-1} \cdot kg^{-1} \cdot d$$

total deposition flux during emission episode

$$DEPtotal := \left(Elocal_{air} + Estp_{air}\right) \cdot \left[Fass_{aer} \cdot DEPstd_{aer} + \left(1 - Fass_{aer}\right) \cdot DEPstd_{gas}\right]$$

$$DEPtotal = 1.602 \cdot 10^{-6} \ mg \cdot m^{-2} \cdot d^{-1}$$

annual average total depostion flux

$$DEPtotal_{ann} := DEPtotal \cdot \frac{Temission}{365 \cdot d \cdot a^{-1}}$$

$$DEPtotal_{ann} = 1.317 \cdot 10^{-6} \ mg \cdot m^{-2} \cdot d^{-1}$$

Atmosphere (OPS-model)

Calculation of Clocal$_{air}$ and PEC local $_{air}$

substance: phenol CAS-Nr.: 108-95-2

stage of life cycle: production at P3

$d := 86400s$

$a := 365 \cdot d$

$mg := 1 \cdot 10^{-6} \cdot kg$

tonnage for specific scenario: $TONNAGE := 100000 tonne \cdot a^{-1}$

release factor (TGD default): $f_{emission} := 0.0001$

fraction of main source (one site): $Fmainsource := 1$

days of use per year (TGD default): $Temission := 300 \cdot d \cdot a^{-1}$

release during life cycle to air: $RELEASE := TONNAGE \cdot f_{emission}$

$RELEASE = 10 \cdot tonne \cdot a^{-1}$

local emission during episode to air: $Elocal_{air} := \frac{Fmainsource \cdot RELEASE}{Temission}$

$Elocal_{air} = 33.333 \cdot kg \cdot d^{-1}$

concentration in air at source strength of 1kg/d: $Cstd_{air} := 2.78 \cdot 10^{-4} \cdot mg \cdot m^{-3} \cdot kg^{-1} \cdot d$

fraction of the emission to air from STP (SIMPLETREAT): $Fstp_{air} := 0.0 \cdot \%$

local emission rate to water during emission episode: $Elocal_{water} := 1.59 \cdot kg \cdot d^{-1}$

local emission to air from STP during emission episode: $Estp_{air} := Fstp_{air} \cdot Elocal_{water}$

$Estp_{air} = 0 \cdot kg \cdot d^{-1}$

local concentation in air during emission episode: $Clocal_{air} := wenn\left(Elocal_{air} > Estp_{air}, Elocal_{air} \cdot Cstd_{air}, Estp_{air} \cdot Cstd_{air}\right)$

$Clocal_{air} = 9.267 \cdot 10^{-3} \cdot mg \cdot m^{-3}$

annual average concentration in air, 100m from point source: $Clocal_{air\_ann} := Clocal_{air} \cdot \frac{Temission}{365 \cdot d \cdot a^{-1}}$

$Clocal_{air\_ann} = 7.616 \cdot 10^{-3} \cdot mg \cdot m^{-3}$

regional concentration in air: $PECregional_{air} := 0.000026 mg \cdot m^{-3}$

annual average predicted environmental concentration in air: $PEClocal_{air\_ann} := Clocal_{air\_ann} + PECregional_{air}$

$PEClocal_{air\_ann} = 7.642 \cdot 10^{-3} \cdot mg \cdot m^{-3}$

Calculation of the deposition rate

standard deposition flux of aerosol-bound compounds at a source strength of 1kg/d

$$DEPstd_{aer} := 1 \cdot 10^{-2} \cdot mg \cdot m^{-2} \cdot d^{-1} \cdot kg^{-1} \cdot d$$

fraction of the chemical bound to aerosol (see: Distribution and Fate)

$$Fass_{aer} := 2.512 \cdot 10^{-6}$$

deposition flux of gaseous compounds as a function of Henry`s Law coefficient,at a source strength of 1kg/d

logH<-2	5*10 $^{-4}$ mg*m^{-2}*d^{-1}
-2<logH<2	4*10^{-4} mg*m^{-2}*d^{-1}
logH>2	3*10^{-4} mg*m^{-2}*d^{-1}

$$DEPstd_{gas} := 4 \cdot 10^{-4} \cdot mg \cdot m^{-2} \cdot d^{-1} \cdot kg^{-1} \cdot d$$

total deposition flux during emission episode

$$DEPtotal := \left(Elocal_{air} + Estp_{air}\right) \cdot \left[Fass_{aer} \cdot DEPstd_{aer} + \left(1 - Fass_{aer}\right) \cdot DEPstd_{gas}\right]$$

$$DEPtotal = 0.013 \, mg \cdot m^{-2} \cdot d^{-1}$$

annual average total depostion flux

$$DEPtotal_{ann} := DEPtotal \cdot \frac{Temission}{365 \cdot d \cdot a^{-1}}$$

$$DEPtotal_{ann} = 0.011 \, mg \cdot m^{-2} \cdot d^{-1}$$

Atmosphere (OPS-model)

Calculation of $Clocal_{air}$ and $PEC\ local_{air}$

substance: phenol CAS-Nr.: 108-95-2

stage of life cycle: processing at Pc19

$d := 86400 \cdot s$

$a := 365 \cdot d$

$mg := 1 \cdot 10^{-6} \cdot kg$

tonnage for specific scenario: $TONNAGE := 24000 \cdot tonne \cdot a^{-1}$

release factor (TGD default): $f_{emission} := 0.001$

fraction of main source (one site): $Fmainsource := 1$

days of use per year (TGD default): $Temission := 300 \cdot d \cdot a^{-1}$

release during life cycle to air: $RELEASE := TONNAGE \cdot f_{emission}$

$RELEASE = 24 \cdot tonne \cdot a^{-1}$

local emission during episode to air: $Elocal_{air} := \frac{Fmainsource \cdot RELEASE}{Temission}$

$Elocal_{air} = 80 \cdot kg \cdot d^{-1}$

concentration in air at source strength of 1kg/d: $Cstd_{air} := 2.78 \cdot 10^{-4} \cdot mg \cdot m^{-3} \cdot kg^{-1} \cdot d$

fraction of the emission to air from STP (SIMPLETREAT): $Fstp_{air} := 0.0 \cdot \%$

local emission rate to water during emission episode: $Elocal_{water} := 0.0 \cdot kg \cdot d^{-1}$

local emission to air from STP during emission episode: $Estp_{air} := Fstp_{air} \cdot Elocal_{water}$

$Estp_{air} = 0 \cdot kg \cdot d^{-1}$

local concentation in air during emission episode: $Clocal_{air} := wenn\left(Elocal_{air} > Estp_{air}, Elocal_{air} \cdot Cstd_{air}, Estp_{air} \cdot Cstd_{air}\right)$

$Clocal_{air} = 0.022 \cdot mg \cdot m^{-3}$

annual average concentration in air, 100m from point source: $Clocal_{air\_ann} := Clocal_{air} \cdot \frac{Temission}{365 \cdot d \cdot a^{-1}}$

$Clocal_{air\_ann} = 0.018 \cdot mg \cdot m^{-3}$

regional concentration in air: $PECregional_{air} := 0.000026 mg \cdot m^{-3}$

annual average predicted environmental concentration in air: $PEClocal_{air\_ann} := Clocal_{air\_ann} + PECregional_{air}$

$PEClocal_{air\_ann} = 0.018 \cdot mg \cdot m^{-3}$

Calculation of the deposition rate

standard deposition flux of aerosol-bound compounds at a source strength of 1kg/d

$$DEPstd_{aer} := 1 \cdot 10^{-2} \cdot mg \cdot m^{-2} \cdot d^{-1} \cdot kg^{-1} \cdot d$$

fraction of the chemical bound to aerosol (see: Distribution and Fate)

$$Fass_{aer} := 2.512 \cdot 10^{-6}$$

deposition flux of gaseous compounds as a function of Henry`s Law coefficient,at a source strength of 1kg/d

logH<-2	5*10 $^{-4}$ mg*m^{-2}*d^{-1}
-2<logH<2	4*10^{-4} mg*m^{-2}*d^{-1}
logH>2	3*10^{-4} mg*m^{-2}*d^{-1}

$$DEPstd_{gas} := 4 \cdot 10^{-4} \cdot mg \cdot m^{-2} \cdot d^{-1} \cdot kg^{-1} \cdot d$$

total deposition flux during emission episode

$$DEPtotal := \left(Elocal_{air} + Estp_{air}\right) \cdot \left[Fass_{aer} \cdot DEPstd_{aer} + \left(1 - Fass_{aer}\right) \cdot DEPstd_{gas}\right]$$

$$DEPtotal = 0.032 \, mg \cdot m^{-2} \cdot d^{-1}$$

annual average total depostion flux

$$DEPtotal_{ann} := DEPtotal \cdot \frac{Temission}{365 \cdot d \cdot a^{-1}}$$

$$DEPtotal_{ann} = 0.026 \, mg \cdot m^{-2} \cdot d^{-1}$$

Appendix C Clocal$_{soil}$ calculation for site Pc19 with and without application of sewage sludge

Exposure of Soil

$d := 86400 \cdot s$

$ppm := mg \cdot kg^{-1}$ $a := 365 \cdot d$

$i := 1..3$

chemical : Phenol CAS-Nr.: 108-95-2
90 percentile of the local concentrations from table 3.11 at site Pc19 with sludge appl.

annual average total deposition flux:

$DEPtotal_{ann} := 0.026 \cdot mg \cdot m^{-2} \cdot d^{-1}$

soil-water partitioning coefficient:

$K_{soil\_water} := 2.683$

concentration in dry sewage sludge:

$C_{sludge} := 1.69 \cdot mg \cdot kg^{-1}$

air-water partitioning coefficient:

$K_{air\_water} := 0.0000092$

rate constant for for removal from top soil:

$kbio_{soil} := 0.1 \cdot d^{-1}$

PECregional:

$PECregional_{natural\_soil} := 5.92 \cdot 10^{-4} \cdot mg \cdot kg^{-1}$

Defaults:

mixing depth of soil:

$DEPTHsoil_i :=$

0.2·m
0.2·m
0.1·m

bulk density of soil:

$RHO_{soil} := 1700 \cdot kg \cdot m^{-3}$

average time for exposure:

$T_i :=$

30·d
180·d
180·d

partial mass transfer coefficient at air-side of the air-soil interface:

$kasl_{air} := 120 \cdot m \cdot d^{-1}$

partial mass transfer coefficient at soilair-side of the air-soil interface:

$kasl_{soilair} := 0.48 \cdot m \cdot d^{-1}$

partial mass transfer coefficient at soilwater-side of the air-soil interface:

$kasl_{soilwater} := 4.8 \cdot 10^{-5} \cdot m \cdot d^{-1}$

fraction of rain water that infiltrates into soil:

$Finf_{soil} := 0.25$

rate of wet precipitation:

$RAINrate := 1.92 \cdot 10^{-3} \cdot m \cdot d^{-1}$

dry sludge application rate:

$$APPLsludge_i :=$$

$0.5 \cdot kg \cdot m^{-2} \cdot a^{-1}$
$0.5 \cdot kg \cdot m^{-2} \cdot a^{-1}$
$0.1 \cdot kg \cdot m^{-2} \cdot a^{-1}$

Calculation:

aerial deposition flux per kg of soil:

$$D_{air_i} := \frac{DEPtotal_{ann}}{DEPTHsoil_i \cdot RHO_{soil}}$$

rate constant for valatilisation from soil:

$$k_{volat_i} := \left[\left(\frac{1}{kasl_{air} \cdot K_{air\_water}} + \frac{1}{kasl_{soilair} \cdot K_{air\_water} + kasl_{soilwater}} \right) \cdot K_{soil\_water} \cdot DEPTHsoil_i \right]^{-1}$$

rate constant for leaching from soil layer:

$$k_{leach_i} := \frac{Finf_{soil} \cdot RAINrate}{K_{soil\_water} \cdot DEPTHsoil_i}$$

removal from top soil:

$$k_i := k_{volat_i} + k_{leach_i} + kbio_{soil}$$

concentration in soil

concentration in soil due to 10 years of continuous deposition:

$$Cdep_{soil\_10_i} := \frac{D_{air_i}}{k_i} \cdot \left(1 - \exp\left(-365 \cdot d \cdot 10 \cdot k_i\right)\right)$$

concentration just after the first year of sludge application:

$$Csludge_{soil\_1_i} := \frac{C_{sludge} \cdot APPLsludge_i \cdot a}{DEPTHsoil_i \cdot RHO_{soil}}$$

initial concentration in soil after 10 applications of sludge:

$$Csludge_{soil\_10_i} := Csludge_{soil\_1_i} \cdot \left[1 + \left[\sum_{n=1}^{9} \left(\exp\left(-365 \cdot d \cdot k_i\right)^n \right) \right] \right]$$

sum of the concentrations due to both processes:

$$C_{soil\_10_i} := Cdep_{soil\_10_i} + Csludge_{soil\_10_i}$$

average concentration in soil over T days:

$$Clocal_{soil_i} := \frac{D_{air_i}}{k_i} + \frac{1}{k_i \cdot T_i} \cdot \left(C_{soil\_10_i} - \frac{D_{air_i}}{k_i} \right) \cdot \left(1 - \exp\left(-k_i \cdot T_i \right) \right)$$

$$PEClocal_{soil_i} := Clocal_{soil_i} + PECregional_{natural\_soil}$$

	$\frac{Clocal_{soil_i}}{ppm}$
$Clocal_{soil}$ =	$1.538 \cdot 10^{-3}$
$Clocal_{agr.soil}$ =	$8.939 \cdot 10^{-4}$
$Clocal_{grassland}$ =	$1.554 \cdot 10^{-3}$

	$\frac{PEClocal_{soil_i}}{ppm}$
$PEClocal_{soil}$ =	$2.13 \cdot 10^{-3}$
$PEClocal_{agr.soil}$ =	$1.486 \cdot 10^{-3}$
$PEClocal_{grassland}$ =	$2.146 \cdot 10^{-3}$

Indicating persistency of the substance in soil

initial concentration after 10 years:

$\frac{C_{soil\_10_i}}{ppm}$
$3.243 \cdot 10^{-3}$
$3.243 \cdot 10^{-3}$
$2.494 \cdot 10^{-3}$

initial concentration in steady-state situation:

$$Facc_i := e^{-365 \cdot d \cdot k_i}$$

$$C_{soil\_ss_i} := \frac{D_{air_i}}{k_i} + Csludge_{soil\_1_i} \cdot \frac{1}{1 - Facc_i}$$

$\frac{C_{soil\_ss_i}}{ppm}$
$3.243 \cdot 10^{-3}$
$3.243 \cdot 10^{-3}$
$2.494 \cdot 10^{-3}$

fraction of steady-state in soil achieved:

$$Fst\_st_i := \frac{C_{soil\_10_i}}{C_{soil\_ss_i}}$$

Fst_st_i
1
1
1

concentration in pore water

$$Clocal_{soil\_porew_i} := \frac{Clocal_{soil_i} \cdot RHO_{soil}}{K_{soil\_water}}$$

	$Clocal_{soil\_porew_i}$ / mg·l^{-1}
$Clocal_{soil\_porew}$ =	$9.74446 \cdot 10^{-4}$
$Clocal_{agr.soil\_porew}$ =	$5.66422 \cdot 10^{-4}$
$Clocal_{grassland\_porew}$ =	$9.84607 \cdot 10^{-4}$

$$PEClocal_{soil\_porew_i} := \frac{PEClocal_{soil_i} \cdot RHO_{soil}}{K_{soil\_water}}$$

	$PEClocal_{soil\_porew_i}$ / mg·l^{-1}
$PEClocal_{soil\_porew}$ =	$1.34955 \cdot 10^{-3}$
$PEClocal_{agr.soil\_porew}$ =	$9.41525 \cdot 10^{-4}$
$PEClocal_{grassland\_porew}$ =	$1.35971 \cdot 10^{-3}$

concentration in ground water

$PEClocal_{grw} = PEClocal_{agr\_soil\_porew}$

Exposure of Soil

$d := 86400 \cdot s$

$ppm := mg \cdot kg^{-1}$ $a := 365 \cdot d$

$i := 1..3$

chemical : Phenol CAS-Nr.: 108-95-2
90 percentile of the local concentrations from table 3.11 at site Pc19 without sludge appl.

annual average total deposition flux:

$DEPtotal_{ann} := 0.026 \cdot mg \cdot m^{-2} \cdot d^{-1}$

soil-water partitioning coefficient:

$K_{soil\_water} := 2.683$

concentration in dry sewage sludge:

$C_{sludge} := 0 \cdot mg \cdot kg^{-1}$

air-water partitioning coefficient:

$K_{air\_water} := 0.0000092$

rate constant for for removal from top soil:

$kbio_{soil} := 0.1 \cdot d^{-1}$

PECregional:

$PECregional_{natural\_soil} := 5.92 \cdot 10^{-4} \cdot mg \cdot kg^{-1}$

Defaults:

mixing depth of soil:

$DEPTHsoil_i :=$

$0.2 \cdot m$
$0.2 \cdot m$
$0.1 \cdot m$

bulk density of soil:

$RHO_{soil} := 1700 \cdot kg \cdot m^{-3}$

average time for exposure:

$T_i :=$

$30 \cdot d$
$180 \cdot d$
$180 \cdot d$

partial mass transfer coefficient at air-side of the air-soil interface:

$kasl_{air} := 120 \cdot m \cdot d^{-1}$

partial mass transfer coefficient at soilair-side of the air-soil interface:

$kasl_{soilair} := 0.48 \cdot m \cdot d^{-1}$

partial mass transfer coefficient at soilwater-side of the air-soil interface:

$kasl_{soilwater} := 4.8 \cdot 10^{-5} \cdot m \cdot d^{-1}$

fraction of rain water that infiltrates into soil:

$Finf_{soil} := 0.25$

rate of wet precipitation:

$RAINrate := 1.92 \cdot 10^{-3} \cdot m \cdot d^{-1}$

dry sludge application rate:

$$APPLsludge_i :=$$

$0.5 \cdot kg \cdot m^{-2} \cdot a^{-1}$
$0.5 \cdot kg \cdot m^{-2} \cdot a^{-1}$
$0.1 \cdot kg \cdot m^{-2} \cdot a^{-1}$

Calculation:

aerial deposition flux per kg of soil:

$$D_{air_i} := \frac{DEPtotal_{ann}}{DEPTHsoil_i \cdot RHO_{soil}}$$

rate constant for valatilisation from soil:

$$k_{volat_i} := \left[\left(\frac{1}{kasl_{air} \cdot K_{air\_water}} + \frac{1}{kasl_{soilair} \cdot K_{air\_water} + kasl_{soilwater}} \right) \cdot K_{soil\_water} \cdot DEPTHsoil_i \right]^{-1}$$

rate constant for leaching from soil layer:

$$k_{leach_i} := \frac{Finf_{soil} \cdot RAINrate}{K_{soil\_water} \cdot DEPTHsoil_i}$$

removal from top soil:

$$k_i := k_{volat_i} + k_{leach_i} + kbio_{soil}$$

concentration in soil

concentration in soil due to 10 years of continuous deposition:

$$Cdep_{soil\_10_i} := \frac{D_{air_i}}{k_i} \cdot \left(1 - \exp\left(-365 \cdot d \cdot 10 \cdot k_i\right)\right)$$

concentration just after the first year of sludge application:

$$Csludge_{soil\_1_i} := \frac{C_{sludge} \cdot APPLsludge_i \cdot a}{DEPTHsoil_i \cdot RHO_{soil}}$$

initial concentration in soil after 10 applications of sludge:

$$Csludge_{soil\_10_i} := Csludge_{soil\_1_i} \cdot \left[1 + \left[\sum_{n=1}^{9} \left(\exp\left(-365 \cdot d \cdot k_i\right)^n \right) \right] \right]$$

sum of the concentrations due to both processes:

$$C_{soil\_10_i} := Cdep_{soil\_10_i} + Csludge_{soil\_10_i}$$

average concentration in soil over T days:

$$Clocal_{soil_i} := \frac{D_{air_i}}{k_i} + \frac{1}{k_i \cdot T_i} \cdot \left(C_{soil\_10_i} - \frac{D_{air_i}}{k_i} \right) \cdot \left(1 - \exp\left(-k_i \cdot T_i \right) \right)$$

$$PEClocal_{soil_i} := Clocal_{soil_i} + PECregional_{natural\_soil}$$

	$\frac{Clocal_{soil_i}}{ppm}$		$\frac{PEClocal_{soil_i}}{ppm}$
$Clocal_{soil}$ =	$7.572 \cdot 10^{-4}$	$PEClocal_{soil}$ =	$1.349 \cdot 10^{-3}$
$Clocal_{agr.soil}$ =	$7.572 \cdot 10^{-4}$	$PEClocal_{agr.soil}$ =	$1.349 \cdot 10^{-3}$
$Clocal_{grassland}$ =	$1.5 \cdot 10^{-3}$	$PEClocal_{grassland}$ =	$2.092 \cdot 10^{-3}$

Indicating persistency of the substance in soil

initial concentration after 10 years:

$\frac{C_{soil\_10_i}}{ppm}$
$7.572 \cdot 10^{-4}$
$7.572 \cdot 10^{-4}$
$1.5 \cdot 10^{-3}$

initial concentration in steady-state situation:

$$Facc_i := e^{-365 \cdot d \cdot k_i}$$

$$C_{soil\_ss_i} := \frac{D_{air_i}}{k_i} + Csludge_{soil\_1_i} \cdot \frac{1}{1 - Facc_i}$$

$\frac{C_{soil\_ss_i}}{ppm}$
$7.572 \cdot 10^{-4}$
$7.572 \cdot 10^{-4}$
$1.5 \cdot 10^{-3}$

fraction of steady-state in soil achieved:

$$Fst\_st_i := \frac{C_{soil\_10_i}}{C_{soil\_ss_i}}$$

Fst_st_i
1
1
1

concentration in pore water

$$Clocal_{soil\_porew_i} := \frac{Clocal_{soil_i} \cdot RHO_{soil}}{K_{soil\_water}}$$

	$Clocal_{soil\_porew_i}$ / mg·l^{-1}
$Clocal_{soil\_porew}$ =	$4.7979 \cdot 10^{-4}$
$Clocal_{agr.soil\_porew}$ =	$4.7979 \cdot 10^{-4}$
$Clocal_{grassland\_porew}$ =	$9.5029 \cdot 10^{-4}$

$$PEClocal_{soil\_porew_i} := \frac{PEClocal_{soil_i} \cdot RHO_{soil}}{K_{soil\_water}}$$

	$PEClocal_{soil\_porew_i}$ / mg·l^{-1}
$PEClocal_{soil\_porew}$ =	$8.5489 \cdot 10^{-4}$
$PEClocal_{agr.soil\_porew}$ =	$8.5489 \cdot 10^{-4}$
$PEClocal_{grassland\_porew}$ =	$1.3253 \cdot 10^{-3}$

concentration in ground water

$PEClocal_{grw} = PEClocal_{agr\_soil\_porew}$

Appendix D Regional Exposure Calculation (SimpleBox2.0a)

SimpleBox2.0a - calculation of continental and regional PEC's			
- adaptation to TGD (1996) / EUSES 1.00			
INPUT - Phenol			
Parameter names acc. SimpleBox20	**Unit**	**Input**	**Parameter names according Euses**
Physicochemical properties			
COMPOUND NAME	[-]	Phenol	Substance
MOL WEIGHT	[g.mol^{-1}]	94.11	Molecular weight
MELTING POINT	[° C]	40.9	Melting Point
VAPOR PRESSURE(25)	[Pa]	20	Vapour pressure at 25°C
log Kow	[log10]	1.47	Octanol-water partition coefficient
SOLUBILITY(25)	[mg.l^{-1}]	84000	Water solubility
Distribution - Partition coefficients			
- Solids water partitioning (derived from K_{oc})			
Kp(soil)	[l.kg$_d^{-1}$]	1.66	Solids-water partitioning in soil
Kp(sed)	[l.kg$_d^{-1}$]	8.28	Solids-water partitioning in sediment
Kp(susp)	[l.kg$_d^{-1}$]	8.28	Solids-water partitioning in sudpended matter
- Biota-water			
BCF(fish)	[l.kg$_w^{-1}$]	17.5	Biocentration factor for aquatic biota
Degradation and Transfromation rates			
- Characterisation and STP			
PASSreadytest	[y / n]	Y	Characterization of biodegradability
- Environmental Total Degradation			
kdeg(air)	[d^{-1}]	2.40E+01	Rate constant for degradation in air
kdeg(water)	[d^{-1}]	5.00E-02	Rate constant for degradation in bulk surface water
kdeg(soil)	[d^{-1}]	1.00E-01	Rate constant for degradation in bulk soil
kdeg(sed)	[d^{-1}]	1.00E-02	Rate constant for degradation in bulk sediment
Sewage treatment (e.g. calculated by SimpleTreat)			
- Continental			
FR(volatstp) [C]	[-]	0,00E+00	Fraction of emission directed to air (STPcont)
FR(effstp) [C]		1,26E-01	Fraction of emission directed to water (STPcont)
FR(sludgestp) [C]	[-]	3,00E-03	Fraction of emission directed to sludge (STPcont)
- Regional			
FR(volatstp) [R]	[-]	0,00E+00	Fraction of emission directed to air (STPreg)
FR(effstp) [R]		1,26E-01	Fraction of emission directed to water (STPreg)
FR(sludgestp) [R]	[-]	3,00E-03	Fraction of emission directed to sludge (STPreg)

Release estimation			
- Continental			
Edirect(air) [C]	[$t.y^{-1}$]	87146.5	Total continental emission to air
STPload [C]	[$t.y^{-1}$]	4618	Total continental emission to wastewater
Edirect(water1) [C]	[$t.y^{-1}$]	1458	Total continental emission to surface water
Edirect(soil3) [C]	[$t.y^{-1}$]	0	Total continental emission to industrial soil
Edirect(soil2) [C]	[$t.y^{-1}$]	5.1	Total continental emission to agricultural soil
- Regional			
Edirect(air) [R]	[$t.y^{-1}$]	9683	Total regional emission to air
STPload [R]	[$t.y^{-1}$]	513	Total regional emission to wastewater
Edirect(water1) [R]	[$t.y^{-1}$]	162	Total regional emission to surface water
Edirect(soil3) [R]	[$t.y^{-1}$]	0	Total regional emission to industrial soil
Edirect(soil2) [R]	[$t.y^{-1}$]	0.6	Total regional emission to agricultural soil
OUTPUT - Phenol			
Parameter names acc. SimpleBox20	**Unit**	**Output**	**Parameter names according Euses**
Physicochemical properties			
COMPOUND NAME	[-]	Phenol	Substance
Output			
- Continental			
PECsurfacewater (total)	[$mg.l^{-1}$]	3.190E-04	Continental PEC in surface water (total)
PECsurfacewater (dissolved)	[$mg.l^{-1}$]	3.190E-04	Continental PEC in surface water (dissolved)
PECair	[$mg.m^{-3}$]	2.80E-06	Continental PEC in air (total)
PECagr.soil	[$mg.kg_{wwt}^{-1}$]	1.84E-05	Continental PEC in agricultural soil (total)
PECporewater agr.soil	[$mg.l^{-1}$]	1.16E-05	Continental PEC in pore water of agricultural soils
PECnat.soil	[$mg.kg_{wwt}^{-1}$]	6.38E-05	Continental PEC in natural soil (total)
PECind.soil	[$mg.kg_{wwt}^{-1}$]	6.38E-05	Continental PEC in industrial soil (total)
PECsediment	[$mg.kg_{wwt}^{-1}$]	7.84E-04	Continental PEC in sediment (total)
- Regional			
PECsurfacewater (total)	[$mg.l^{-1}$]	2.41E-03	Regional PEC in surface water (total)
PECsurfacewater (dissolved)	[$mg.l^{-1}$]	2.41E-03	Regional PEC in surface water (dissolved)
PECair	[$mg.m^{-3}$]	2.60E-05	Regional PEC in air (total)
PECagr.soil	[$mg.kg_{wwt}^{-1}$]	1.72E-04	Regional PEC in agricultural soil (total)
PECporewater agr.soil	[$mg.l^{-1}$]	1.09E-04	Regional PEC in pore water of agricultural soils
PECnat.soil	[$mg.kg_{wwt}^{-1}$]	5.92E-04	Regional PEC in natural soil (total)
PECind.soil	[$mg.kg_{wwt}^{-1}$]	5.92E-04	Regional PEC in industrial soil (total)
PECsediment	[$mg.kg_{wwt}^{-1}$]	5.83E-03	Regional PEC in sediment (total)

Appendix E Calculation of Indirect Exposure via the Environment

INDIRECT EXPOSURE VIA THE ENVIRONMENT

(TGD On New and Existing Chemicals, chapter 2)

Parameter [Unit]	*Symbol*
Definitions (for the use in this document)	
definition of the unit 'kg$_{bw}$' for body weight	$kg_{bw} := 1 \cdot kg$
definition of the unit 'd' for day	$d := 1 \cdot Tag$
	$scenario := 1..2$
	local := 1 regional := 2
Constants	
gas - constant R	$R := 8.314 \cdot J \cdot K^{-1} \cdot mol^{-1}$
Defaults	
volumefraction air in plant tissue [-]	$Fair_{plant} := 0.3$
volumefraction water in plant tissue [-]	$Fwater_{plant} := 0.65$
volumefraction lipids in plant tissue [-]	$Flipid_{plant} := 0.01$
bulk density of plant tissue [kg$_{wet\ plant}$ *m$_{plant}^{-3}$]	$RHO_{plant} := 700 \cdot kg \cdot m^{-3}$
leaf surface area [m^2]	$AREA_{plant} := 5 \cdot m^2$
conductance (0.001 m*s^{-1}) [m*d^{-1}]	$g_{plant} := 0.001 \cdot m \cdot s^{-1}$
shoot volume [m^3]	$V_{leaf} := 0.002 \cdot m^3$
transpiration stream [m^3*d^{-1}]	$Q_{transp} := 1 \cdot 10^{-3} \cdot m^3 \cdot d^{-1}$
correction exponent for differences between plant lipids and octanol [-]	$b := 0.95$
growth rate constant for dilution by growth [d^{-1}]	$kgrowth_{plant} := 0.035 \cdot d^{-1}$
pseudo-first order rate constant for metabolism in plants [d^{-1}]	$kmetab_{plant} := 0 \cdot d^{-1}$
pseudo-first order rate constant for photolysis in plants [d^{-1}]	$kphoto_{plant} := 0 \cdot d^{-1}$

concentration in meat and milk

daily intake of grass [$kg_{wet\ grass}*d^{-1}$]	$IC_{grass} := 67.6 \cdot kg \cdot d^{-1}$
daily intake of soil [$kg_{wet\ soil}*d^{-1}$]	$IC_{soil} := 0.46 \cdot kg \cdot d^{-1}$
daily intake of air [$m_{air}^3*d^{-1}$]	$IC_{air} := 122 \cdot m^3 \cdot d^{-1}$
daily intake of drinkingwater [$l*d^{-1}$]	$IC_{drw} := 55 \cdot l \cdot d^{-1}$

daily intake for human

daily intake for the several pathways [$kg_{chem}*d^{-1}$] or [$m^{3*}d^{-1}$]	$IH_{drw} := 2 \cdot l \cdot d^{-1}$
	$IH_{fish} := 0.115 \cdot kg \cdot d^{-1}$
	$IH_{stem} := 1.2 \cdot kg \cdot d^{-1}$
	$IH_{root} := 0.384 \cdot kg \cdot d^{-1}$
	$IH_{meat} := 0.301 \cdot kg \cdot d^{-1}$
	$IH_{milk} := 0.561 \cdot kg \cdot d^{-1}$
	$IH_{air} := 20 \cdot m^3 \cdot d^{-1}$
bioavailability through route of intake [-]	$BIO_{inh} := 0.75$
	$BIO_{oral} := 1.0$
average body weight of human [kg]	$BW := 70 \cdot kg_{bw}$

Input

chemical properties

octanol-water partitioning coefficient [-]	$logK_{OW} := 1.47$ $K_{OW} := 10^{logK_{OW}}$
Henry - partitioning coefficient [Pa*m^3*mol^{-1}]	$HENRY := 0.022 \cdot Pa \cdot m^3 \cdot mol^{-1}$
air-water partitioning coefficient [-]	$K_{air\_water} := 0.0000092$
fraction of the chemical associated with aerosol particles [-]	$F_{ass\_aer} := 2.512 \cdot 10^{-6}$
half-life for biodegration in surface water [d]	$DT_{50\_bio\_water} := 14 \cdot d$

environmental concentrations

annual average local PEC in surface water (dissolved) [$mg_{chem} * l_{water}^{-1}$]	$PEClocal_{water\_ann} := 0.0023 \cdot mg \cdot l^{-1}$
annual average local PEC in air (total) [$mg_{chem} * m_{air}^{-3}$]	$PEClocal_{air\_ann} := 0.018 \cdot mg \cdot m^{-3}$
local PEC in grassland (total), averaged over 180 days [$mg_{chem} * kg_{soil}^{-1}$]	$PEClocal_{grassland} := 0.0021 \cdot mg \cdot kg^{-1}$
local PEC in porewater of agriculture soil [$mg_{chem} * l_{porewater}^{-1}$]	$PEClocal_{agr\_soil\_porew} := 0.0009 \cdot mg \cdot l^{-1}$
local PEC in porewater of grassland [$mg_{chem} * l_{porewater}^{-1}$]	$PEClocal_{grassland\_porew} := 0.0013 \cdot mg \cdot l^{-1}$
local PEC in groundwater under agriculture soil [$mg_{chem} * l_{water}^{-1}$]	$PEClocal_{grw} := 0.0009 \cdot mg \cdot l^{-1}$
regional PEC in surface water (dissolved) [$mg_{chem} * l_{water}^{-1}$]	$PECregional_{water} := 0.0024 \cdot mg \cdot l^{-1}$
regional PEC in air (total) [$mg_{chem} * m_{air}^{-3}$]	$PECregional_{air} := 2.6 \cdot 10^{-5} \cdot mg \cdot m^{-3}$
regional PEC in agriculture soil (total) [$mg_{chem}*kg_{soil}^{-1}$	$PECregional_{agr\_soil} := 1.72 \cdot 10^{-4} \cdot mg \cdot kg^{-1}$
regional PEC in porewater of agriculture soils [$mg_{chem}*l_{water}^{-1}$	$PECregional_{agr\_soil\_porew} := 1.1 \cdot 10^{-4} \cdot mg \cdot l^{-1}$

Definition of the concentrations used for indirect exposure

$C_{water_{local}} := PEClocal_{water\_ann}$ $C_{water_{regional}} := PECregional_{water}$

$C_{air_{local}} := PEClocal_{air\_ann}$ $C_{air_{regional}} := PECregional_{air}$

$C_{grassland_{local}} := PEClocal_{grassland}$ $C_{grassland_{regional}} := PECregional_{agr\_soil}$

$C_{agr\_porew_{local}} := PEClocal_{agr\_soil\_porew}$ $C_{agr\_porew_{regional}} := PECregional_{agr\_soil\_porew}$

$C_{grass\_porew_{local}} := PEClocal_{grassland\_porew}$ $C_{grass\_porew_{regional}} := PECregional_{agr\_soil\_porew}$

$C_{grw_{local}} := PEClocal_{grw}$ $C_{grw_{regional}} := PECregional_{agr\_soil\_porew}$

bioconcentration in fish

bioconcentration factor for fish
[$m_{water}^3 * kg_{chem}^{-1}$]

$$BCF_{fish} := 10^{0.85 \cdot \log K_{OW} - 0.7} \cdot l \cdot kg^{-1}$$

modified equation for logKow > 6

$$BCF_{fish} := wenn\left[\log K_{OW} > 6, \left[-0.278 \cdot \left(\log K_{OW}\right)^2 + 3.38 \cdot \log K_{OW} - 5.94\right] \cdot l \cdot kg^{-1}, BCF_{fish}\right]$$

$$C_{fish_{scenario}} := BCF_{fish} \cdot C_{water_{scenario}}$$

bioconcentration in plants

$$K_{plant\_water} := Fwater_{plant} + Flipid_{plant} \cdot K_{OW}^{b}$$

$$Croot_{agr\_plant_{scenario}} := \frac{K_{plant\_water} \cdot C_{agr\_porew_{scenario}}}{RHO_{plant}}$$

$$TSCF := 0.784 \cdot e^{\frac{-\left(\log K_{OW} - 1.78\right)^2}{2.44}}$$

remark: for $\log K_{OW}$ out of the range from -0.5 to 4.5
the TSCF is limited by the values for $\log K_{OW}$ = -0.5 resp. 4.5

$$TSCF := wenn\left(\log K_{OW} < -0.5, 0.903, TSCF\right)$$

$$TSCF := wenn\left(\log K_{OW} > 4.5, 0.832, TSCF\right)$$

$$K_{leaf\_air} := Fair_{plant} + \frac{K_{plant\_water}}{K_{air\_water}}$$

$$kelim_{plant} := kmetab_{plant} + kphoto_{plant}$$

$$\alpha := \frac{AREA_{plant} \cdot g_{plant}}{K_{leaf\_air} \cdot V_{leaf}} + kelim_{plant} + kgrowth_{plant}$$

$$\beta_{agr\_plant_{scenario}} := C_{agr\_porew_{scenario}} \cdot TSCF \cdot \frac{Q_{transp}}{V_{leaf}} + \left(1 - F_{ass\_aer}\right) \cdot C_{air_{scenario}} \cdot g_{plant} \cdot \frac{AREA_{plant}}{V_{leaf}}$$

$$C_{leaf\_crops_{scenario}} := \frac{\beta_{agr\_plant_{scenario}}}{\alpha \cdot RHO_{plant}}$$

$$\beta_{grass\_plant_{scenario}} := C_{grass\_porew_{scenario}} \cdot TSCF \cdot \frac{Q_{transp}}{V_{leaf}} + \left(1 - F_{ass\_aer}\right) \cdot C_{air_{scenario}} \cdot g_{plant} \cdot \frac{AREA_{plant}}{V_{leaf}}$$

$$C_{leaf\_grass_{scenario}} := \frac{\beta_{grass\_plant_{scenario}}}{\alpha \cdot RHO_{plant}}$$

purification of drinking water

system may defined dependent from the aerobic biodegradation

$$system := wenn\left(DT_{50\_bio\_water} < 10 \cdot d, 0, 1\right)$$

select a column on dependence from log K_{OW}

$$FIndex := wenn\left(logK_{OW} < 4, 0, wenn\left(logK_{OW} > 5, 2, 1\right)\right)$$

$$Fpur_{logKow} := \begin{bmatrix} 1 & \frac{1}{4} & \frac{1}{16} \\ 1 & \frac{1}{2} & \frac{1}{4} \end{bmatrix}$$

$$Fpur := \frac{Fpur_{logKow_{system, FIndex}}}{wenn\left(HENRY > 100 \cdot Pa \cdot m^3 \cdot mol^{-1}, 2, 1\right)}$$

$$C_{drw_{scenario}} := wenn\left[C_{grw_{scenario}} > \left(C_{water_{scenario}} \cdot Fpur\right), C_{grw_{scenario}}, C_{water_{scenario}} \cdot Fpur\right]$$

Biotransfer to meat and milk

$$BTF_{meat} := 10^{-7.6 + logK_{OW}} \cdot kg^{-1} \cdot d$$

remark: for $logK_{OW}$ out of the range from 1.5 to 6.5
the BTF_{meat} is limited by the values for $logK_{OW}$ = 1.5 resp. 6.5

$$BTF_{meat} := wenn\left(logK_{OW} < 1.5, 7.943 \cdot 10^{-7} \cdot kg^{-1} \cdot d, BTF_{meat}\right)$$

$$BTF_{meat} := wenn\left(logK_{OW} > 6.5, 0.07943 kg^{-1} \cdot d, BTF_{meat}\right)$$

$$C_{meat_{scenario}} := BTF_{meat} \cdot \left(\begin{array}{l} C_{leaf\_grass_{scenario}} \cdot IC_{grass} + C_{grassland_{scenario}} \cdot IC_{soil} \cdots \\ + C_{air_{scenario}} \cdot IC_{air} + C_{drw_{scenario}} \cdot IC_{drw} \end{array} \right)$$

$$BTF_{milk} := 10^{-8.1 + logK_{OW}} \cdot kg^{-1} \cdot d$$

remark: for $logK_{OW}$ out of the range from 3 to 6.5
the BTF_{milk} is limited by the values for $logK_{OW}$ = 1.5 resp. 6.5

$$BTF_{milk} := wenn\left(logK_{OW} < 3, 7.943 \cdot 10^{-6} \cdot kg^{-1} \cdot d, BTF_{milk}\right)$$

$$BTF_{milk} := wenn\left(logK_{OW} > 6.5, 0.02512 \cdot kg^{-1} \cdot d, BTF_{milk}\right)$$

$$C_{milk_{scenario}} := BTF_{milk} \cdot \left(\begin{array}{l} C_{leaf\_grass_{scenario}} \cdot IC_{grass} + C_{grassland_{scenario}} \cdot IC_{soil} \cdots \\ + C_{air_{scenario}} \cdot IC_{air} + C_{drw_{scenario}} \cdot IC_{drw} \end{array}\right)$$

total daily intake for human

daily dose through intake of several pathways
[$kg_{chem}*kg_{bw}^{-1}*d^{-1}$]

$$DOSE_{drw_{scenario}} := \frac{C_{drw_{scenario}} \cdot IH_{drw}}{BW} \qquad DOSE_{air_{scenario}} := \frac{C_{air_{scenario}} \cdot IH_{air} \cdot BIO_{inh}}{BW \cdot BIO_{oral}}$$

$$DOSE_{stem_{scenario}} := \frac{C_{leaf\_crops_{scenario}} \cdot IH_{stem}}{BW} \qquad DOSE_{root_{scenario}} := \frac{Croot_{agr\_plant_{scenario}} \cdot IH_{root}}{BW}$$

$$DOSE_{meat_{scenario}} := \frac{C_{meat_{scenario}} \cdot IH_{meat}}{BW} \qquad DOSE_{milk_{scenario}} := \frac{C_{milk_{scenario}} \cdot IH_{milk}}{BW}$$

$$DOSE_{fish_{scenario}} := \frac{C_{fish_{scenario}} \cdot IH_{fish}}{BW}$$

total daily intake for human

total daily intake for human as sum of each pathway
[$kg_{chem}*kg_{bw}^{-1}*d^{-1}$]

$$DOSE_{tot_{scenario}} := DOSE_{drw_{scenario}} + DOSE_{fish_{scenario}} + DOSE_{stem_{scenario}} + DOSE_{root_{scenario}} \ldots + DOSE_{meat_{scenario}} + DOSE_{milk_{scenario}} + DOSE_{air_{scenario}}$$

relative doses of specific different pathway (%)

$$RDOSE_{drw_{scenario}} := \frac{DOSE_{drw_{scenario}} \cdot 100 \cdot \%}{DOSE_{tot_{scenario}}} \qquad RDOSE_{air_{scenario}} := \frac{DOSE_{air_{scenario}} \cdot 100 \cdot \%}{DOSE_{tot_{scenario}}}$$

$$RDOSE_{stem_{scenario}} := \frac{DOSE_{stem_{scenario}} \cdot 100 \cdot \%}{DOSE_{tot_{scenario}}} \qquad RDOSE_{root_{scenario}} := \frac{DOSE_{root_{scenario}} \cdot 100 \cdot \%}{DOSE_{tot_{scenario}}}$$

$$RDOSE_{meat_{scenario}} := \frac{DOSE_{meat_{scenario}} \cdot 100 \cdot \%}{DOSE_{tot_{scenario}}} \qquad RDOSE_{milk_{scenario}} := \frac{DOSE_{milk_{scenario}} \cdot 100 \cdot \%}{DOSE_{tot_{scenario}}}$$

$$RDOSE_{fish_{scenario}} := \frac{DOSE_{fish_{scenario}} \cdot 100 \cdot \%}{DOSE_{tot_{scenario}}}$$

Results of calculation

$DOSE_{tot_{local}} = 0.04637 \frac{mg}{kg_{bw} \cdot d}$

$DOSE_{tot_{regional}} = 1.50975 \cdot 10^{-4} \frac{mg}{kg_{bw} \cdot d}$

$RDOSE_{drw_{local}} = 0.141718\%$

$RDOSE_{drw_{regional}} = 45.608287\%$

$RDOSE_{air_{local}} = 8.31824\%$

$RDOSE_{air_{regional}} = 3.690297\%$

$RDOSE_{stem_{local}} = 91.472954\%$

$RDOSE_{stem_{regional}} = 40.876968\%$

$RDOSE_{root_{local}} = 0.013677\%$

$RDOSE_{root_{regional}} = 0.513411\%$

$RDOSE_{meat_{local}} = 1.249158 \cdot 10^{-3}\ \%$

$RDOSE_{meat_{regional}} = 8.577692 \cdot 10^{-4}\ \%$

$RDOSE_{milk_{local}} = 0.023282\%$

$RDOSE_{milk_{regional}} = 0.015987\%$

$RDOSE_{fish_{local}} = 0.02888\%$

$RDOSE_{fish_{regional}} = 9.294191\%$

European Commission
DG Joint Research Centre, Institute of Health and Consumer Protection
European Chemicals Bureau

EUR 22522 EN/1 **European Union Risk Assessment Report**
phenol, **Volume 64, Revised Edition**

Editors: S.J. Munn, K. Aschberger, O. Cosgrove, S. Pakalin, A. Paya-Perez, B. Schwarz-Schulz, S. Vegro

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The report provides the comprehensive risk assessment of the substance Phenol. It has been prepared by Germany in the frame of Council Regulation (EEC) No. 793/93 on the evaluation and control of the risks of existing substances, following the principles for assessment of the risks to humans and the environment, laid down in Commission Regulation (EC) No. 1488/94.

Part I - Environment

This part of the evaluation considers the emissions and the resulting exposure to the environment in all life cycle steps. Following the exposure assessment, the environmental risk characterisation for each protection goal in the aquatic, terrestrial and atmospheric compartment has been determined.

The environmental risk assessment concludes that there is concern for some industrial waste-water treatment plants. For aquatic, terrestrial and atmospheric compartments, and as regards secondary poisoning, there is no concern.

There is a need for further information and for testing regarding the unintentional release of phenol to the aquatic and terrestrial compartments.

Part II – Human Health

This part of the evaluation considers the emissions and the resulting exposure to human populations in all life cycle steps. The scenarios for occupational exposure, consumer exposure and humans exposed via the environment have been examined and the possible risks have been identified.

The human health risk assessment concludes that there is concern for workers, consumers and humans exposed via the environment with regard to irritation/corrosivity of skin and eye and systemic effects induced by repeated exposure.

For human health, as far as physico-chemical properties are concerned, there is no concern.

The conclusions of this report will lead to risk reduction measures to be proposed by the Commission’s committee on risk reduction strategies set up in support of Council Regulation (EEC) N. 793/93.

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