Environmental Health Criteria 161

PHENOL

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World Health Organization

INTERNATIONAL PROGRAMME ON CHEMICAL SAFETY

ENVIRONMENTAL HEALTH CRITERIA 161

PHENOL

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First draft prepared by Ms G.K. Montizaan,
National Institute of Public Health and
Environmental Hygiene, Bilthoven, Netherlands

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The International Programme on Chemical Safety (IPCS) is a joint venture of the United Nations Environment Programme, the International Labour Organisation, and the World Health Organization. The main objective of the IPCS is to carry out and disseminate evaluations of the effects of chemicals on human health and the quality of the environment. Supporting activities include the development of epidemiological, experimental laboratory, and risk-assessment methods that could produce internationally comparable results, and the development of manpower in the field of toxicology. Other activities carried out by the IPCS include the development of know-how for coping with chemical accidents, coordination of laboratory testing and epidemiological studies, and promotion of research on the mechanisms of the biological action of chemicals.

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WHO TASK GROUP ON ENVIRONMENTAL HEALTH CRITERIA FOR PHENOL

Members

Dr L.E. Hansen, dk-Teknik, Soeborg, Denmark

Dr R.J. Kavlock, Developmental Toxicology Division, Health Effects Research Laboratory, US Environmental Protection Agency, Research Triangle Park, North Carolina, USA

Dr C.J. Price, Neurotoxicology Program Development, Center for Life Sciences and Toxicology, Research Triangle Institute, Research Triangle Park, North Carolina, USA

Mr D. Renshaw, Department of Health, Elephant and Castle, London, United Kingdom

Dr A. Smith, Health and Safety Executive, Toxicology Unit, Bootle, Merseyside, United Kingdom (*Joint Rapporteur)*

Professor J.A. Sokal, Institute of Occupational Medicine and Environmental Health, Sosnowiec, Poland (*Chairman)*

Dr S.H.H. Swierenga, Health and Welfare Canada, Drugs Directorate, Ottawa, Ontario, Canada (*Joint Rapporteur)*

Dr T. Vermeire, National Institute of Public Health and Environmental Protection, Toxicology Advisory Centre, Bilthoven, The Netherlands

Secretariat

Professor F. Valic, IPCS Consultant, World Health Organization, Geneva, Switzerland, *also* Vice-Rector, University of Zagreb, Zagreb, Croatia (*Responsible Officer* and *Secretary)*

NOTE TO READERS OF THE CRITERIA MONOGRAPHS

Every effort has been made to present information in the criteria monographs as accurately as possible without unduly delaying their publication. In the interest of all users of the Environmental Health Criteria monographs, readers are kindly requested to communicate any errors that may have occurred to the Director of the International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland, in order that they may be included in corrigenda.

* * *

A detailed data profile and a legal file can be obtained from the International Register of Potentially Toxic Chemicals, Case postale 356, 1219 Châtelaine, Geneva, Switzerland (Telephone No.

9799111).

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ENVIRONMENTAL HEALTH CRITERIA FOR PHENOL

A Task Group on Environmental Health Criteria for Phenol met at the British Industrial and Biological Research Association (BIBRA) Toxicology International, Carshalton, United Kingdom from 26 to 30 April 1993. Dr D. Anderson welcomed the participants on behalf of the host institution, and Professor F. Valic opened the Meeting on behalf of the three cooperating organizations of the IPCS (UNEP/ILO/WHO). The Task Group reviewed and revised the draft monograph and made an evaluation of the risks for human health and the environment from exposure to phenol.

The first draft of this monograph was prepared by Ms G.K. Montizaan, National Institute of Public Health and Environmental Hygiene, Bilthoven, the Netherlands.

Professor F. Valic was responsible for the overall scientific content of the monograph and for the organization of the meeting, and Dr P.G. Jenkins, IPCS, was responsible for the technical editing of the monograph.

The efforts of all who helped in the preparation and finalization of the monograph are gratefully acknowledged.

ABBREVIATIONS

DMBA	dimethylbenzathraline
EEC	European Economic Community
LOAEL	lowest-observed-adverse-effect level
MATC	maximum acceptable tolerance concentration
NOAEL	no-observed-adverse-effect level
NOEL	no-observed-effect level
NOLC	no-observed lethal concentration
PCE	polychromatic erythrocytes
TT	toxicity threshold

1. SUMMARY

1.1 Identity, physical and chemical properties, analytical methods

Phenol is a white crystalline solid which melts at 43 °C and liquefies upon contact with water. It has a characteristic acrid odour and a sharp burning taste. It is soluble in most organic solvents; its solubility in water is limited at room temperature; above 68 °C it is entirely water-soluble. Phenol is moderately volatile at room temperature. It is a weak acid, and in its ionized form very sensitive to electrophile substitution reactions and oxidation.

Phenol may be collected from environmental samples by absorption in NaOH solution or onto solid sorbents. Desorption is achieved by acidification, steam distillation and ether extraction (from solutions) or by thermal or liquid desorption (from solid sorbents). The most important analytical techniques are gas chromatography in combination with flame ionization/electron capture detection, and high-performance liquid chromatography in combination with ultraviolet detection. The lowest reported detection limit for air is 0.1 µg/m^3. Phenol can be measured in blood and urine; in urine samples a detection limit of 0.5 µg/litre has been reported.

1.2 Sources of human and environmental exposure

Phenol is a constituent of coal tar, and is formed during the natural decomposition of organic materials. The major part of phenol present in the environment, however, is of anthropogenic origin. Production and use of phenol and its products, especially phenolic resins and caprolactam, exhaust gases, residential wood burning and cigarette smoke are potential sources. Another potential source is the atmospheric degradation of benzene under the influence of light, whereas the presence of phenol in liquid manure may also contribute considerably to its atmospheric levels. Benzene and phenol derivatives may, by *in vivo* conversion, form a source of endogenous human phenol exposure.

The worldwide production of phenol appeared to be fairly constant throughout the 1980s, the USA being the most important producer. Its major use is as a feedstock for phenolic resins, bisphenol A and caprolactam. Some medical and pharmaceutical applications are also known.

1.3 Environmental transport, distribution and transformation

The main emissions of phenol occur to air. The major part of phenol in the atmosphere will be degraded by photochemical reactions to dihydroxybenzenes, nitrophenols and ring cleavage products, with an estimated half-life of 4-5 h. A minor part will disappear from the air by wet deposition (rain). Phenol is expected to be highly mobile in soil, but transport and reactivity may be affected by pH.

Phenol in water and soil may be degraded by abiotic reactions as well as microbial activity to a number of compounds, the most important being carbon dioxide and methane. The proportion of biodegradation to the overall degradation of phenol is determined by many factors, such as concentration, acclimation, temperature, and the presence of other compounds.

1.4 Environmental levels and human exposure

No data are available on atmospheric phenol levels. Background levels are expected to be less than 1 ng/m^3. Urban/suburban levels vary from 0.1 to 8 µg/m^3, while concentrations in source-dominated areas (industry) were reported to be up to two orders of magnitude higher. Phenol has been detected in rain, surface water and ground water, but data are very scarce. Elevated phenol levels have been reported in sediments and ground waters due to industrial pollution.

Occupational exposure to phenol may occur during the production of phenol and its products, during the application of phenolic resins (wood and iron/steel industry) and during a number of other industrial activities. The highest concentration (up to 88 mg/m^3) was reported for workers in the ex-USSR quenching coke with

phenol-containing waste water. Most other reported concentrations did not exceed 19 mg/m^3.

For the general population, cigarette smoke and smoked food products are the most important sources of phenol exposure, apart from the exposure via air. Exposure by way of drinking-water and inadvertently contaminated food products should be low; phenol has an objectionable smell and taste, which in most cases leads to non-acceptance by the consumer.

1.5 Kinetics and metabolism

Phenol is readily absorbed by all routes of exposure. After absorption, the substance is rapidly distributed to all tissues.

Absorbed phenol mainly conjugates with glucuronic acid and sulfuric acid and, to a lesser extent, hydroxylates into catechol and hydroquinone. Phosphate conjugation also occurs. The formation of reactive metabolites (4,4-biphenol and diphenoquinone) has been demonstrated in *in vitro* studies with activated human neutrophils and leucocytes.

The relative amounts of glucuronide and sulfate conjugates vary with dose and animal species. A shift from sulfation to glucuronidation was observed in rats after increasing the phenol dose.

The liver, the lung, and the gastrointestinal mucosa are the most important sites of phenol metabolism. The relative role played by these tissues depends on route of administration and dose.

In vivo and *in vitro* studies have demonstrated covalent binding of phenol to tissue and plasma proteins. Some phenol metabolites also bind to proteins.

Urinary excretion is the major route of phenol elimination in animals and humans. The rate of urinary excretion varies with dose, route of administration, and species. A minor part is excreted in the faeces and expired air.

1.6 Effects on laboratory mammals, and in vitro test systems

Phenol has moderate acute toxicity for mammals. Oral LD_{50} values in rodents range from 300 to 600 mg phenol/kg body weight. Dermal LD_{50} values for rats and rabbits range from 670 to 1400 mg/kg body weight, respectively, and the 8-h LC_{50} for rats by inhalation is more than 900 mg phenol/m^3. Clinical symptoms after acute exposure are neuromuscular hyperexcitability and severe convulsions, necrosis of skin and mucous membranes of the throat, and effects on lungs, nerve fibres, kidneys, liver, and the pupil response to light.

Solutions of phenol are corrosive to skin and eyes. Phenol vapours can irritate the respiratory tract. There is evidence that phenol is not a skin sensitizer.

The most important effects reported in short-term animal studies were neurotoxicity, liver and kidney damage, respiratory effects and growth retardation. Toxic effects in rat kidney have been reported to occur at oral dose levels of 40 mg/kg per day or more. Liver toxicity was evident in rats administered at least 100 mg/kg per day. In a limited 14-day study in rats, an oral no-observed-adverse-effect level (NOAEL) of 12 mg/kg per day was reported, based on kidney effects. In this experiment miosis (an

iris response to light) was still inhibited at 4 mg/kg per day; however, the health significance of this finding is not clear. Some biological changes were reported to occur in the intestinal mucosa and kidneys of mice at dose levels below 1 mg/kg per day, a finding of uncertain toxicological significance.

There are no adequate studies on the reproductive toxicity of phenol. Phenol has been identified as a developmental toxicant in studies with rats and mice. In two multiple dose rat studies, NOAEL values of 40 mg/kg per day (the lowest-observed-adverse-effect level (LOAEL) was 53 mg/kg per day) and 60 mg/kg per day (the LOAEL was 120 mg/kg per day) have been reported. In the mouse, the NOAEL was 140 mg/kg per day (the LOAEL was 280 mg/kg per day).

The majority of bacterial mutagenicity tests have given negative results. Mutations, chromosomal damage and DNA effects have been observed in mammalian cells in vitro. Phenol has no effect on intercellular communication (measured as metabolic cooperation) in cultured mammalian cells. Induction of micro-nuclei in bone marrow cells of mice has been observed in some studies. No micronuclei were observed in mice studies at lower doses.

Two carcinogenicity studies have been conducted with male and female rats and mice receiving phenol in their drinking-water. Malignancies (e.g., C-cell thyroid carcinoma, leukaemia) were only seen in low-dose male rats. No adequate dermal or inhalation carcinogenicity studies have been conducted. Two-stage carcinogenicity studies have shown that phenol, applied repeatedly to mouse skin, has promoting activity.

1.7 Effects on humans

A wide range of adverse effects has been reported following well-documented human exposure to phenol by the dermal, oral or intravenous routes. Gastrointestinal irritation has been reported following ingestion. Local effects following dermal exposure range from painless blanching or erythema to corrosion and deep necrosis. Systemic effects include cardiac dysrhythmias, metabolic acidosis, hyperventilation, respiratory distress, acute renal failure, renal damage, dark urine, methaemoglobinaemia, neurological effects (including convulsions), cardiovascular shock, coma and death. The lowest reported dose resulting in a human death was 4.8 g by ingestion; death occurred within 10 min.

The potential for poisoning through inhalation of phenol vapours has long been recognized, but no cases of death following this route of exposure have been reported. Symptoms associated with inhalation of phenol included anorexia, weight loss, headache, vertigo, salivation and dark urine.

Phenol is not a sensitizing agent.

The human odour threshold for phenol has been reported to range from 0.021 to 20 mg/m^3 in air. The odour threshold for phenol in water has been reported to be 7.9 mg/litre, and the taste threshold 0.3 mg/litre in water.

Adequate human data on the carcinogenicity of phenol are not available.

1.8 Effects on organisms in the environment

In studies on single bacteria species, the EC_{50} values found for growth inhibition varied from 244 to 1600 mg phenol/litre. A

toxicity threshold of 64 mg phenol/litre was found. Values for protozoa and fungi were of the same order of magnitude as for bacteria; for algae, they were somewhat lower.

Phenol is toxic to higher freshwater organisms. The lowest LC_{50} or EC_{50} values for crustaceans and fish lie between 3 and 7 mg phenol/litre. The data on the acute toxicity to marine organisms are comparable with those for freshwater organisms. In long-term studies on crustacea and fish species, a remarkable difference in sensitivity has been observed; the LC_1 values from embryo-larval tests on *Salmo* and *Carassius* proved to be much lower (0.2 and 2 µg phenol/litre, respectively) than the corresponding values for other fish species (NOLC 2.2-6.1 mg/litre) and amphibia, or from reproduction tests on crustacea (NOLC 10 mg phenol/litre). Data from long-term tests on marine organisms are not available.

The bioconcentration factors of phenol in various types of aquatic organisms are in general very low (< 1-10), although some higher values (up to 2200) have also been reported. Phenol, therefore, is not expected to bioaccumulate significantly.

The available data concerning the fate and effects of phenol in terrestrial organisms are very scarce. A 120-h EC_{50} for millet was found to be 120-170 mg/litre, and in a contact test the LC_{50} for earthworm species was 2.4-10.6 µg/cm^2.

1.9 Summary of evaluation

1.9.1 Human health

The general population is primarily exposed to phenol by inhalation. Repeated oral exposure may arise from consumption of smoked food or drinking-water.

Data are inadequate to determine the degree of exposure of the general population, but an upper-limit estimate of the daily intake can be made. On the basis of "the worst case scenario", an estimate can be made assuming that an individual will be maximally exposed to phenol through continuous inhalation of heavily contaminated air with frequent consumption of smoked food items and of drinking-water containing phenol up to the taste threshold. The estimated maximal total daily intake of phenol for such a 70-kg individual is calculated to be 0.1 mg/kg body weight per day.

The lowest NOAEL values identified in animal experiments are for kidney and developmental effects, and in rats lie within the range of 12-40 mg/kg body weight per day. Using an uncertainty factor of 200, a range of 60-200 µg/kg body weight per day is recommended as the upper limit of the total daily intake (TDI). Considering the upper-limit estimate of human daily intake of 100 µg/kg body weight per day, it is concluded that the average general population exposure to phenol from all sources is below this range.

A reason for concern is some evidence that phenol may be genotoxic and the fact that there is insufficient data to discount with certainty the possible carcinogenicity of the compound. The evaluation must be kept under periodic review.

1.9.2 Environment

Phenol is not expected to bioaccumulate significantly. Phenol is toxic to aquatic organisms; an environmental concern level of 0.02 µg/litre can be determined applying the modified US EPA method.

Adequate data on plants and terrestrial organisms are lacking.

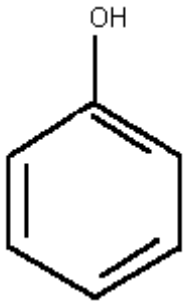
Intercompartmental transport of phenol mainly occurs by wet deposition and by leaching through soil. Generally, the compound is not likely to persist in the environment. The scarce exposure data do not allow the evaluation of the risk from phenol to either aquatic or terrestrial ecosystems. However, in view of the derived environmental concern level for water, it is reasonable to assume that aquatic organisms may be at risk in any surface or sea water contaminated with phenol.

2. IDENTITY, PHYSICAL AND CHEMICAL PROPERTIES, ANALYTICAL METHODS

2.1 Identity

Chemical formula: C_6H_6O

Chemical structure:



Relative molecular mass:	94.11
Common name:	phenol
Common synonyms:	acidum carbolicum, acidum phenolicum, acidum phenylicum, benzaphenol, benzene phenol, benzenol carbolic acid, hydroxybenzene (IUPAC), oxybenzene, monohydroxybenzene, monophenol, phenic acid, phenol alcohol, phenyl hydrate, phenyl hydroxide, phenylic acid
Common trade names:	carbololie (NLD), fenololie (NLD), kristalliertes Kreosot (GER), Steinkohlenkreosot (GER), Steinkohlenteerkreosot (GER), venzénol (FRA), ENT 1814.
CAS registry number:	108-95-2
CAS chemical name:	phenol

2.2 Physical and chemical properties

Some physical and chemical properties of phenol are given in Table 1.

Table 1. Some physical and chemical properties of phenol[a]

Boiling point (101.3 Pa)	181.75 °C
Melting point	43 °C

		40.9 °C (ultrapure material)
Relative density (20 °/4 °)[b]		1.071
Relative vapour density (air = 1)		3.24
Vapour pressure	(20 °C)	0.357 mmHg
	(50 °C)	2.48 mmHg
	(100 °C)	41.3 mmHg
Saturation concentration in air (20°C)		0.77 g/m^3
Solubility in water (16 °C)		67 g/litre[c]
Log n-octanol/water partition coefficient (log P_{ow})		1.46d
Dissociation constant in water at 20 °C (K_a)		1.28 x 10^{-10}
Flash-point	(closed cup)	80 °C
	(open cup)	79 °C
		85 °C[e]
Flammability limits		1.3-9.5%

[a] From: Kirk-Othmer (1980); RIVM (1986)
[b] Weast (1987)
[c] Above 68.4 °C phenol is entirely soluble in water
[d] The P_{ow} of phenol is very much dependent on pH; pH at log P_{ow} = 1.46 was not given
[e] Budavari *et al.* (1989)

Phenol has a melting point of 43 °C and forms white to colourless crystals (Budavari *et al.*, 1989). It has also been described as a colourless to pink solid or thick liquid (NIOSH, 1985a). Phenol has a characteristic acrid smell and a sharp burning taste. Odour and taste threshold values are reported in section 8.3. In the molten state, it is a clear, colourless liquid with a low viscosity. A solution with approximately 10% water is called phenolum liquefactum, as this mixture is liquid at room temperature. Phenol is soluble in most organic solvents (aromatic hydrocarbons, alcohols, ketones, ethers, acids, halogenated hydrocarbons). The solubility is limited in aliphatic solvents.

The chemical properties of phenol are affected by the resonance stabilization possibilities of phenol and, in particular, of the phenolate ion. Because of this, phenol reacts as a mild acid. In the presence of electrophilic groups (meta-indicators), the acidic properties are emphasized.

Phenol is sensitive to oxidizing agents. Splitting of the hydrogen atom from the phenolic hydroxyl group is followed by resonance stabilization of the resulting phenyloxy radical. The radical formed can easily be further oxidized. Depending on the oxidizing agent applied and the reaction conditions, various products, such as dihydroxy- and trihydroxybenzenes and quinones are formed. These properties make phenol suitable as an antioxidant, functioning as a radical trapping agent. Phenol undergoes numerous electrophilic substitution reactions, such as halogenation and sulfonation. It also reacts with carbonyl compounds in both acidic and alkaline media. In the presence of formaldehyde, phenol is

readily hydroxymethylated with subsequent condensation to resins.

2.3 Conversion factors

1 mg/m^3 = 0.26 ppm
1 ppm = 3.84 mg/m^3

2.4 Analytical methods

Analytical methods for phenol are shown in Table 2.

2.4.1 Sampling and pre-treatment

Phenol in air samples may be collected by absorption in NaOH solution contained in wash bottles or on filters impregnated with NaOH solution. Phenol in air, water and solid waste samples may be collected (directly or after extraction) in tubes containing solid sorbent (Tenax, silica gel or, less commonly, carbon) (IARC, 1989). For large air volumes, the NaOH method is usually preferred, whereas for smaller quantities (personal air sampling, for instance) solid sorbent tubes have been reported to be more practical (RIVM, 1986).

Release of phenol from aqueous solutions (including NaOH sorbent, and also urine) is achieved by acidification, steam distillation and/or ether extraction. After adsorption onto Tenax, thermal desorption at 250 °C is usually preferred (the whole sample may be inserted directly into a gas chromatograph), whereas, in the case of silica gel, liquid desorption with chloroform is generally applied. There is a small possibility of chemical conversion during heating, whereas Tenax may react with ozone to form small quantities of phenol. Only one analysis per sample is possible in the case of thermal desorption. The use of liquid desorption allows more analyses per sample, but because of the unavoidable dilution the detection limit is higher (RIVM, 1986).

Table 2. Methods for the detection of phenol in air

Sampling	Volume of air (litre)	Pre-treatment before analysis
Absorbance in NaOH solution in a wash bottle; 1 litre/min	100 sample	acidification
Absorbance in NaOH solution in an impinger; 20 litre/min	25 000	acidification and steam distillation
Glass fibre filter impregnated with NaOH and glycerol; 120 litre/min	600	acidification and extraction with ether
Absorbance in NaOH solution in an impinger; 28 litre/min	1000	acidification and steam distillation
Absorbance in NaOH solution in a wash bottle; 1 litre/min	-	none
Absorbance in NaOH solution in a sinter wash bottle; 1-2 litre/min	150	conversion in an azophenol derivate
Absorbance in Na_2CO_3 solution; 1 litre/min	30	calibration at pH = 10 and pH = 7

Absorbance in NaOH solution in an impinger; 28 litre/min	300	calibration at pH = 12 and at pH = 6
Tenax with and without KOH; 0.25 litre/min	5	thermal desorption; 250 °C
Tenax; 0.1 litre/min	4	thermal desorption; 260 °C
Tenax; 0.5-1 litre/min	70	thermal desorption; 250 °C

Table 2 (contd)

Sampling	Volume of air (litre)	Pre-treatment before analysis
Tenax; 0.75 litre/min	90	thermal desorption; 300 °C
Silica gel	25	liquid desorption with chloroform
Silica gel; 0.05-2 litre/min	10	liquid desorption with chloroform
Drägen tube gas detection	0.5	none

2.4.2 Analysis

The most important analytical techniques for the detection of phenol are gas chromatography (GC) in combination with flame ionization detection (FID), and high-performance liquid chromatography (HPLC) in combination with ultraviolet (UV) detection. The identification of phenol by GC/FID has been improved by reaction of phenols with bromide or pentafluoro-benzyl bromide, and the use of electron capture detection (Hoshika & Muto, 1979; US EPA, 1986a). The identification of phenol using HPLC can be improved by reaction with, for example, *p*-nitrobenzene diazonium tetrafluoroborate to form azo derivatives (Kuwata *et al.*, 1980).

Detection limits of the above techniques for air samples are given in Table 2. For the GC/FID detection of phenol in water, using electron capture detection following derivatization with pentafluorobenzyl bromide, a detection limit of approximately 0.2 µg/litre has been reported (US EPA, 1986a).

GC in combination with mass spectrometry (MS) is more sensitive than with FID, but is more expensive. This technique, using either packed or capillary columns, was reported to have practical quantitative limits of approximately 1 mg phenol/kg wet weight for soil/sediment samples, 1-200 mg phenol/kg for wastes, and 10 µg/litre for groundwater samples (US EPA, 1986b,c).

Another reported analytical technique is colorimetry after reaction of phenol with 4-amino antipyrine, in the presence of potassium ferricyanide, to form an antipyrine dye. The detection limit of this technique for water samples, after steam distillation, was reported to be 1 µg/litre (American Public Health Association,

1985). For air samples of 1 m^3, the detection limit was reported to be 2 µg/m^3 (see Table 2). The interference by para-substituted phenols and chlorophenols is low (RIVM, 1986).

Infrared (IR) detection of phenol is a rather insensitive method, and is highly susceptible to interference by other compounds such as water vapour. However, it is a rapid and specific method which allows directly readable continuous measurement. It is considered to be attractive only at air concentrations of more than 1000 µg/m^3, for example in leakage tests and industrial warning systems (RIVM, 1986). Also directly readable is the Dräger gas detection tube (see Table 2); however, the detection limit is very high (> 19 000 µg/m^3).

For the GC/FID detection of total phenol in urine samples, after acidification and ether extraction, a detection limit of 0.5 µg/litre was estimated (NIOSH, 1985b). Colorimetric methods for the determination of free phenol in both urine and blood are available. In one method, phenol reacts with *p*-nitroaniline following deproteinization and extraction with diethyl ether. Other phenols will interfere (Müting *et al.*, 1970). In another method, phenol reacts with ammonia and *N*-chlorosuccinimide in alkaline media with sodium nitroprusside as a catalyst. This method was found to be applicable in the range of 3-24 mg/litre, using spiked samples of urine (Amlathe *et al.*, 1987). The concentration of total phenol in urine and plasma can be determined by GC/MS following hydrolysis of glucuronide and sulfate conjugates with sulfuric acid and derivatization with propanoic anhydride. The detection limit is reported to be 10 µg/litre (Pierce & Nerland, 1988).

3. SOURCES OF HUMAN AND ENVIRONMENTAL EXPOSURE

3.1 Natural sources

Phenol is a constituent of coal tar, and is formed during the natural decomposition of organic materials. Increased environmental levels may result from forest fires (Hubble *et al.*, 1981).

Phenol has been detected among the volatile components from liquid manure at concentrations of 7-55 µg/kg dry weight (Spoelstra, 1978). In the Netherlands, for example, the contribution from this source to the overall phenol emission into air in 1983 has been calculated to be 15%, assuming complete volatilization of phenol and an average phenol concentration in manure of 30 µg/kg dry weight (RIVM, 1986).

3.2 Anthropogenic sources

3.2.1 Production

The most commonly used production method for phenol, on a worldwide scale, is from cumene (isopropylbenzene). In the USA, for example, more than 98% of phenol is produced by this method (IARC, 1989). Phenol is also produced from chlorobenzene and toluene. A small but steady supply of phenol is recovered as a by-product of metallurgical coke manufacture (IARC, 1989). The emission factor of phenol into air during production by the cumene process has been reported to be 0.16 g phenol emitted per kg phenol produced (UBA, 1981).

In Table 3, information is presented concerning the production of phenol in various countries in 1981. This information was derived from the open literature (Chemfacts, 1978-1981; United Nations,

1980; SRI, 1982; CID-TNO, 1984; IARC, 1989) and, where necessary, was extrapolated to 1981. There have been no major production changes according to data available up to 1986 (IARC, 1989).

3.2.2 Industrial processes

Phenol is the basic feedstock from which a number of commercially important materials are made, including phenolic resins, bisphenol A (2,2-bis-1-hydroxyphenylpropane), capro-lactam, alkyl phenols, as well as chlorophenols such as pentachlorophenol (IARC, 1989).

Table 3. Production of phenol in 1981 and 1986 (kilotonne/year)

Country	Production in 1981[a]	Production in 1986[b]
Brazil	50	
Bulgaria	35	
Czechoslovakia	44	46
Finland	32	
France	150	
Germany, Federal Republic of	247	
Italy	223	
India	14	
Japan	215	260
Mexico	20	
The Netherlands	166	
Poland	66	
Romania	66	
Spain	55	70
United Kingdomc	110	53
USA	1350	1413
USSR	497	515
Other countries	34	
European Community (total)	920	
Total	3374	

[a] Chemfacts (1978-1981); United Nations (1980); SRI (1982); CID-TNO (1984); IARC (1989)

[b] From IARC (1989)

[c] Phenol is no longer produced in the UK

The most important phenol emissions result from the use of phenolic resins. Phenolic resins are used as a binding material in, for example, insulation materials, chipboard and triplex, paints and casting sand foundries. Their contents vary from 2-3% for insulation material to > 50% for moulds (Bollig & Decker, 1980). Emissions are approximately proportional to the concentration of free phenol, which is present as a monomer in these materials (1-5%) (Bollig & Decker, 1980). In addition, phenol may be released as a result of thermal decomposition of the resins.

In foundries, phenol emissions develop both during the production of moulds and kernels and during founding (TNO, 1978). The content of free phenol may rise by up to 12% (Ryser & Ulmer, 1980). Emission factors reported by RIVM (1986) were 0.35 g phenol emitted per kg used casting sand, 2-5 g phenol emitted per kg resin in the production of casting sand, and 10 g phenol emitted per kg resin during the production of moulds by the "hot-box" procedure.

Other industrial activities in which phenol may be emitted to the air, as well as some of their reported emission factors, are listed below:

* production of phenol resins (0-0.5 g phenol emitted per kg resin produced) (RIVM, 1986)
* production of phenols and phenol derivatives
* production of caprolactam (0.02-0.05 g phenol emitted per kg cyclohexanone (an intermediate) produced (RIVM, 1986)
* production of cokes
* production of insulation materials
* process emissions

Emissions to water may also result from processing.

3.2.3 Non-industrial sources

Phenol has been detected in the exhaust gases of private cars at concentrations of 0.3 ppm (approximately 1.2 mg/m^3) to 1.4-2.0 ppm (5.4-7.7 mg/m^3) (Kuwata *et al.*, 1980; Verschueren, 1983). It has also been identified in cigarette smoke, in quantities that are comparable to an average emission of 0.4 mg/cigarette (Groenen, 1978). Emission gases from all material incinerators and home fires, especially wood-burning, may contain substantial quantities of phenol (Den Boeft *et al.*, 1984).

Another potential source of phenol is the atmospheric degradation of benzene under the influence of light (Hoshino & Akimoto, 1978).

Phenols have been detected in smoked foods (section 5.3.2).

3.3 Endogenous sources

An important additional source of human phenol exposure may be the *in vivo* formation from various xenobiotics, e.g., benzene (Pekari *et al.*, 1992).

3.4 Uses

The largest single use of phenol is the production of phenolic resins. Next is its use in the production of caprolactam, an intermediate in the production of nylon 6, and 2,2-bis-1-hydroxyphenylpropane (bisphenol A), which is mainly used in the production of phenolic resins (Kirk-Othmer, 1980).

The various applications of phenol as a percentage of total 1981 consumption, in the USA and western Europe, are summarized in Table 4 (Kirk-Othmer, 1980). The data presented are in close agreement with the 1986 USA data reported by IARC (1989).

Table 4. Use of phenol in 1981 (% total consumption)[a]

Production of	USA	West Europe
Phenolic resins	48	36
Bisphenol A(2,2-bis-1-hydroxyphenylpropane)	18	17
Caprolactam	15	28
Other products	19	19
Total	100	100

[a] From: Kirk-Othmer (1980)

Phenol was widely used in the 19th century for wound treatment and as an antiseptic and local anaesthetic. The medical uses of phenol today include incorporation into disinfectants, antiseptics, lotions, salves and ointments (IARC, 1989). Another medical application of phenol is its use as a neurolytic agent, applied in order to relieve spasm and chronic pain (Wood, 1978).

In addition to the applications mentioned in section 3.2.2, phenol is used in the manufacture of paint and varnish removers, lacquers, paints, rubber, ink, illuminating gases, tanning dyes, perfumes, soaps and toys (IARC, 1989).

4. ENVIRONMENTAL TRANSPORT, DISTRIBUTION AND TRANSFORMATION

4.1 Transport and distribution between media

No data have been found concerning wet and dry deposition of phenol. Since phenol in air is present almost exclusively in the gas phase, dry deposition (by particle deposition) is expected to be negligible. Wet deposition may contribute to the disappearance of phenol from the atmosphere: when phenol was measured during seven episodes of rain in Portland, Oregon, USA, relatively high concentrations were found in the rain water (Leuenberger *et al.*, 1985).

Based on its relatively high solubility in water and the relatively low vapour pressure at room temperature, phenol is expected to end up largely in the water phase upon distribution between air and water. Consequently, transport from air to soil and water is likely (RIVM, 1986). Volatilization from dry near-surface soil should be relatively rapid (Howard, 1989).

Theoretical deposition rates for phenol were estimated assuming a behaviour similar to SO2, and comparing with the rate of reaction of phenol with hydroxyl radicals (see below). Based on this comparison, it was concluded that most phenol in the atmosphere is degraded chemically, rather than transported (RIVM, 1986).

Partition coefficient (K_{oc}) values of phenol for two silt

loams were reported to be 39 and 91 dm^3/kg. Based on these K_{oc} values, phenol would be expected to be highly mobile in soil, and therefore may leach to ground water (Howard, 1989). This was confirmed by Scott *et al.* (1982) who found low adsorption of phenol to two sterile silt loams (pH 5.4, organic matter content 1.1 and 3.6, respectively), as shown by Freundlich K values of 0.57 and 1.19, respectively. Based on the pK_a (log (1.28×10^{-10})), phenol exists in a partially dissociated state in water and moist soils and, therefore, its transport and reactivity may be affected by pH (Howard, 1989). Upon measurement of the sorption and desorption of phenol from water to surface sediment (pH 6.21-6.35; organic matter content of fine fraction (< 2 µM) was 10.2%), phenol appeared to bind strongly to the soil. The estimated K_{oc} was 2900 dm^3/kg (Isaacson & Frink, 1984). However, no correction was made for any degradation occurring during the experiments. The adsorption of phenol onto soil or microbial biomass may be decreased by the presence of phenol derivatives (Boyd, 1982; Selvakumar & Hsieh, 1988). Phenol has been detected in ground water as a result of leaching (see section 5.1.2).

4.2 Abiotic degradation

4.2.1 Air

Phenol may react in air with hydroxyl and NO_3 radicals, and undergo other photochemical reactions to form dihydroxy-benzenes, nitrophenols, and ring cleavage products (Atkinson *et al.*, 1979; Bruce *et al.*, 1987). The half-life for phenol in air was found to be 4-5 h under photochemically reactive conditions in a smog chamber (Spicer *et al.*, 1985); this is in good agreement with the estimated half-life of phenol in air of 5 h based on its estimated reaction rate with hydroxyl radicals (RIVM, 1986). Howard (1989) reported an estimated half-life of 15 h for the reaction of phenol with hydroxyl radicals in air. The reaction of phenol with nitrate radicals during the night may be a significant removal process; a half-life of 15 min has been estimated at an atmospheric concentration of 2×10^8 nitrate radicals per cm^3 (Howard, 1989).

Phenol absorbs light in the region of 290-330 nm and therefore could photolyse (Howard, 1989).

4.2.2 Water

Phenols generally react in sunlit natural water via reaction with photochemically produced hydroxyl and peroxy radicals; typical half-lives were reported to be 100 and 19.2 h, respectively (Howard, 1989).

Phenol was found to be oxidized to carbon dioxide in water under experimental conditions (temperature approximately 50 °C), in the presence of oxygen and sunlight, at a rate of 11% per 24 h (Knoevenagel & Himmelreich, 1976). It was reported to react with nitrate ions in dilute aqueous solutions to form dihydroxybenzenes, nitrophenols, nitrosophenol and nitroquinone, presumably by a radical mechanism involving hydroxyl and phenoxyl radicals (Niessen *et al.*, 1988). Phenol has been found to react with nitrous acid in waste water to form cyanide (Adachi *et al.*, 1987), and to form chlorophenols in chlorinated drinking-water (Jarvis *et al.*, 1985) and p-benzoquinone in the presence of chlorine dioxide (Wajon *et al.*, 1982).

4.3 Biodegradation

Bacteria play a major role in the degradation of phenol in soil, sediment and water. The number of bacteria capable of utilizing phenol is usually a small percentage of the total population present in, for example, a soil sample (Hickman & Novak, 1989). However, repeated phenol exposure may result in acclimation

(the promotion of strains capable of utilizing phenol as food) (Young & Rivera, 1985; Colvin & Rozich, 1986; Shimp & Pfaender, 1987; Wiggins & Alexander, 1988; Tibbles & Baecker, 1989).

Phenol may be converted by bacteria under aerobic conditions to carbon dioxide (Southworth *et al.*, 1985; Ursin, 1985; Aelion *et al.*, 1987; Dobbins *et al.*, 1987; Aquino *et al.*, 1988), and under anaerobic conditions to carbon dioxide (Bak & Widdell, 1986; Tschech & Fuchs, 1987) or methane (Healy & Young, 1979; Ehrlich *et al.*, 1982; Young & Rivera, 1985; Fedorak & Hrudey, 1986; Fedorak *et al.*, 1986). Benzoate, catechol, *cis-cis*-muconate, ß-ketoadipate, succinate and acetate have all been identified as intermediates in the biodegradation of phenol (Paris *et al.*, 1982; Krug *et al.*, 1985; Fedorak *et al.*, 1986; Knoll & Winter, 1987). Some of the carbon derived from the degradation of phenol may be incorporated into the bacterial biomass (Chesney *et al.*, 1985).

Phenol may be degraded in its free form as well as after adsorption onto soil or sediment, although the presence of sorbent reduces the rate of biodegradation (Shimp & Young, 1987; Knezovich *et al.*, 1988).

When phenol is the only carbon source, it can be degraded in a biofilm reactor with first-order kinetics at concentrations below about 20 µg/litre at 10 °C. The first-order rate constants are 3 to 30 times higher than those of easily degraded organic compounds at 100- to 1000-fold higher concentrations (Arvin *et al.*, 1991). Reported phenol degradation rates suggest rapid aerobic degradation in sewage (typically > 90% with an 8-h retention time), soil (typically complete biodegradation in 2-5 days), fresh water (typically complete biodegradation in < 1 day), and sea water (typically 50% in 9 days) (Howard, 1989). Anaerobic biodegradation is slower (Baker & Mayfield, 1980).

The contribution of bacteria to the overall rate of degradation may be affected by a number of factors such as phenol concentration (Baker & Mayfield, 1980; Ursin, 1985; Hwang *et al.*, 1989), temperature (Baker & Mayfield, 1980; Bak & Widdell, 1986; Hwang *et al.*, 1986; Thornton-Manning et al, 1987; Gurujeyalashmi & Oriel, 1989), sunlight (Hwang *et al.*, 1986), soil depth (Dobbins *et al.*, 1987; Federle, 1988), the presence of other nutrients required for bacterial growth (Rubin & Alexander, 1983; Fedorak & Hrudey, 1986; Rozich & Colvin, 1986; Thorton-Manning *et al.*, 1987), the presence of other pollutants (Southworth *et al.*, 1985; Hoffmann & Vogt, 1988; Wang *et al.*, 1988; Namkoong *et al.*, 1989) and bacterial abundance (Tranvik *et al.*, 1991).

5. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

5.1 Environmental levels

5.1.1 Air

No data are available for background levels of phenol in air, away from emission sources. They are expected to be low (< 1 ng phenol/m^3) (RIVM, 1986).

Higher levels of phenol in air may be expected for urban areas,

mainly due to traffic emissions. Urban phenol concentrations have been reported for Osaka, Japan (1-4 µg phenol/m^3; Kuwata *et al.*, 1980), Nagoya, Japan (0.2-8 µg phenol/m^3 with an average of 1.7 µg phenol/m^3; Hoshika & Muto, 1979, 1980), Paris, France (0.7-8 µg phenol/m^3; Hagemann *et al.*, 1978), and Portland, USA (0.22 to 0.42 µg phenol/m^3; Leuenberger *et al.*, 1985). Despite differences in analytical techniques, the first three series of measurements showed good agreement. The Portland results were lower, but came from air samples taken during rain periods; phenol was also detected in rain water (see section 5.1.2).

Ambient air levels of phenol have been extensively monitored in the highly industrialized and urbanized Upper Silesia region of Poland (Sanitary Epidemiological Station, Katowice, 1991). Levels during 1990 ranged from 3.8 to 26.6 µg/m^3, the highest values being in the areas of greatest industrial concentration.

Hoshika & Muto (1979, 1980) reported a phenol level of approximately 190 µg/m^3 "near" a phenolic resin factory (no details). Kuwata *et al.* (1980) found phenol levels of 0.8-3.5 mg/m^3 in foundry emissions (no details).

Based on limited data, median ambient atmospheric levels of phenol (based on estimated 24-h averages) were estimated by Brodzinsky & Singh (1982) to be 0.12 µg/m^3 for urban/suburban areas (7 samples) in the USA (which is lower than reported above for several cities), and 104 µg/m^3 (2-170 µg/m^3) for source-dominated areas (83 samples) in the USA.

5.1.2 Water and sediment

Levels of phenol dissolved in rain water from Portland, USA, were found to range from 0.08 to 1.2 µg/litre and averaged above 0.28 µg/litre; gas phase concentrations ranged from 220-410 ng/m^3 (Leuenberger *et al.*, 1985).

Concentrations reported for surface water in the Netherlands were 2.5-6.5 µg/litre for two major rivers, 0.3-7 µg/litre for lakes, and 1.5 µg/litre for coastal waters (the given concentrations include other phenolic substances) (RIVM, 1986). Industrial rivers in the USA were reported to contain 0-5 µg/litre, but 3-24 µg/litre was reported for Lake Huron. Phenol was also detected in 2/100 raw water supplies in 1977 in the US EPA National Organics Monitoring Survey (Howard, 1989).

Drinking-water levels of phenol in the USA have been reported to be around 1 µg/litre or otherwise below the detection limit (summarized by Howard, 1989). Phenol was detected (no quantitative data) in drinking-water in the USA from 5 out of 14 drinking-water plants surveyed and in Great Britain in 2 out of 4 sites (Fielding *et al.*, 1981). Higher groundwater levels have been reported following industrial activity (e.g. 6.5-10 000 µg/litre in two aquifers 15 months after a coal gasification project; summarized by Howard, 1989). Phenol was detected at a maximum concentration of 1130 mg/litre in nine wells in Wisconsin after a spill, and was detectable for at least 1.5 years after the spill (Delfino & Dube, 1976).

Phenol was not detected in water samples from three areas in Japan analysed for an environmental survey; however, levels of 0.03-0.04 mg/litre were detected in 3 out of 9 bottom sediment samples from the same regions (Fujii, 1978).

Other sediment concentrations reported were 13 000 µg/kg in samples from Lake Huron, "not detected" in an unspecified industrial river in the USA, < 1000 µg/kg (dry weight) as the median concentration in 9% of sediment samples from 318 data points in the USA, and 10 µg/kg (dry weight) in samples collected 6 km from a wastewater treatment discharge zone in California (summarized by Howard, 1989).

Phenol was detected in 63 out of 165 sediments from sampling areas in the Puget Sound region (Tetra Tech. Inc., 1986). Half the samples had a concentration of phenol below 40 µg/kg sediment (dry weight); the maximum level was 1700 µg/kg.

Levels of phenol with means of 0.01-5.7 mg/litre (maximum up to 53 mg/litre) have been reported in effluents from various industrial sources (summarized by Howard, 1989). Highest levels were associated with the iron and steel industry. Limited quantitative data from the VIEW Database (ATSDR, 1989) for ground water at hazardous waste sites indicated maximum levels of 2.48 to 85 000 µg/litre (average 33 800 µg/litre, 6 data points).

No data have been found indicating the presence of phenol in soil. Phenol is not likely to persist in soil because of rapid biodegradation (section 4.3) or transport to ground water or air (section 4.1).

5.2 Occupational exposure

Occupational exposure to phenol may occur during the production of phenol and phenol derivatives, during the production of phenolic resins and other products derived from phenol, during processing of the latter materials, and during a number of other activities.

5.2.1 Production

Personal air samples of workers involved in the production of phenol by the cumene process in the ex-USSR contained on average 5.8 mg phenol/m^3. For workers occupied in the production of phenol from chlorobenzene, the mean exposure level was 1.2 mg phenol/m^3 (Mogilnicka & Piotrowski, 1974). Values reported in the same publication for workers in two phenol resin-producing industries were 0.6-3 mg phenol/m^3.

5.2.2 Application of phenolic resins

Occupational exposure during the processing of phenolic resins appears to be partly determined by the content of free phenol in the applied resin (Bollig & Decker, 1980; Ryser & Ulmer, 1980).

In the wood industry, indoor phenol concentrations of 0.3 mg per m^3 (Winkler, 1981) and 1.5 mg/m^3 (range 0.8-2.6) (Gilli *et al.*, 1980) have been reported. Concentrations in the breathing zone of wood workers were 1.3-2.6 mg phenol/m^3 (Gspan *et al.*, 1984). In another study, concentrations of < 0.04 to 1.9 mg phenol/m^3 were found at plywood plants (Kauppinen *et al.*, 1986).

In iron and steel foundries, average hourly phenol concentrations of 0.4-4.5 mg/m^3 were reported in the manufacture of moulds or kernels (Schütz & Wolf, 1980). Phenol concentrations of 1-4 mg/m^3 were measured in a foundry in Osaka, Japan (Kuwata *et al.*, 1980). Local phenol concentrations were reported to be as high as 75-420 mg/m^3 due to the thermal degradation of the resin.

However, this effect of thermal degradation was not reflected in hourly concentrations measured during the foundry process: values of 3-16 mg phenol/m^3, with an average of 10 mg phenol/m^3, were reported by Schütz & Wolf (1980), and a maximum hourly average of 2.7 mg phenol/m^3 was reported by Ryser & Ulmer (1980). (It is not known whether these results were obtained in personal or area air samples). Phenol concentrations during the operation of an electric furnace in a steel factory in Pueblo, Colorado, USA, were 0.04, 0.18 and 0.20 mg/m^3 in the vicinity of the furnace. General room air samples taken during operation of a grey iron foundry were below the detection limit (Gunter, 1987).

5.2.3 Other occupational situations

Exposure levels of 5-88 mg phenol/m^3 have been reported for employees in the ex-USSR who quenched coke with waste water containing 0.3-0.8 g/litre phenol (Petrov, 1960).

Measurements at coal gasification and liquefaction plants in the USA showed relatively low phenol concentrations ($\leq$ 0.08 mg per m^3) at various sites (Dreibelbis & Hawthorne, 1985).

In a Japanese bakelite factory, area samples contained 0-12.5 mg phenol/m^3 (Ohtsuji & Ikeda, 1972).

In a synthetic fibre factory in Japan, concentrations of 19 mg phenol/m^3 were measured, whereas in a USA fibrous glass wool factory concentrations of 0.05-1.3 mg phenol/m^3 were reported (Dement *et al.*, 1973; Ogata *et al.*, 1986).

The concentrations of phenol in creosote vapour, analysed in seven creosote impregnation plants in Finland, ranged from < 0.1 to 1.8 mg/m^3 air (Heikkilä *et al.*, 1987). The highest exposures occurred during the cleaning of creosote warming chambers.

During the dissection of cadavers by dental students, phenol breathing zone concentrations ranged from 5 to 19 mg phenol/m^3. (The high phenol concentrations resulted from the applied embalming solution, in combination with inadequate ventilation) (Boiano, 1985).

5.3 General population exposure

5.3.1 Indoor air

Borovik & Dmitriev (1981) found a maximal concentration of 0.02 µg phenol/m^3 in hospitals in the ex-USSR. It is, however, not clear from where the phenol originated; it may have been used as a disinfectant in these hospitals.

No information has been found with regard to phenol concentrations in residential houses and apartments. Cigarette smoking must be considered as the most important potential source in dwellings. A distinction should be made between the main stream (the smoke inhaled by the smoker) and the side stream (produced by the smouldering cigarette itself). It was estimated that 0.01-0.22 mg phenol per cigarette was released in the mainstream, while the sidestream phenol content was 2.6 times higher. In the case of various Japanese cigarettes, 0.3-0.4 mg phenol was emitted into air during burning (Kuwata *et al.*, 1980). For an unventilated room of 50 m^3, the smoking of one cigarette would thus result in a phenol concentration of 6-8 µg/m^3.

5.3.2 Food and drinking-water

Phenol is found in smoked meat and fish products. The wood smoke with which such products are treated contains, among other ingredients, a wide range of phenols and phenol ethers, which contribute significantly to the characteristic smoke aroma (smell and taste) of the product.

Phenol is absorbed into the food products during smoking. Quantitative data, however, are scarce, since phenols are usually determined as a group. According to Toth (1982), the total phenol content of smoked sausage is 70 mg/kg; Bratzler *et al.* (1969) found a content of 37 mg/kg in the outer layer of the product, and lower contents in the inner part. Luten *et al.* (1979) determined a number of individual phenols in smoked herring and found a phenol content, depending on the duration of smoking, of approximately 10-30 mg/kg. Potthast (1976, 1982) measured 2-18 mg/kg in smoked ham and liver sausage.

If liquid smoke derivates are used in order to give a smoky flavour to fish and meat products, the end product also contains phenol. However, with regard to smell and taste aspects, phenol is not the most important phenolic compound from wood smoke. In this respect, methoxy and dimethoxy phenols are more important, together with aliphatic fatty acids and carboxyl compounds.

Phenol may also enter food unintentionally by, for instance, contamination in transport or from packaging materials, or contact with other phenol-containing materials. However, these accidental cases would probably be detected and lead to non-acceptance by the consumer, owing to the conspicuous phenol smell and taste (see section 8.3 for odour and taste thresholds).

Phenol has been found in botton pits fish from 5 sites in Commencement Bay in Tacoma, USA, at a maximum average of 0.14 mg/kg and an overall maximum of 0.22 mg/kg (Nicola *et al.*, 1987).

Little information is available with respect to the occurrence of phenol in drinking-water. Surface and ground waters intended for the production of drinking-water in the Netherlands were reported to contain 1-9 µg phenol/litre (phenol index, including other phenolic compounds) (RIVM, 1986). Phenol was found in a domestic water supply in the USA at a level of 1 µg/litre (Ramanathan, 1984). Cases of drinking-water pollution with phenol have been reported in the UK and the USA; the phenol water concentrations were reported to be 5-10 µg and 5-120 mg per litre, respectively (see section 8.1.2.2). Chlorination of drinking-water may result in the formation of chlorophenols from phenol, which greatly adds to the objectionable smell and taste (Jarvis *et al.*, 1985).

6. KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS

Phenol and conjugated metabolites of phenol occur naturally in animal and human tissue and can be detected in the urine, faeces, saliva and sweat. The body's production of phenol depends on the type of diet: a high protein or meat diet promotes phenol formation.

6.1 Absorption

Phenol is readily absorbed through all routes, such as the lungs, intact and abraded skin, and the gastrointestinal tract of both humans and animals (Von Oettingen, 1949; Deichmann & Keplinger, 1963).

6.1.1 Animal uptake studies

6.1.1.1 Pulmonary

There are no *in vivo* data on absorption of phenol following inhalation exposure. However, *in vitro* studies by Hogg *et al.* (1981), using ^{14}C-phenol with excised trachea-lung preparations and isolated perfused rat lung, demonstrated that phenol can be rapidly and efficiently absorbed in the lungs.

6.1.1.2 Dermal

The extent of absorption of phenol through rabbit skin is more strongly influenced by the area of the skin exposed than by the concentration of the applied solution in water (Deichmann & Witherup, 1944; Liao & Oehme, 1980).

In studies with the hairless mouse, phenol destroyed the stratum corneum (Behl *et al.,* 1983a). Similar effects were reported by Huq *et al.* (1986) and Jetzer *et al.* (1986). Absorption of phenol through thermally damaged mouse skin *in vitro* was also reported to be greatly enhanced (Behl *et al.,* 1983b). In contrast, Deichmann *et al.* (1952) observed that injury of the rabbit skin caused by phenol appeared to retard the rate of absorption.

The permeability of mouse skin to phenol from aqueous solution *in vitro* increased with increasing temperature of the carrier solution (from 10 to 37 °C) (Jetzer *et al.,* 1988).

Measurement of the permeation constant of phenol through hairless mouse skin at 37 °C *in vitro* yielded a value of 18 800 ± 3000 cm/h (Huq *et al.,* 1986; Jetzer *et al.,* 1986).

6.1.1.3 Intestinal

When a single oral dose of 25 mg/kg body weight was administered to rats, pigs or sheep, more than 95% was absorbed (Kao *et al.,* 1979).

In vitro studies showed that aqueous solutions of phenol placed into ligated sections of the gastrointestinal tract had the fastest absorption rate in the colon, followed by the ileum. The absorption rate in the stomach was much slower (Deichmann & Keplinger, 1963).

6.1.2 Human uptake studies

6.1.2.1 Pulmonary

The retention of phenol in the bodies of eight human volunteers exposed to 6-20 mg/m^3 by inhalation only for 8 h was 70%-80% during the course of the study (Piotrowski, 1971). Ohtsuji & Ikeda (1972) reported similar observations.

6.1.2.2 Dermal

Human skin absorption of phenol vapour (5-25 mg/m^3) occurs rapidly (Ruedemann & Deichmann, 1953). Fatal cases reflect the rapid rate of absorption of phenol through the skin (Turtle & Dolan, 1922; Duverneuil & Ravier, 1962; Hinkel & Kintzel, 1968; Lewin & Cleary, 1982). The retention in eight human volunteers, exposed to phenol vapour at concentrations of 6-20 mg/m^3, by skin only, for 6 h was

70-80% (Piotrowski, 1971). Piotrowski (1971) proposed the following formula for calculating the absorption rate of phenol vapour through the skin:

$$A = (0.35)C$$

where A is the amount of phenol absorbed in mg/h per unit area and C is the phenol air concentration in mg/m^3.

Concentrations of between 5 and 10% phenol denature epidermal protein, and this can partly prevent absorption. The phenol-protein complex is not stable and by dissociation of phenol the substance may exert its action over a period of time (Schmidt & Maibach, 1981).

Phenol was detected in the urine of 4 out of 16 infants (2-5 months) with seborrhoeic eczema who were skin-painted twice daily for 48 h with a commercial paint containing 4% (w/v) phenol and 8% (w/v) resorcinol (Rogers *et al.*, 1978). In adults, a single topical application of 4 µg phenol/cm^2 on 13 cm^2 of the ventral forearm, reportedly gave an absorption of 4.4% of the administered dose (Feldman & Maibach, 1970). The period of exposure and the concentration of phenol are both factors that determine the extent of absorption (Piotrowski, 1971; Roberts *et al.*, 1977; Baranowska-Dutkiewicz, 1981).

In vitro studies have also shown that phenol from aqueous solutions (1% w/v) readily penetrates human skin (Roberts *et al.*, 1977, 1978). A value of 8200 cm/h was obtained as the permeation constant of phenol through human skin at 25 °C (Flynn & Yalkowsky, 1972). In an *in vitro* study with human abdominal skin, 10.9% of the applied dose was absorbed. This study showed an excellent qualitative, but a somewhat less accurate quantitative, agreement between the *in vivo* and *in vitro* skin absorption of 12 compounds (Franz, 1975).

6.2 Distribution

Phenol is rapidly distributed to all tissues in exposed animals.

In rabbits, 15 min after oral administration of 0.5 g phenol/kg, chemical analysis indicated that the liver contained the highest concentration of total phenol followed by the central nervous system, lungs and blood. After 82 min, phenol was fairly uniformly distributed over all tissues. The proportion of free to conjugated phenol changed with time, and, after 360 min, most of the phenol was conjugated (Deichmann, 1944).

After a single oral administration of ^{14}C-phenol (207 mg/kg) to rats, the highest concentration ratios between tissue and plasma were found in liver (42%), followed by spleen, kidney, adrenal, thyroid and lungs, with a peak tissue level occurring after 0.5 h (Liao, 1980; Liao & Oehme, 1981a).

Highest tissue residues were found after 2 h in the kidneys and livers of mice and rats treated intravenously (Gbodi & Oehme, 1978; Wheldrake *et al.*, 1978; Greenlee *et al.*, 1981).

6.3 Metabolic transformation

6.3.1 Metabolite identification

Studies employing several species have demonstrated that conjugation with glucuronic acid and sulfate are major metabolic pathways for phenol. Hydroxylation to hydroquinone and catechol also occurs (Williams, 1938, 1959; Garton & Williams, 1949; Bray *et al.,* 1952a,b,c; Parke & Williams, 1953).

In vitro studies have shown the formation of 4, 4'-biphenol and diphenoquinone by neutrophils, activated leucocytes and by horseradish peroxidase following addition of phenol (Eastmond *et al.,* 1986).

Phenol metabolism in rabbits was studied by Deichmann & Keplinger (1963). During the first 24 h following oral administration of a sublethal dose of 300 mg phenol/kg body weight, 23% of the administered dose was recovered as exhaled carbon dioxide. Trace amounts of catechol and hydroquinone were also detected in the breath. Over the same period, 72% of the dose was excreted in the urine (48% of which was excreted as free and 52% as conjugated phenols), 1% was excreted in the faeces, 4% remained in the carcass, and trace amounts were exhaled.

Oral administration of ^{14}C-phenol (1.2 mg/kg) to rats resulted in at least 80% excretion in urine within 24 h, with 68% as phenyl sulfate and 12% as phenyl glucuronate (Edwards *et al.,* 1986).

A pronounced shift from sulfation to glucuronidation was observed in rats after increasing the phenol dose (Koster *et al.,* 1981). This observed shift is apparently due to a saturation of the overall sulfation process, rather than to a depletion of inorganic sulfate (Weitering *et al.,* 1979; Koster *et al.,* 1981; Koster, 1982). A limited availability of 3-phosphoadenosine-5-phosphosulfate may account for the decreased proportion of phenol conjugation to sulphate at relatively high doses (Ramli & Wheldrake, 1981). Repeated administration of phenol, however, did not affect glucuronide synthesis in rats (Takemori & Glowacki, 1962).

The pig has limited ability for phenol sulfation. The domestic cat lacks the ability for glucuronic acid conjugation of phenol. In cats, phenyl phosphate has been detected as a metabolite in small amounts, in addition to sulfate conjugates (Capel *et al.,* 1974; French *et al.,* 1974).

Following oral administration of ^{14}C-phenol (0.01 mg/kg) to three men, 90% of the dose was excreted in the urine within 24 h, mainly as phenyl sulfate (77%) and phenyl glucuronide. Small amounts of guinol sulfate and guinol glucuronide were also present (Capel *et al.,* 1972b).

Several investigators have confirmed the above-mentioned results using *in vitro* methods (DeMeio & Arnolt, 1944; Capel *et al.,* 1972b; Shirkey *et al.,* 1979; Hogg *et al.,* 1981; Koster *et al.,* 1981; Sawahata & Neal, 1983).

6.3.2 Covalent binding to macromolecules

Early pharmacokinetic studies (measuring distribution volumes) in dogs, pigs and goats suggested that tissue binding occurs (Oehme, 1969). Further animal studies have indicated that phenol and/or its metabolites bind covalently to tissue protein, mainly in the liver (Bolt, 1977; Illing & House, 1980; Jergil *et al.,* 1982; Smart & Zannoni, 1984). Binding to rabbit bone marrow mitochondrial DNA in

studies with isolated cells has also been reported (Rushmore *et al.*, 1984). *in vivo* and *in vitro* studies have demonstrated covalent binding of radiolabelled phenol to plasma proteins from humans, dogs, rats and trout (Liao, 1980; Liao & Oehme, 1981a,b; Judis, 1982; Schmieder & Henry, 1988). Reactive phenol metabolites formed by peroxidases bind readily to proteins (Eastmond *et al.*, 1986, 1987a) and DNA (Subrahmanyam & O'Brien, 1985).

6.3.3 Location

Quantitatively, the most important sites of phenol conjugation are the liver, lung and gastrointestinal mucosa. The relative roles played by these tissues depend on the route of administration and the dose.

The liver is an important site of phenol metabolism. After direct administration of phenol into the hepatic circulation, the liver showed considerable first-pass metabolism in rats (Cassidy & Houston, 1980; Houston & Cassidy, 1982). Phenol-metabolizing enzymes have been detected in rabbit hepatic microsomes (Koop *et al.*, 1989).

Other tissues, such as lungs, intestines and kidneys, also play an important role in phenol metabolism (Quebbemann & Anders, 1973; P_{ow}ell *et al.*, 1974; Houston & Cassidy, 1982). Phenol sulfotransferases, which catalyse phenol sulfation, occur in a variety of human tissues (intestinal wall, lungs, platelets, adrenal glands, brain, placenta, etc.) (Campbell *et al.*, 1987; Gibb *et al.*, 1987). After oral uptake of phenol, there is a very large first-pass metabolism in the intestines. The lungs also show considerable first-pass metabolism (as was established after direct administration into the pulmonary circulation of rats) (Cassidy & Houston, 1980; Houston & Cassidy, 1982). Due to saturation of hepatic enzymes, extrahepatic tissues play an increasing role in the conjugation of phenol as the dose of phenol increases; at doses higher than 5 mg/kg body weight, intestinal conjugation in rats exceeds the contribution of the hepatic and pulmonary enzymes (Cassidy & Houston, 1984).

Myeloperoxidases isolated from human neutrophils and peroxidative enzymes from activated human leucocytes mediate the formation of reactive phenol metabolites including 4,4'-biphenol and diphenoquinone. Myeloperoxidase-mediated hydroxylation occurs in addition to hepatic cytochrome P-450 oxidation. In several species, myeloperoxidase activity has been reported in bone marrow, where it may play a role in phenol metabolism and toxicity (Eastmond *et al.*, 1986, 1987a; Subrahmanyam *et al.*, 1991).

6.4 Elimination and excretion

Urinary excretion is the major route of phenol elimination in animals and humans. The rate of excretion varies with dose, route of administration and animal species (Deichmann, 1944; Capel *et al.*, 1972a,b). Of 18 animal species studied by Capel *et al.* (1972a,b), the 24-h urinary excretion of phenol was greatest in the rat (95% of the 25 mg/kg body weight oral dose) and the lowest in the squirrel monkey (only 31% of the dose). Liao & Oehme (1981a,b) reported a half-life of 4 h in rats.

Five days after oral gavage with ^{14}C-phenol (0.1 mg/kg body weight), only 0.3% of the applied dose was retained in rats (Freitag *et al.*, 1985).

Only minor amounts of unchanged phenol are excreted in exhaled

air or in faeces (Deichmann & Keplinger, 1963). Less than 1% of an orally administered dose of 300 mg phenol/kg body weight to rabbits was found in the faeces after 24 h (Deichmann, 1944).

Phenol conjugates may also be excreted in the bile of rats (4.6% of a 50 mg/kg dose) (Abou-el-Makarem *et al.*, 1967). It has been suggested that biliary excretion of phenol plays an important role when urinary excretion is impeded. Rats, whose kidneys were ligated, showed a marked increase in biliary excretion of phenol metabolites (Weitering *et al.*, 1979). Furthermore, it has been reported that phenol and its metabolites can undergo enterohepatic circulation in rats (Gbodi & Oehme, 1978).

Urinary excretion of phenol in human volunteers exposed to phenol vapour via inhalation (chamber studies) or skin, occurred with an excretion rate constant of k = 0.2/h. For a one-compartment model, this corresponds to a half-life of approximately 3.5 h (Piotrowski, 1971).

6.5 Biological monitoring

The US ACGIH has listed a biological exposure index for phenol of 250 mg/g creatinine for end-of-shift urine samples (ACGIH, 1991).

The excretion of phenol and phenol conjugates in the urine may be used as an index of exposure, but it should be noted that there are other causes that may lead to phenol excretion in the urine. One of these is benzene exposure; other possible significant sources are food and drugs (Docter & Zielhuis, 1967; Ikeda & Ohtsuji, 1969; Fishbeck *et al.*, 1975; Paradowski *et al.*, 1981). Elevated urinary phenol excretion is thus not a specific index of exposure to phenol. Furthermore, the large range of "normal" urine values (phenol concentrations have been found to vary from 0.5 to 81.5 mg/litre) (Deichmann & Schafer, 1942; Docter & Zielhuis, 1967; Piotrowski, 1971; Gspan *et al.*, 1984; Pekari *et al.*, 1992) would appear to limit the usefulness of urinary phenol excretion as an accurate index of low occupational exposure levels.

In volunteers, after a single 8-h exposure to phenol vapour concentrations of up to 6.8 mg/m^3, the phenol excretion in urine increased up to a maximum of 100 mg total phenol/litre (Piotrowski, 1971). In workers occupationally exposed to 10 mg phenol/m^3, concentrations in urine of up to 262 mg/litre were reported (Ohtsuji & Ikeda, 1972). However, another recent study, using more specific methods of analysis, showed good correlation (R=0.91) between exposure levels in the range 5-17 mg/m^3 and the total concentration of phenyl sulfate and phenyl glucuronide in the urine at the end of the workshift (Ogata *et al.*, 1986).

7. EFFECTS ON LABORATORY MAMMALS, AND IN VITRO TEST SYSTEMS

7.1 Single exposure

7.1.1 LD50 values

After oral administration of phenol to mice, rats and rabbits, LD_{50} values ranged from 300-600 mg phenol/kg body weight. No LC_{50} values have been reported in the published literature. However, after inhalation of 900 mg phenol/m^3 by rats for 8 h, no deaths were observed. The dermal LD_{50} (by occlusive and non-occlusive techniques) was 670 mg/kg body weight for rats and 850-1400 mg phenol/kg body weight for rabbits. LD_{50} values for intraperitoneal injection were in the range of 127-223 mg phenol/kg

body weight for rats.

A summary of LD_{50} values is given in Table 5.

7.1.2 Effects

The acute lethality of phenol, associated with exposure to high concentrations, is generally attributed to a depressing effect on the central nervous system (see also section 7.8.1). The clinical effects of phenol poisoning are independent of the route of administration. Reported symptoms include neuromuscular hyperexcitability, including twitching and severe convulsions. Heart rate at first increases, then becomes slow and irregular. Blood pressure at first increases slightly, then falls markedly. Salivation, marked dyspnoea and a decrease in body temperature are also among the effects reported (Deichmann & Witherup, 1944; Von Oettingen & Sharples, 1946; Farquharson *et al.*, 1958; Ernst *et al.*, 1961; Deichmann & Keplinger, 1963; Oehme & Davis, 1970; Pullin *et al.*, 1978; Liao & Oehme, 1980; Reid *et al.*, 1982).

After oral ingestion, the mucous membranes of the throat and oesophagus showed swelling, corrosion, and necrosis, with haemorrhages (Deichmann & Keplinger,1963).

In a study by Schlicht *et al.* (1992), female Fischer-344 rats were administered 0, 12, 40, 120 or 224 mg phenol/kg body weight by gavage in a water vehicle. Animals were examined for clinical signs, and neurotoxicity and systemic (liver, kidney, adrenal and thymus) effects, 4-20 h after treatment. Tremors were observed 1-2 min after dosing in the two highest dose groups. The pupil response to light (miosis) was significantly inhibited at all dose levels at 24 h after exposure. Locomotor activity was reduced at 224 mg/kg. At this dose level, 2/6 animals had hepatocyte necrosis, 4/6 had renal vascular stasis and 4/6 had necrosis of the thymus. At 120 mg/kg, liver necrosis was present in 1/7 animals, as was necrosis of the thymus gland.

Table 5. Acute animal toxicity of phenol LD_{50} values

Species	Route of administration	LD_{50} values (mg/kg body weight)	Vehicle	Reference
Mouse	oral	300		Von Oettingen & Sharples (1946)
Mouse	oral	427		Kostovetskii & Zholdakova (1971)
Rat	oral	340-530	2-7% in water	Deichmann & Witherup (1944)
Rat	oral	512		Kostovetskii & Zholdakova (1971)
Rat	oral	445-520	water	Thompson & Gibson (1984)
Rat	oral	400	water	Schlicht *et al.* (1992)
Rat	dermal	670 (570-780)	undiluted	Conning & Hayes (1970); Brown et al

				(1975)
Rat	intraperitoneal	127-223	water or undiluted	Thompson & Gibson (1984)
Rabbit	oral	400-600	2-7% in water	Deichmann & Witherup (1944)
Rabbit	dermal	850 (600-1200)		Flickinger (1976)
Rabbit	dermal	1400 (740-2670)		Vernot *et al.* (197

In various animal species, inhalation of phenol adversely affected the lungs, causing hyperaemia, infarcts, bronchopneumonia, purulent bronchitis and hyperplasia of the peribronchial tissues (Von Oettingen, 1949).

Sensory irritation was measured in mice by the Alarie assay. A 50% decrease in respiratory rate (RD_{50}) was found at 638 mg phenol/m^3 (De Ceaurriz *et al.*, 1981).

Ocular and nasal irritation, tremors and incoordination were reported in rats exposed via inhalation to 906 mg/m^3 for 8 h (Flickinger, 1976).

Other pathological abnormalities induced by phenol by various routes of administration included demyelination of nerve fibres (see also section 7.8.1), myocardial degeneration and necrosis (Deichmann & Keplinger, 1963; Liao & Oehme, 1980). Kidney damage (vacuolization and enlargement of cells) and liver damage (e.g., enlargement of hepatic cells) were also observed (Oehme & Davis, 1970; Coan *et al.*, 1982). Urine was usually dark or "smoky" in appearance, probably due to oxidation products of phenol (Solliman, 1957).

7.2 Short-term exposure

7.2.1 Oral exposure

In a study by Schlicht *et al.* (1992), groups of eight female Fischer-344 rats received oral doses of phenol in a water vehicle of 0, 4, 12, 40 or 120 mg/kg body weight daily for 14 days. Tremors were apparent only after the first dose at the highest level. Exposure to 120 mg/kg per day was lethal to all rats within 11 days. The pupil response (miosis) was decreased one day after the last dose for all but the highest surviving dose group (the incidences were 100%, 50%, 62% and 76% for the 0, 4, 12 and 40 mg/kg groups, respectively). Locomotor activity was not affected after the 4th, 9th or 14th dose. No hepatic effects were observed at 40 mg/kg per day, while 3/8 animals had renal vascular stasis. There were no histological effects at 12 mg/kg per day. At 40 mg/kg per day, the pathological changes in the kidneys included two animals with tubular degeneration in the papillar region, and one with protein casts in the tubules. The pathological report attributed these findings to decreased vascular perfusion (MacPhail, personal communication to the IPCS).

Rats were administered, by gavage, 20 daily doses of 10, 50 or 100 mg phenol/kg body weight. At necropsy, slight effects on liver and kidneys were reported at 100 mg phenol/kg body weight (Dow Chemical Company, 1976).

Rats receiving 50 or 100 mg phenol/kg body weight, by gavage, over a 6-month period (135 doses, presumably daily, 5 days/week) were reported to show slight to moderate kidney damage. Administration of 100 mg phenol/kg body weight apparently resulted in slight liver changes (Dow Chemical Company, 1976).

In a range-finding study, carried out prior to a long-term carcinogenicity study, mice and rats were provided with tap water containing 0, 100, 300, 1000, 3000 or 10 000 mg phenol/litre for 13 weeks. Mean body weight gain was decreased only in mice and rats receiving 10 000 mg phenol/litre (NCI, 1980). In these drinking-water studies, the highest daily doses were calculated to be approximately 2000 mg phenol/kg body weight for mice and 1000 mg phenol/kg body weight for rats.

Phenol was provided to rats in drinking-water for 12 months at 0, 800, 1200, 1600, 2000 and 2400 mg phenol/litre. Depressed weight gain was observed in rats receiving doses $\geq$ 2000 mg/litre. The corresponding daily dose was calculated by the authors of the study to be $\geq$ 200 mg/kg body weight (Deichmann & Oesper, 1940).

7.2.2 Dermal exposure

In a study by Deichmann *et al.* (1950), rabbits were exposed to 1.18-7.12% phenol in water (64-380 mg phenol/kg body weight) for 5 h/day, 5 days/week, for 18 days. Dose-related systemic effects (tremors, death) were observed in rabbits exposed to $\geq$ 2.37% phenol (130 mg phenol/kg body weight), while skin irritation (hyperaemia, tissue necrosis) occurred at doses of $\geq$ 3.56% phenol (190 mg phenol/kg body weight). This effect was particularly apparent when the application sites were bandaged.

7.2.3 Inhalation exposure

No studies reported or conducted according to contemporary standards were available.

In a study by Deichmann *et al.* (1944), rats, rabbits and guinea-pigs were exposed to concentrations of 100-200 mg phenol vapour/m^3, 7 h/day, for 5 days/week. Rats exposed for a period of 74 days did not show any gross or microscopic evidence of injury. Rabbits survived a 3-month exposure but, at autopsy, lung and heart damage and indications of liver and kidney damage were found. Guinea-pigs were the most susceptible. Five out of twelve died after 12 days of exposure, and the remaining seven were killed after 29 days of exposure. Prior to death, guinea-pigs showed weight loss, respiratory difficulties, and signs of paralysis. At autopsy, there was evidence of acute lobular pneumonia, vascular damage, and hepatic and renal damage; the total (free and conjugated) phenol content of the blood was 14 mg/litre. The rabbits had similar, but less severe, symptoms.

Groups of 10 monkeys, 50 rats and 100 mice were exposed to 19 mg phenol/m^3, 8 h/day, 5 days/week for 90 days. Concurrent control groups were exposed to fresh air only. No deaths occurred and there was no reduction in weight gain of treated animals. There were no statistically significant adverse effects observed when the animals were assessed by a stress test involving swimming performance. A range of clinical chemistry, haematology and urinalysis parameters were not affected by exposure to phenol. Routine histology was performed on the liver, lungs, kidneys, brain and heart. The results of the percentage of animals showing evidence of "pathological

change" indicated effects in the liver and kidneys of exposed animals. However, the author of the study concluded that no clinical or pathological changes occurred that were of toxicological importance. It is not clear if the upper respiratory tract was examined in this study in order to look for evidence of irritation (Sandage, 1961).

Continuous exposure to 100 mg phenol/m^3 for 15 days significantly affected the central nervous system of rats, as was demonstrated by their performance in the "tilted plane" test. Plasma levels of potassium, magnesium, lactate dehydrogenase, aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT) and glutamate dehydrogenase were elevated. Haemoglobin, haematocrit, and plasma sodium, calcium and chloride levels were unaffected (Dalin & Kristofferson, 1974).

7.2.4 Subcutaneous exposure

Subcutaneous exposure to phenol was studied principally to obtain information about neurological or haematopoietic effects (see sections 7.8.1 and 7.8.2). No other effects were reported.

7.2.5 Ear exposure

Instillation of phenol (form and amount not specified) into the inner ear round window of Sprague-Dawley rats caused morphological damage to the organ of Corti in the basal coil. The outer hair cells appeared to be more sensitive to phenol than the inner hair cells, which were mostly intact. As a result of the damage, impairment of inner ear function was noted (as determined by auditory brain stem recordings) which was regressive for lower sound frequencies, but appeared to be permanent for higher frequencies (Anniko *et al.,* 1988).

7.3 Skin and eye irritation; sensitization

Local damage to the skin, following exposure to phenol, was found to include erythema, inflammation, discoloration, eczema, papillomas and necrosis (Deichmann, 1949; Deichmann *et al.,* 1950; Conning & Hayes, 1970; Pullin *et al.,* 1978). For example, in rabbits, 0.5 g phenol, moistened with physiological saline, produced necrosis of both the intact and abraded skin (Flickinger, 1976).

Solutions of 10-14% (v/v) phenol in water have been reported to cause transient delayed erythema (after 0.5-5 h) and acute vascular permeability, as assessed by exudation of intravenously injected Evans blue, in guinea-pigs after dermal treatment for 1 min (Steele & Wilhelm, 1966).

In one study, an increase in ear thickness was used as an index of skin irritation (inflammation). Maximal responses to phenol were observed one hour after application of 1-2 mg phenol to the ear of female ICR mice. Significant thickening could still be detected 6 weeks after exposure (Patrick *et al.,* 1985).

When phenol, in glycerine dilutions down to 10% or 5% aqueous solutions, was applied to the rabbit eye, severe damage (complete destruction to opaque corneas) was seen. Immediate water irrigation was very effective in preventing the opacity. A delay of 10 seconds reduced this effectiveness (Murphy *et al.,* 1982).

Fourteen days after the application of 0.1 g phenol to the rabbit eye, all eyes exhibited keratoconus and pannus formation

(Flickinger, 1976).

Phenol gave negative results in a Magnussen and Kligman skin sensitization test (Itoh, 1982).

7.4 Long-term exposure

No adequate data are available. Studies on carcinogenicity are presented in section 7.7.

7.5 Reproduction, embryotoxicity and teratogenicity

7.5.1 Reproductive toxicity

No adequate studies conducted according to current protocols are available.

Heller & Pursell (1938) exposed rats to 100-12 000 mg phenol/litre drinking-water, corresponding to calculated approximate daily oral doses of 10-1200 mg phenol/kg body weight. General appearance, growth and fecundity were normal for rats exposed to 100-1000 mg/litre for five generations and to 3000 or 5000 mg/litre for three generations. Stunted growth was noted in the offspring of rats exposed to 7000 mg/litre. Many of the offspring died at levels of 8000 mg/litre because of maternal neglect. At 10 000 mg/litre, the offspring died at birth, and at 12 000 mg/litre there was no reproduction.

7.5.2 Embryotoxicity/teratogenicity

7.5.2.1 In vivo studies

Phenol was evaluated for maternal and developmental toxicity in timed-pregnant Sprague-Dawley rats (20-22 confirmed pregnancies per group). Distilled water (vehicle) or phenol (30, 60 or 120 mg/kg per day) was administered daily by gavage in a volume of 5 ml/kg of body weight throughout the period of major organogenesis (gestational days 6-15). Dams were weighed on the day of sperm detection (gestational day 0), prior to daily dosing, and at termination

(gestational day 20); observations for clinical signs of toxicity were conducted during the treatment period. At termination (gestational day 20), maternal liver weight, gravid uterine weight and status of uterine implantation sites (i.e. number of implants, resorptions, late fetal deaths and live fetuses) for each dam were recorded. Each live fetus was weighed, sexed and examined for external morphological abnormalities. Visceral examination of each fetus was performed using a fresh tissue dissection method; approximately one-half of the fetal heads from each litter were fixed (Bouins' solution) and sectioned free-hand for examination of internal structures; carcasses (one-half without heads) were cleared and stained with Alizarin Red S prior to skeletal examination. All control and phenol-treated dams survived to scheduled sacrifice, and no distinctive treatment-related signs of toxicity were noted. Pregnancy rates at termination were high (95-100% per group) and no litters were totally resorbed, so that a total of 20-22 live litters per group (268-293 fetus per group) was available for examination. No significant dose-related changes were noted for the following end-points: maternal body weight (gestational day 0, 6, 11, 15 or 20), maternal body weight gain (treatment period, gestational period or gestational period corrected for gravid uterine weight), maternal liver weight, gravid uterine weight, prenatal mortality, live litter size or incidence of morphological abnormalities (malformations or variations). However, average fetal body weight per litter was

significantly reduced at the high-dose (93% of average control weight) (Jones-Price *et al.,* 1983a).

In a study by Kavlock (1990), phenol was administered by oral gavage to groups of Sprague-Dawley rats on day 11 of gestation (day 1 : sperm plug) at 0, 100, 333, 667 and 1000 mg phenol/kg body weight. The vehicle used in this study was a 4:4:1:1 mixture of water, Tween 20, propylene glycol and ethanol. Maternal toxicity (decreased weight gain) was seen at the two highest doses. Offspring viability and growth were not affected up to postnatal day 6,but hind limb paralysis was observed in some offspring in the two highest dose groups.

In a screening assay, groups of 17-21 Fischer-344 rats received 0, 40 or 53.3 mg phenol/kg body weight by gavage in water on gestation days 6-15. There were no significant effects on maternal body weight gain. One of 15 pregnant females resorbed the entire litter at 40 mg/kg and 2 of 16 did so at 53.3 mg/kg (there were no similar effects in 153 control litters in the study). All three females had severe respiratory syndromes (rales and dyspnoea). One high-dose female with symptoms of respiratory toxicity delivered a low weight litter that had poor viability. Kinked tails were present in 2 of 4 surviving pups in that litter. Litter size on postnatal days 1 and 6 was significantly reduced at 53.3 mg/kg but not at 40 mg/kg. There were no effects on pup body weights on postnatal days 1 or 6 (Narotsky & Kavlock, 1993).

Phenol was evaluated for maternal and developmental toxicity in timed-pregnant Swiss albino (CD-1) mice (22-29 confirmed pregnancies per group). Distilled water (vehicle) or phenol (70, 140 or 280 mg/kg per day) was administered daily by gavage in a volume of 10 ml/kg of body weight throughout the period of major organogenesis (gestational days 6-15). Dams were weighed on the day of vaginal plug detection (gestational day 0), prior to daily dosing (gestational days 6-15), and at termination (gestational day 17); observations for clinical signs of toxicity were conducted during the treatment period. Evaluation of maternal and developmental end-points at termination (gestational day 17) were the same as for rats (see description from the study by Jones-Price *et al.,* 1983a, above). Toxicity observed at the high-dose level included 11% mortality (4/36 treated females), clinical signs (especially tremor and ataxia), reduced maternal body weight (gestational day 17), reduced maternal body weight gain (treatment period, gestational period and gestational period corrected for gravid uterine weight), and a trend only toward reduced maternal liver weight. Pregnancy rates at termination ranged from 71 to 84%; no litters were totally resorbed so that 22-29 live litters (214-308 fetuses) were available for examination. No dose-related changes were noted for prenatal mortality, live litter size or incidence of morphological abnormalities, except for an apparent increase in cleft palate (8/214 fetuses in the high dose versus 0/308 among controls). (It should be noted that cleft palate is a malformation to which the CD-1 mouse is predisposed under conditions of maternal stress). Average fetal body weight per litter was significantly reduced (82% of average control weight) in the highest dose group (Jones-Price *et al.,* 1983b).

In a study by Minor & Becker (1971), groups of Sprague-Dawley rats were given 20, 63, or 200 mg phenol/kg body weight intraperitoneally on days 9-11 or 12-14 of gestation. Fetal body weight was reduced in the highest dose group treated on days 12-14. No gross anomalies were observed, and intrauterine death was not increased at any dose level.

7.5.2.2 In vitro studies

In the chick embryotoxicity screening test (CHEST), 130 substances were tested. For each compound, 120 selected White Leghorn Fowl embryos, aged 1.5, 2, 3 and 4 days of incubation, were used. Phenol did not exhibit embryotoxic properties in this test up to 100 µg, and was one of the least embryotoxic compounds tested (Jelinek *et al.*, 1985).

In a study by Oglesby *et al.* (1992), phenol was added to cultures of five rat embryos on gestational day 10 at concen-trations of 0 to 100 µg/ml. Embryos were examined 42 h later for viability, growth and morphology. Viability was not affected at any concentration, but a low incidence of tail defects was observed

at 100 µg/ml, and embryonic growth was decreased at 75 and 100 µg/ml. When hepatocytes isolated from pregnant rats were co-cultured with the embryos, the toxicity to the embryos was increased. Tail defects were observed at 25 and 50 µg/ml, and growth was reduced at these concentrations. Without the presence of hepatocytes, phenol was the least toxic of 13 para-substituted phenols tested in this system; however, it was the only one which became more embryotoxic when hepatocytes were present.

When phenol was added to cultures of human embryonic palatal mesenchyme cells, cell growth was 50% inhibited at a concentration (IC_{50}) of 0.8 mM (78 µg/litre) (Pratt & Willis, 1985).

7.6 Mutagenicity and related end-points

Data on mutagenicity and related end-points are summarized in Tables 6, 7, 8 and 9, respectively.

7.6.1 Mutagenicity studies

7.6.1.1 Bacterial systems

Phenol has been tested for mutagenicity by a number of authors in various strains of *Salmonella typhimurium* and was shown to be reproducibly negative, both with and without metabolic activation (Epler *et al.*, 1979; Gilbert *et al.*, 1980; Rapson *et al.*, 1980; Pool & Lin, 1982; Haworth *et al.*, 1983). A positive effect was observed in strain TA98 in the presence of an exogenous metabolic activation system in a study employing a modified culture medium (Wild *et al.*, 1980; Gocke *et al.*, 1981).

A positive effect was reported for phenol in a fluctuation test with strain TA100 after metabolic activation, but no data were given on toxicity (Koike *et al.*, 1988; abstract). A positive result was reported in a mutation test with *Escherichia coli* B/Sd-4; however, the applied dose levels were highly toxic (Demerec *et al.*, 1951).

7.6.1.2 Non-mammalian eukaryotic systems

Negative data were obtained in the absence of exogenous metabolic activation with the eukaryotic microorganism *Saccharomyces cerevisiae.* At high doses and in the presence of an activation system, a positive result was obtained (Cotruvo *et al.*, 1977). Phenol induced mitotic segregation in *Aspergillus nidulans* (Crebelli *et al.*, 1987).

Table 6. Tests for genotoxicity in bacteria

Species	Strain	Measured end-point	Test conditions
Escherichia coli	Sol-4	reverse mutation	0.1-0.2%; 3-24 h (survival less than 2%)
	AB1899 nm	filamentation	10-500 µg/ml; 3-4 h
Salmonella typhimurium	TA100	reverse mutation	fluctuation test 0-500 ng/well
	TA98 TA100	reverse mutation range in DMSO[c]	1000-fold concentration (1979)
	TA1535	reverse mutation	0-100 µg/plate
	TA1538	reverse mutation	0-50 µg/plate
	TA98 TA100 TA1535 TA1537	reverse mutation	0-3333 µg/plate in DMSO; preincubation
	TA98 TA100 TA1535 TA1537	reverse mutation preincubation H_2O;	0-3333 µg/plate in
	TA98 TA100 TA1535 TA1537 TA1538	reverse mutation DMSO (5000 µg toxic)	0.5-5000 µg/plate in

Table 6 (contd).

Species	Strain	Measured end-point	Test conditions
	TA100 (1980)	reverse mutation	0.1-1000 µg/plate
	TA98	reverse mutation	0-100 µmol/plate (99.5% purity with 0.15% + (ra cresols as main impurit non-standard media)

[a] + = present; - = absent
[b] + = positive; - = negative
[c] DMSO = dimethyl sulfoxide

Table 7. Tests for genotoxicity in non-mammalian eukaryotic systems

Species	Strain	Measured end-point	Test conditions

Fungi			
Saccharomyces cerevisiae	D3	mitotic recombination	10^{-5}, 10^{-3} dilution of phenol in saline
Aspergillus nidulans		mitotic segregation	5-20 mM
Insects			
Drosophila melanogaster	Oregon-R	SLRL[b]	phenol vapour 24 h; 0.2, 0.25, 0.5% in saline, injection
			0.01, 0.1, 1.2% in Holtfreter solution; vaginal douch
	Berlin K	SLRL	50 nM in 5% saccharos feeding, 3 broods F_1 generation
			injection
Fish			
Salmo gairdneri		chromosomal aberrations	0.3-0.6 µl/litre, 72

[a] + = positive; - = negative
[b] SLRL = sex-linked recessive lethal mutations

Table 8. *In vitro* phenol genotoxicity in mammalian cells

Species	Cell type	End-point[a]	Conditions
Chinese hamster	CHO-WBL	CA	500-800 µg/ml
			2000-3000 µg/ml
Chinese hamster	V79 lung	forward mutation HPRT	0-500 µg/ml (500 µg/ml toxic)
Chinese hamster	CHO-WBL	SCE	300-400 µg/ml
			2000-3000 µg/ml
Chinese hamster	V79 lung	intercellular communication	not reported
	V79 lung	intercellular communication	250 µg/ml
	V79 lung	intercellular communication	10-75 µg/ml
Mouse	L5178Y lymphoma	forward mutation TK	600-1800 µg/ml

	L5178Y	forward mutation	180-890 µg/ml (530 µg/ml toxic)
			5.6-41 µg/ml (20 µg/ml toxic)
Mouse	L5178Y	DNA synthesis inhibition	9.4-940 µg/ml
	L5178Y	DNA strand breaks	16-470 µg/ml
			16-470 µg/ml

Table 8 (contd).

Species	Cell type	End-point[a]	Conditions
	L5178Y	DNA strand breaks	94 µg/ml
Human	T-lymphocytes	SCE	0.47-282 µg/ml
	lymphocytes	SCE	188 µg/ml
	lymphocytes	SCE	1.7-470 µg/ml (470 µg/ml toxic)
	lymphocytes	SCE	282 µg/ml
Human	fibroblast	DNA repair	0.094-9400 µg/ml
	HeLa	DNA synthesis inhibition	188 µg/ml
	WI-38	DNA synthesis inhibition	0.094-9400 µg/ml

[a] CA = chromosome aberrations; HPRT = hypoxanthine guanine phosphoribosyl tr
SCE = sister chromatid exchange
[b] - = absent; + = present;
[c] - = negative; + = positive

Table 9. Phenol genotoxicity in in vivo mammalian systems

Species/Strain	Measured end-point	Test conditions (sampling times)
Mouse/CD-1	micronuclei in bone marrow	265 mg/kg, oral (0, 18, 24, 42 or 48 h)
Mouse/CD-1	micronuclei in maternal bone marrow and fetal liver	gestation day 13, 265 mg/kg oral (15, 18, 24, 30, 36 or
Mouse/CD-1	micronuclei in bone marrow	250 mg/kg, oral (30 h)
Mouse/CD-1	micronuclei in bone	265 mg/kg, i.p.

	marrow	(18, 24, 42 or 48 h)
Mouse/CD-1	micronuclei in bone marrow	40, 80 or 160 mg/kg, i.p. (18 h)
Mouse/NMRI	micronuclei in bone marrow	47, 94 or 188 mg/kg, i.p. 0, 24 h (30 h)
Mouse/Porton	chromosomal aberrations in spermatogonia, primary spermatocytes	2 ml of 0.08, 0.8 or 8 mg/l solution, oral, daily for f generations
Rat/Sprague-Dawley	chromosomal aberrations in bone marrow	72-180 mg/kg, i.p. 300-510 mg/kg, oral (20 h)
Rat/Sprague-Dawley	DNA strand breaks (alkaline elution in rat testis)	7.9, 26 or 79 mg/kg, i.p. (or 24 h) 4, 13.2 or 39.5 mg i.p. for 5 days

[a] + = positive; - = negative; i.p. = intraperitoneal injection

In *Drosophila melanogaster,* no statistically significant sex-linked recessive lethals were obtained after exposure to phenol via a variety of techniques (Sturtevant, 1952; Wild *et al.,* 1980; Gocke *et al.,* 1981; Woodruff *et al.,* 1985). However, when an unusual technique was used, i.e. exposing isolated gonads *in vitro* and implanting them in host larvae, several types of mutations were induced (Hadorn & Niggli, 1946).

When rainbow trout (*Salmo gairdneri)* were exposed to phenol for 72 h at concentrations of 0.3 and 0.6 µl phenol/litre water, the percentage of chromosomal aberrations in gill and kidney tissue was significantly increased, at both concentrations, in a dose-related way. Of these aberrations, 30% were structural, 45% consisted of aneuploidy, and 25% were non-specified metaphases (Al-Sabti, 1985).

7.6.1.3 Mammalian in vitro systems

Data on *in vitro* genotoxicity in mammalian cells are given in Table 8.

In a Chinese hamster V79 lung cell/HPRT mutation test, phenol gave a positive result with metabolic activation. The highest dose decreased survival by approximately 50% (Pashin & Bakhitova, 1982). In a mouse lymphoma L5178Y cell/TK mutation test, there were statistically significant and dose-related increases in mutation frequency in the presence and absence of metabolic activation (Wangenheim & Bolcsfoldi, 1988). However, in another laboratory this test yielded non-conclusive results (McGregor *et al.,* 1988).

As part of the US NTP testing program, phenol was evaluated for induction of chromosomal aberrations and sister chromatid exchange (SCE) in Chinese hamster ovary (CHO) cells (Ivett *et al.,* 1989). At a delayed harvest time (22.5 h), there were significantly increased incidences of aberrations in cultures that included a metabolic activation system from induced rat liver. Although a dose-response effect was seen, the frequency of aberrations in the absence of activation was low and the authors reported a negative result. Regarding SCE induction, positive results were obtained, both with and without activation. In additional studies, phenol induced SCE in human lymphocytes *in vitro,* both in the presence

and in the absence of metabolic activation (Morimoto & Wolff, 1980; Morimoto *et al.,* 1983; Erexson *et al.,* 1985). Negative results (SCE) have also been reported (Jansson *et al.,* 1986).

Phenol gave negative results in three studies in Chinese hamster V79 cell metabolic cooperation assays (Chen *et al.,* 1984; Malcolm *et al.,* 1985; Bohrman *et al.,* 1988).

7.6.1.4 Mammalian in vivo system: somatic cells

In a bone marrow micronucleus test, groups of four Swiss CD-1 mice (sex not specified) were orally administered 265 mg phenol/kg body weight and were sacrificed at 0, 18, 24, 42 and 48 h. Bone marrow depression (decreased polychromatic erythrocytes/normocytes (PCE/NCE) ratio) persisted at least up to 48 h after dosing. A slight, but statistically significant, increase in the number of micronuclei was seen at 24 h (3 micronuclei/1000 cells versus 1.5 micronuclei/1000 cells; 3000 cells scored per mouse) (Ciranni *et al.,* 1988b).

In a further study to asses the transplacental clastogenicity of phenol, groups of 4 pregnant Swiss CD-1 mice received 265 mg phenol/kg/body weight by oral gavage on day 13 of gestation. After 15, 18, 24, 30, 36 or 40 h, animals were sacrificed and adult bone marrow cells and fetal liver cells were scored for micronuclei. Slight, but statistically significant, increases in the frequency of micronucleated PCE in adult bone marrow were observed at 15, 18 and 24 h (3.8, 4.0 and 5.0 micronuclei/1000 cells, respectively, compared with 2/1000 for negative controls). A statistically significant reduction in the PCE/NCE ratio was seen at 18 and 36 h. Phenol had no effect on the frequency of micronuclei in fetal liver (Ciranni *et al.,* 1988a).

Bone marrow liver cells were also evaluated for the formation of micronuclei, 30 h after oral administration of 0 or 250 mg phenol/kg body weight to groups of five males Swiss CD-1 mice (Gad-El Karim *et al.,* 1986). Uptake was indicated by convulsive seizures in all mice receiving phenol (1000 PCEs scored per mouse).

Phenol (265 mg/kg body weight), administered to Swiss CD-1 mice by a single intraperitoneal injection, was reported to increase the frequency of micronuclei in bone marrow PCEs 18 h post-treatment (7 micronuclei/1000 cells). The increased frequency decreased at 24 h and was no longer statistically significant at 42 h. A decreased PCE/NCE ratio persisted in tests up to 48 h post-treatment (Ciranni *et al.,* 1988b).

Barale *et al.* (1990) reported a negative result in a bone marrow micronucleus test in Swiss CD-1 mice 18 h after treatment with phenol. There was no effect on the PCE/NCE ratio.

Gocke *et al.* (1981) briefly reported a negative result in a bone marrow micronucleus test, in which NMRI mice were sampled at 30 h, following i.p. injection of 47-188 mg phenol/kg. No information on toxicity was given.

The results of these and other studies are summarized in Table 9.

7.6.1.5 Mammalian in vivo systems: germ cells

Skare & Schrotel (1984) obtained negative results in studies of DNA strand breakage in rat testis. In one experiment, rats received by intraperitoneal injection 0, 7.9, 26 or 79 mg phenol/kg body

weight and were sacrificed at 2.6 or 24 h post-treatment. Similar results were obtained with further groups of rats that received 4, 13.2 and 39.5 mg phenol/kg body weight daily for 5 days before sacrifice.

In an unconventional study involving dosing (0, 6.4, 64 and 640 mg phenol/kg body weight) of five successive generations of male and female mice, large numbers of structural and numerical chromosomal aberrations were reported in spermatocytes and spermatozoa, with dose- and generation-related increases. The study was carried out with 138 male mice from an inbred stock after skin testing (Bulsiewicz, 1977).

7.7 Carcinogenicity

The evidence for the carcinogenicity of phenol in experimental animals, based on the studies summarized below, was recently considered by the IARC (1989) to be inadequate. Phenol was classified by US EPA in Group D (data inadequate for evaluating the carcinogenic potential) (Bruce *et al.*, 1987).

7.7.1 Oral exposure

In an NCI (1980) study, groups of 50 male and 50 female B6C3F_1 mice were given drinking-water containing 0, 2500 or 5000 mg phenol/litre for 103 weeks. As matched controls, groups of 50 male and 50 female mice received tap water. There was a dose-related decrease in water consumption and mean body weight gain in all groups of mice. In mice receiving 5000 mg phenol/litre, an increase in the number of uterine endometrial stromal polyps (5/48 = 10%) was observed (in matched controls the incidence was 1/50 = 2%). There was no evidence of an increased incidence of malignant tumours. The other observed neoplasms were of the usual number and type found in mice of this strain and age (NCI, 1980).

Groups of 50 male and 50 female Fischer-344 rats received 0, 2500 or 5000 mg phenol/litre drinking-water for 103 weeks, while the matched control group received tap water. Male and female rats given 5000 mg/litre showed a decrease in mean body weight from week 20 onwards. There were statistically significant increased incidences of phaeochromocytomas, leukaemias, lymphomas and C-cell thyroid carcinomas in males of the low-dose group (NCI, 1980). NTP considered this study negative for carcinogenicity due to the lack of a dose-response for the neoplasms and the lack of response in females.

7.7.2 Dermal exposure

Three studies examined the potential carcinogenicity of phenol following dermal application (Rusch *et al.*, 1955, Boutwell *et al.*, 1956; Bernard & Salt, 1982). However, none is considered adequate for the evaluation of carcinogenicity due to the short duration of exposure and/or use of inappropriate vehicles.

7.7.3 Inhalation exposure

No studies have been reported for this route of exposure.

7.7.4 Two-stage carcinogenicity studies

A dose of 3 mg phenol in acetone was applied to ICR/Ha Swiss mice 3 times per week for 52 weeks after initiation with 150 µg DMBA. Papilloma development was enhanced, compared with that of mice exposed to DMBA alone (Van Duuren *et al.*, 1968; Van Duuren &

Goldschmidt, 1976). These observations were in agreement with those from earlier reports on the promotional activity of phenol (Boutwell *et al.,* 1955, 1956; Salamon & Glendenning, 1957; Boutwell & Bosch, 1959; Wynder & Hoffmann, 1961).

A dose of 3 mg phenol in acetone applied 3 times weekly for 460 days to female ICR/Ha Swiss mice after initiation with 5 µg benzo[a]pyrene had a slight promoting activity. Simultaneous application of both agents showed a partial reduction in carcinomas compared with mice treated with benzo[*a]*pyrene alone (Van Duuren *et al.,* 1971, 1973; Van Duuren & Goldschmidt, 1976).

7.8 Special studies

7.8.1 Neurotoxicity

Tremors, convulsions, coma and death were reported after intraperitoneal and subcutaneous doses of phenol (Deichmann & Witherup, 1944; Ernst *et al.,* 1961; Windus-Podehl *et al.,* 1983). The tremors were enhanced by prior monoamine depletion following reserpine treatment (Suzuki & Kisara, 1985).

Upon histological examination of rats in which convulsions had been induced by subcutaneous phenol injection (200 mg/kg body weight given once a week for two weeks), two out of six animals showed spinal cord and spinal root degeneration (Veronesi *et al.,* 1986).

Phenol, given either intravenously or intra-arterially (250 µg), facilitated neuromuscular transmission and antagonized neuromuscular blockade by D-tubocurarine in cats. The effect was determined to be pre-synaptic in origin (Blaber & Gallagher, 1971).

Phenol caused diminution of the compound action potential in preparations of the saphenous nerve after acute and chronic perfusion (Schaumburg *et al.,* 1970).

Groups of five male CD-1 mice were supplied with drinking-water containing 0, 4.7, 19.5 or 95.2 mg phenol/litre for 4 weeks, at the end of which the concentrations of various neurotransmitters and their metabolites were measured in different parts of the brain. The largest effects were seen in levels of noradrenaline in the hypothalamus (significant decreases of 29 and 40% in the mid- and high-dose groups) and of dopamine in the corpus striatum (significant decreases of 21, 26 and 35% in the low-, mid- and high-dose groups). There were dose-related, but not always statistically significant, decreases in all of the neurochemicals measured in the hypothalamus: noradrenaline, dopamine, vanillylmandelic acid (VMA), 3,4-dihydroxy-phenylacetic acid (dopac), homovanillic acid (HVA), serotonin (5-HT) and 5-hydroxyindoleacetic acid (5-HIAA). There were significant decreases in VMA in the midbrain, corpus striatum and cortex, 5-HT in the midbrain, corpus striatum and medulla oblongata, and dopac in the cerebellum in the high-dose group only. There were also significant decreases in 5-HT and 5-HIAA in the hypothalamus of the mid- and high-dose groups (Hsieh *et al.,* 1992).

Continuous exposure of rats to 0.012, 0.12 and 5.3 mg phenol/m^3 for 61 days caused a shorter extensor muscle chronaxy and an increase in whole-blood cholinesterase activities in rats at concentrations above 0.012 mg phenol/m^3 (Mukhitov, 1964).

7.8.2 Myelotoxicity

Because phenol is an important metabolite of benzene, which is

known to exert a toxic effect on bone marrow (including leukaemia) after metabolic activation, many studies have been performed to investigate the possible myelotoxic action of phenol.

In an *in vitro* assay for toxicity to primary murine haematopoietic cell cultures, phenol showed slight and variable activity at a concentration of 0.4 mM, but there was marked toxicity at 2 mM. In comparison, the phenol metabolites catechol and hydroquinone exhibited marked toxicity at 0.04 mM (Seidel *et al.,* 1991).

Subcutaneous treatment with phenol (245 mg/kg body weight) significantly inhibited erythropoiesis in mice 48 h after treatment, as indicated by a ^{59}Fe uptake assay (Bolcsak & Nerland, 1983).

Intraperitoneal injection of 0-150 mg phenol/kg body weight to male $B6C3F_1$ mice, twice daily for 12 days, did not result in a suppression of bone marrow cellularity. However, simultaneous treatment of mice with 75 mg phenol/kg body weight and 25-75 mg hydroquinone/kg body weight (another benzene metabolite), produced a dose-related decrease in bone marrow cellularity, which was much more pronounced than after treatment with hydroquinone only. The observed effect closely resembled the myelotoxic effect of benzene (Eastmond *et al.,* 1987b). Subsequent *in vitro* studies by these and other investigators confirmed that phenol (0.01-1 mM) stimulates further bioactivation of hydroquinone to myelotoxic compounds in bone-marrow cells (Eastmond *et al.,* 1987b; Subrahmanyam *et al.,* 1989).

No haematopoietic toxicity was found in rats after daily subcutaneous injections of 250-750 mg phenol/kg body weight for 1 week. Of the rats receiving 750 mg phenol/kg body weight, 50% died (Mitchell, 1972).

Six consecutive subcutaneous injections of 50 mg phenol/kg body weight to mice resulted in a slightly but significantly reduced number of granulopoietic stem cells and bone marrow cellularity in the tibia (Tunek *et al.,* 1981).

7.8.3 Immunotoxicology

One immunological study has been reported. Female CD1 mice were exposed to 19 mg phenol/m^3 (5 ppm), either as a single 3-h exposure or as five daily 3-h exposures. Neither the susceptibility of the animals to experimentally induced streptococcus aerosol infection nor their pulmonary bactericidal activity was significantly affected (Aranyi *et al.,* 1986).

Groups of five male CD-1 mice were supplied with drinking-water containing 0, 4.7, 19.5 or 95.2 mg phenol/litre for 4 weeks, at the end of which various haematological and immunological parameters were measured. The erythrocyte count was statistically significantly decreased, compared with control values, in all treated groups in a dose-related manner, but total and differential leucocyte counts were unaffected. Total spleen cellularity was decreased in a non-significant dose-related manner. The highest dose suppressed the stimulation of cultured splenic lymphocytes by the B-cell mitogen lipopolysaccharide, the T-cell mitogen phytohaemagglutinin, and the T- and B-cell mitogen pokeweed, but not by concanavatin. The mid and high doses suppressed the animals' antibody production in response to a T-cell-dependent antigen, i.e. sheep erythrocytes (Hsieh *et al.,* 1992).

7.8.4 Biochemical effects

In a study on the biochemistry of intestinal mucosa, mice were provided with 0,5, 50 or 500 mg phenol/litre drinking-water (calculated by the authors to be 1, 10 and 100 mg phenol/kg body weight) for 5 days or 5 months at 1-day intervals. An increase in glucose-6-phosphatase, succinate dehydrogenase and cytochrome

oxidase activities in the intestinal mucosa was observed in mice receiving $\geq$ 0.02 mg phenol/kg body weight for 5 days. A decrease in these activities was seen at 2 mg phenol/kg body weight. After 5 months administration of 0.02 and 0.2 mg phenol/kg body weight, the enzyme activity had returned to normal, but the highest dose group showed a decline (or even a lack) of activity in the cells of the intestinal mucosa (Olowska *et al.*, 1980).

In another study of biochemical effects, mice were provided for 5 days (killed 24 h after the last application) and 35 days (killed 30 days after the last application) with aqueous solutions of 0.08, 0.8 or 8 mg phenol/litre. The authors of the study calculated the doses to be approximately 0.016, 0.16 and 1.6 mg phenol/kg body weight per day, respectively. Only the lowest dose of 0.08 mg phenol/litre evoked considerable changes in the localization of glucose-6-phosphatase, 5 days after treatment. Changes in alkaline phosphatase localization in the kidney were seen at 0.8 and 8 mg phenol/litre. Full recovery occurred after 30 days (Laszczynska *et al.*, 1983).

Inhalation exposure of 50 male white rats to 0.4 mg phenol/m^3, 24 h/day, 7 days/week, for 3 months, resulted in some inhibition of oxidative phosphorylation in the lungs, liver and kidneys. An increase in the rate of glycolysis was also observed in the lungs and kidneys (Skvortsova & Vysochina, 1976).

8. EFFECTS ON HUMANS

8.1 General population exposure

8.1.1 Controlled studies

In the Kligman maximization test, phenol did not cause sensitization in 24 human volunteers (Kligman, 1966).

It was reported by Rea *et al.* (1987) that, in a group of 134 "chemically sensitive" patients where several volatile organic chemicals were detected in the blood, 107 (80%) reacted adversely after a challenge exposure to phenol alone (0.008 mg/m^3). The criteria used to identify "sensitive patients" and "adverse reactions" were not specified. The toxicological significance of this finding is not known.

Mukhitov (1964) reported that six 5-min inhalation exposures to phenol at 0.015 mg/m^3 produced an increased sensitivity to light in each of 3 dark-adapted subjects.

8.1.2 Case reports

Various reports have appeared on the adverse effects of phenol in individuals or groups of humans after intentional (e.g., therapeutic) as well as accidental short-term exposure to phenol.

8.1.2.1 Dermal exposure

The use of phenol as a disinfectant and antiseptic was

introduced by Lister (1867). However, its use has been restricted by intoxications caused by these applications (Table 10).

Local effects after dermal phenol exposure consisted of erythema or painless blanching (Dreisbach, 1983), and, in more severe cases, corrosion (Schmidt & Maibach, 1981) and necrosis. The use of 5-10% phenol dressings for antiseptic purposes, for example, has led to many cases of necrosis of the skin and underlying tissues. When fingers and toes have been involved, amputation has sometimes been necessary. Due to their high toxicity, these dressings are no longer used (Cronin & Brauer, 1949; Deichmann, 1949; De Groote & Lambotte, 1960; Abraham, 1972).

Phenol chemical peel is a technique which has been used in superficial surgery of the skin for the last 30 years (Ersek, 1991). The phenolic mixture used classically is 3 ml of 50% phenol, 2 ml of water, 8 drops of soap and 8 drops of croton oil. This is applied to the skin to reduce pigmentation. Topical use of phenol as a chemical face-peel has been reported as being associated with cardiac dysrhythmias in "up to 30% of adults" (Morrison *et al.*, 1991), but only a single case report has been published (Warner & Harper, 1985). This report concerned a 10-year-old boy who had a solution, consisting of 40% phenol and 0.8% croton oil in hexachlorophene soap and water, applied to a large nevus covering 1.9% of his body surface whilst under anaesthesia (60% nitrous oxide and 3% halothane) and receiving a total of 200 ml of lactated Ringer's solution intravenously. After 55 min of treatment, multifocal and coupled premature ventricular complexes were detected by ECG, but blood pressure remained stable and plasma sodium and potassium concentrations were normal. An intravenous infusion of 250 mg bretylium sulfate suppressed the dysrhythmia and the boy had an uneventful recovery.

Systemic intoxication can occur very rapidly after absorption of phenol through the skin (Table 10). Most significantly, cardiovascular shock (sometimes resulting in death) and severe metabolic acidosis occur. Truppman & Ellenby (1979) observed cardiac arrhythmias (supraventricular as well as ventricular) in 10 out of 42 patients within 10 min after the application of approximately 5% phenol on half of the face for cosmetic treatment. Hyperventilation, kidney damage and methaemoglobinaemia have also been observed in several cases of exposure to phenol.

Table 10. Human dermal toxicity of phenol

Concentration (%)	Medium	Contact duration	Circumstances
100	crystals	30 min	in glove
80-100	water	20 min	spill on hip, thigh, death scrotum
80-100	water	2-4 days	closed dressings on open wounds
78	water	2-5 min	4-5 litres spilt on upper half of body
43.5	waste water	1 min	spill on lower half of body

5	ointment	7 days	closed dressing on cut
2	water	2.5 days	moist dressing over burns on 30% of body surface
2	water	11 h	closed bandage on infant umbilicus

Foxall *et al.* (1991) reported a case of acute renal failure following an industrial accident in which a man was partially submerged for a few seconds in a solution of 20% phenol in dichloromethane. He immediately showered, but was subsequently found in a state of collapse. His extremities were cold and he had 50% body burns. He developed nausea and vomiting after taking fluids. Anuria ensued, with a rise in plasma creatinine, but treatment with intravenous furosemide and haemodyalisis (daily for seven days, then with decreasing intervals for a further 18 days), allowed adequate urinary volumes to be produced. Respiratory distress required intensive care treatment. Marginal polyuria persisted one year after the accident.

8.1.2.2 Oral exposure

Cases of oral intoxication have occurred as a result of accidental and intentional ingestion. Local and systemic effects have been described in the literature, symptoms being similar to those following dermal exposure. Case reports have been published (Model, 1889; Stajduhar-Caric, 1968; Haddad *et al.,* 1979).

Death occurred within 10 min of ingestion of 4.8 g phenol (Andersen, 1869). However, ingestion of 56.7 g of a phenol-saline mixture was reported to have occurred without complaints (Leider & Moser, 1961), and an individual survived the ingestion of 57 g phenol (88%) after intensive treatment. Symptoms in the latter study included severe gastrointestinal irritation, as well as the expected cardiovascular and respiratory effects (Bennett *et al.,* 1950).

A severe accidental phenol spill in Wisconsin in 1974 contaminated ground water which was being used as drinking-water. Approximately one month later, several people living near the spill complained of health effects. Six months after the spill, medical histories were taken from 100 people who had consumed phenol-contaminated water (the authors estimated the daily exposure to be 10-240 mg phenol/person). In retrospect, a statistically significant increase was found in diarrhoea, mouth sores, dark urine and burning of the mouth, which had persisted for an average of 2 weeks. No significant abnormalities were found 6 months after initial exposure upon physical examination or laboratory analysis. Urinary phenol levels were not elevated (Delfino & Dube, 1976; Baker *et al.,* 1978).

A river in North Wales, United Kingdom, used for the preparation of drinking-water, was accidentally contaminated with phenol (Jarvis *et al.,* 1985). When the water was chlorinated, various chlorophenols appeared to have been formed. A retrospective postal survey of 344 households that received the contaminated tap water and 250 control households was carried out. Significantly more gastrointestinal illnesses, as well as other symptoms, were claimed in the contaminated areas than in the unexposed areas. Phenol

concentrations in drinking-water were conservatively estimated to have been 4.7-10.3 µg/litre for some days (Jarvis *et al.*, 1985).

8.1.2.3 Inhalation exposure

Very few cases of adverse effects after short-term phenol vapour exposure have been reported.

Hospital outbreaks of severe idiopathic neonatal unconjugated hyperbilirubinaemia have been associated with the phenol-containing disinfectant used for cleaning the nursery equipment, floors and walls. When the disinfectant was no longer used, the epidemic subsided (Daum *et al.*, 1976; Wysowski *et al.*, 1978; Doan *et al.*, 1979).

Studies of occupational inhalation exposure are described in section 8.2.

8.1.2.4 Exposure by injection

Phenol has been used as a neuron blocking agent in patients suffering from spasm following, for example, spinal cord damage or cerebrovascular stroke (Wood, 1978, review; Nathan, 1959; Cooper *et al.*, 1965; Khalili & Betts, 1967; Gibson, 1987). It has also been used to relieve chronic pain (Wood, 1978; Benzon, 1979; Smith, 1984). Treatment involved administering the phenol by intravenous injection or perfusion, or by direct injection into the spinal cord. Reported side-effects of phenol therapy were convulsions, transient paraesthesia, leg weakness, urinary and fecal incontinence, one case of a severe arterial block in the upper arm requiring amputation, and one case of acute bronchospasm (Wood, 1978, review; Benzon, 1979; Gibson, 1987; Atkinson & Skupak, 1989). In addition, there have been reports of phenol-induced cardiac dysrhythmia in adults (Forrest & Ramage, 1987) and in children, in whom an incidence of 19% was reported (Morrison *et al.*, 1991).

8.2 Occupational exposure

Poisoning due to chronic inhalation of phenol was known 100 years ago, primarily as a disorder in physicians and their helpers, under the term "carbol marasmus" (Lister, 1867). A classical case of phenol marasmus was described in a worker employed for 13´ years in a laboratory boiling phenol solutions. Symptoms were anorexia, weight loss, headache, vertigo, salivation and dark urine (Merliss, 1972).

A few studies are available concerning occupational exposure of workers in bakelite factories. Workers were exposed to phenol, and simultaneous exposure to formaldehyde occurred. Elevated phenol urine levels, unspecified complaints, and chronic airway obstruction were observed (Schoenberg & Mitchell, 1975; Knapik *et al.*, 1980).

Twenty-nine cases of poisonings among workers, who, during a 3-year period, quenched coke with a waste-water solution containing 0.3-0.8 g phenol/litre, were attributed to phenol intoxication. Phenol vapour concentrations in the air ranged from 0.5 to 12.2 mg/m^3. The number of workers and the symptoms of intoxication were not specified. The author did not consider the potential of dermal absorption (Petrov, 1960).

A case-control study was carried out on 57 cases among 3805 workers from the Finnish wood industry (particle board, plywood, sawmill or formaldehyde glue) suffering from respiratory cancer. The

inhalatory exposure level to phenol and frequency of multiple exposure to pesticides were found to be significantly higher for cancer cases, but the exposure to wood dust was not significantly different between cases and controls (Kauppinen *et al.*, 1986). The number of cases in this study was small, and confounding exposures were inadequately controlled.

In a case-control study of 6678 rubber workers, employed in areas where phenol was used, exposure to phenol was not associated with increased risks of cancer of the respiratory tract, stomach or prostate or of lymphosarcoma or lymphatic leukaemia (Wilcosky *et al.*, 1984).

A mortality study was conducted among 14 861 white male workers engaged in the production or use of phenol and formaldehyde in five companies within the USA. The follow-up comprised more than 360 000 man-years. Mortality rates from all causes combined were similar to those in the general population of the USA. Excesses of cancer of the oesophagus, cancer of the kidney and Hodgkin's disease were observed among the workers exposed to phenol, but these did not show any exposure-response relationship and were not statistically significant. Reduced mortality ratios were observed for cancer of the buccal cavity and pharynx, cancer of the stomach, cancer of the brain, arteriosclerotic heart disease, emphysema, disease of the digestive system and cirrhosis of the liver, although these reductions were not statistically significant. For arteriosclerotic heart disease, emphysema and cirrhosis of the liver, there were inverse relationships between mortality rates and duration of phenol exposure and cumulative phenol exposure levels (Dosemeci *et al.*, 1991).

A cardiovascular disease (CVD) mortality study was conducted among 1282 white male production workers in a large rubber- and tyre-manufacturing plant. Exposure estimates for 25 solvents were available (concentrations were not measured). The CVD mortality during 15-year follow-up period was analyzed in exposed and not exposed workers. The known association between CS2 exposures and ischemic heart diseases (IHD) was confirmed, and two other solvents, ethanol and phenol, were also found to be predictors of IHD. Phenol showed the strongest association with CVD mortality. However, some confounders (cigarette smoking, hypertension and high serum cholesterol) were not controlled and unrecognized chemical atherogens could also, according to the authors, influence the results (Wilcosky & Tyroler, 1983).

8.3 Organoleptic data

The odour threshold for phenol has been reported to range from 0.021 to 20 mg/m^3 (Van Gemert & Nettenbreijer, 1977; Van Gemert, 1984).

The geometric mean of 16 air odour thresholds and 6 water odour thresholds for phenol was reported by Amoore & Hautala (1983) to be 0.16 mg/m^3 (0.040 ppm, with a standard error of 0.026 ppm). In this calculation, the original literature was reviewed and values which diverged more than 100-fold from the nearest of two or more other thresholds were eliminated. Both detection and recognition values were included. The water detection threshold for phenol, based upon multiplying the calculated air odour threshold by the water-air distribution ratio, was reported by the same authors to be 7.9 mg/litre.

A taste threshold value of 0.3 mg/litre in water has been

reported (US EPA, 1992).

9. EFFECTS ON OTHER ORGANISMS IN THE LABORATORY AND FIELD

The toxicity of phenol has been studied in microorganisms (e.g., bacteria, fungi, algae and protozoa) and numerous aquatic invertebrates and vertebrates (Buikema *et al.*, 1979). Because of this vast amount of data, a selection has been made, based on the reliability of the data and the relevance of the test organisms. Details of acute and long-term aquatic toxicity studies, considered to be adequately performed and reported, are included in Tables 11 and 12. Less adequate studies are reported in the text only.

9.1 Microorganisms

Reliable phenol toxicity data for microorganisms are given in Table 11.

In microorganisms, growth inhibition is usually observed after phenol exposure. In studies on single bacterial species, the EC_{50} values (EC_{50} = calculated concentration affecting 50% of test population) found for growth inhibition varied from 244 mg phenol/litre in a newly developed, 6-h test with *Pseudomonas putida* (Slabbert, 1986) to 1600 mg phenol/litre after 18 h of exposure in a more conventional test with *Aeromonas hydrophila* (Dutka & Kwann, 1981). Bringmann & Kühn (1977) reported a toxicity threshold of 64 mg/litre after 16 h. EC_{50} values for reduced photoluminescence in *Photobacterium phosphoreum* of 28-34 mg phenol/litre (Dutka *et al.*, 1983) and 40 mg phenol/litre (Curtis *et al.*, 1982) have been reported. In activated sludge, the EC_{50} for a reduced oxygen uptake was reported to be 520-1500 mg phenol/litre, whereas a lower value was found for substrate consumption inhibition (104 mg phenol/litre) (Miksch & Schürmann, 1988; Volskay & Grady, 1988). The lowest reported concentration affecting activated sludge was 10 mg phenol/litre; 1 mg phenol/litre had no effect (Baird *et al.*, 1974).

Reported toxicity thresholds for protozoa were of the same order of magnitude as for bacteria: 33-144 mg phenol/litre (Bringmann & Kühn, 1959, 1980; Dive & LeClerq, 1977; Bringmann *et al.*, 1980). For algae, values were somewhat lower, but were observed after a longer exposure period: 6 mg phenol/litre for cyanobacteria (blue-green algae) and 8 mg phenol/litre for green algae, after 7-8 days of exposure (Bringmann & Kühn, 1978, 1980). The IC_{50} values (concentration causing 50% growth inhibition) reported for various fungi by Kwasniewska & Kaiser (1983) were of the same order of magnitude as the above EC_{50} values for bacterial growth inhibition: 460-1000 mg phenol/litre. These values are also within the range of concentrations observed by Babich & Stotzky (1985) to cause initial or complete growth inhibition in various fungi (100-1000 mg phenol/litre and 750->1000 mg phenol/litre, respectively).

Table 11. Acute aquatic toxicity of phenol

Organism	Temperature (°C)	pH	Dissolved oxygen (mg/litre)	Hardness (mg $CaCO_3$/ litre)
Freshwater Organisms				

Bacteria					
Photobacterium phosphoreum	15	6.5-6.7			
Pseudomonas putida	25	7.0		80.1	
	27	7.2			
Cyanobacteria					
Microcystis aeruginosa	27	7.0		72.3	
Green algae					
Scenedesmus quadricauda	27	7.0		72.3	
Protozoa					
Chilomonas paramaecium	20	6.9			
Colpidium campylum	20				
Entosiphon sulcatum	25	6.9		80.1	
Microregma heterostoma	27	7.5-7.8	213.6		

Table 11 (contd).

Organism	Temperature (°C)	pH	Dissolved oxygen (mg/litre)	Hardness (mg $CaCO_3$/ litre)	
Uronema parduczi	25	7.3			
Crustacea					
Asellus aquaticus	11 ± 1	7.5-8.1		99.5 ± 7.7	
Cypris subglobosa	20.4	7.9	8.4	204	
Daphnia magna	19.8-20.9	7.7-8.3		157 ± 4	
	19 ± 1	8.2 ± 0.3		199.4	
	19 ± 1	8.2 ± 0.3		199.4	
	17.2 ± 0.5	7.4 ± 0.2	8.7 ± 1.1	44.7	
	22 ± 1	6.8-7.8	7.6 ± 0.2	146 ± 15	
Gammarus pulex	11 ± 1	7.5-8.1	99.5 ± 7.7		
	7 ± 1	8.3	10.9	250	

Ceriodaphnia dubia	25 ± 1	8.18 ± 0.04		57.1 ± 4.1	
Mollusca					
Indoplanorbis exustus					

Table 11 (contd).

Organism	Temperature (°C)	pH	Dissolved oxygen (mg/litre)	Hardness (mg $CaCO_3$/ litre)	
Lymnaea acuminata	20 ± 2	7.9 ± 0.2	5.5 ± 1.5	190-223	
Worms					
Limnodrilus hoffmeisteri	11 ± 1	7.5-8.1		99.5 ± 7.7	
Polycelis felina	18	7-8.5	-[i]**	300-500	
Polycelis tenuis	11 ± 1	7.5-8.1		99.5 ± 7.7	
Fish					
Brachydanio rerio	25 ± 0.5	8.0-8.3	-[i]	350-375	
	24 ± 1		> 6	64	
Campostoma anomalum	23		-[i]		
Catostomus commersoni	17.2 ± 0.5	7.4 ± 0.2	8.7 ± 1.1	44.7	
Jordanella floridae	25 ± 0.5	8.0-8.3	-[i]	350-375	
Lebistes reticulatus	28-31.8	7.8-8.2	5.7-7.2	218-239	

Table 11 (contd).

Organism	Temperature (°C)	pH	Dissolved oxygen (mg/litre)	Hardness (mg $CaCO_3$/ litre)	
Lepomis macrochirus	17.2 ± 0.5	7.4 ± 0.2	8.7 ± 1.1	44.7	
Leuciscus idus melanotus	20				

Notopterus notopterus	23-26.5	6.8-7.6	5.9-7.8	60-70	
Pimephales promelas	17.2 ± 0.5	7.4 ± 0.2	8.7 ± 1.1	44.7	
	25 ± 2		6.2-8.2	43-49	
Rasbora heteromorpha	20	7.2		250	
Rutilus rutilus	10.3 ± 0.3	7.8 ± 0.02		257-260	
Salmo gairdneri	15 ± 0.5	8.0-8.3	-[i]	350-375	
	17.2 ± 0.5	7.4 ± 0.2	8.7 ± 1.1	44.7	
Insects					
Baetis rhodani	11 ± 1	7.5-8.1		99.5 ± 7.7	
Chironomus riparius	11 ± 1	7.5-8.1		99.5 ± 7.7	

Table 11 (contd).

Organism	Temperature (°C)	pH	Dissolved oxygen (mg/litre)	Hardness (mg $CaCO_3$/ litre)	
Hydropsyche angustipennis	11 ± 1	7.5-8.1		99.5 ± 7.7	
Marine Organisms					
Crustacea					
Artemia salina					
Canthocamptus	synthetic medium according to Cairns				
Gammarus duebeni	5 ± 0.6	7.7 ± 0.1	8.4 ± 0.3	0.6%[k]	
	16 ± 0.6	7.7 ± 0.1	8.4 ± 0.3	0.6%[k]	
Mesidotea entomon	5 ± 0.6	7.7 ± 0.1	8.4 ± 0.3	0.6%[k]	
	10 ± 0.6	7.7 ± 0.1	8.4 ± 0.3	0.6%[k]	
Panopeus herbstii	25			25 ppt[k]	
Mollusca					
Crassostrea	24 ± 1			sea[k]	

virginica					
Mercenaria mercenaria	24 ± 1			sea[k]	F

Table 11 (contd).

Organism	Temperature (°C)	pH	Dissolved oxygen (mg/litre)	Hardness (mg $CaCO_3$/ litre)	
Worms					
Ophryotrocha diadema	21			sea[k]	S
Fish					
Phoxinus phoxinus	5 ± 0.7	7.7 ± 0.1	8.4 ± 0.3	0.6%[k]	C

[a] S = static test; CF = continuous flow test; R = renewal test (semi-static
[b] EC_{50} = median effect concentration = calculated concentration causing effe
TT = toxicity threshold, i.e. concentration affecting growth in $\geq$ 3% of p
[c] effect: reduction in photoluminescence
[d] minimal concentration affecting growth
[e] river water
[f] concentration of test compound analysed during assay
[g] immobility
[h] simultaneous testing of 8 species
[i] no data; aerated
[j] reported was TL_m, or median toxicity limit
[k] salinity; sea = sea water

Table 12. Long-term aquatic toxicity of phenol

Organism	Temperature (°C)	pH	Dissolved oxygen (mg/litre)	Hardness (mg/litre $CaCO_3$)	Method[a]	Test
Freshwater Organisms						
Crustacea						
Daphnia magna	19 ± 1	8.2		199	R (48 h)	16 d
	19 ± 1	8.2 ± 0.3		199	R	21 d
Ceriodaphnia dubia	25 ± 1	8.18 ± 0.04		57.1 ± 4.1	R (48 h)	4 da 7 da
Fish						
Brachydanyo rerio	24 ± 1	6.1-6.5	6.4-8.5	57-61	R (24 h)	3 mo

					R (48 h)	2 mo with expo conc eggs 2-3

Table 12 (contd).

Organism	Temperature (°C)	pH	Dissolved oxygen (mg/litre)	Hardness (mg/litre $CaCO_3$)	Method[a]	Test
Carassius auratus	19-24	7.78	6.2-9.0	197.5	CF	8 da (tes eggs spaw hatc with
Pimephales promelas	25 ± 1	8.0	5.3	725.3	CF	30 d
Pimephales promelas	25 ± 1	8.0	5.3	725.3	CF	
	25 ± 2	7.2-7.9	7.7	46.0	CF	38 d (tes eggs spaw
Salmo gairdneri	12-14	7.78	6.2-9.0	197.5	CF	8 da (tes eggs fert hatc with

Table 12 (contd).

Organism	Temperature (°C)	pH	Dissolved oxygen (mg/litre)	Hardness (mg/litre $CaCO_3$)	Method[a]	Test
	13.3-14.2	7.4-8.1	8.6-10.2	100	CF	4 da (tes eggs fert hatc 23 d
		7.8	5.7	579.9	CF	58 d (tes eyed comp

[a] S = static test; CF = continuous flow test; R = renewal test (semi-static)
[b] NOEC = no-observed-effect concentration = highest tested concentration wit

An LC_1 is a calculated value which is, to some extent, comparable to the c

[c] phenol concentration analysed during test
[d] survival was a more sensitive end-point than reproduction
[e] calculated from results by Task Group
[f] highest concentration tested
[g] extrapolated by authors

An increase in salinity (0-30%) increased the toxicity of phenol to fungi (Babich & Stotzky, 1985).

9.2 Aquatic organisms

9.2.1 Freshwater organisms

9.2.1.1 Short-term studies

The most important sublethal acute effects observed in freshwater species after phenol exposure were a reduced heart rate and damage to the epithelium of gills (with loss of function), liver, kidneys, intestines and blood vessels. One study reported the occurrence of severe seizures, mediated by the central nervous system, in *Salmo gairdneri* after exposure to sublethal phenol concentrations (Bradbury *et al.*, 1989). In invertebrates, growth inhibition was usually observed. Some EC_{50} values for the latter organisms are given in Table 11.

Most toxicity studies concentrated on lethal effects. Death was usually preceded by immobility, loss of equilibrium, paralysis and respiratory distress (Razani *et al.*, 1986a; Tonapi & Varghese, 1987; Green *et al.*, 1988; Chagnon & Hlohowskyj, 1989). Toxicity testing, where the same species was used by different research workers in different waters, resulted in LC_{50} values (LC_{50} : calculated concentration causing death in 50% of test group) that varied widely, as can be seen from Table 11.

Environmental factors may affect the toxicity of phenol (Brown *et al.*, 1967; Miller & Ogilvie, 1975; Ruessink & Smith, 1975; Cairns *et al.*, 1976; Reynolds *et al.*, 1978; Birge *et al.*, 1979; Dalela *et al.*, 1980; Gluth & Hanke, 1983; Gupta *et al.*, 1983a,b; Stephenson, 1983). Hardness and pH, however, do not appear to have a large impact on phenol toxicity. The toxicity for various fungi and fish species, for example, did not change significantly over the pH range of 5-8; toxicity for fungi and some fish species was not influenced at all by hardness, whereas phenol was slightly more toxic in soft than in hard waters for the carp (Herbert, 1962; Pickering & Henderson, 1966; EIFAC, 1972; Babich & Stotzky, 1985). The effect of temperature appeared to be variable (Cairns *et al.*, 1978; Babich & Stotzky, 1985). Since temperature influences both the uptake and the detoxification (conjugation) of phenol (Green *et al.*, 1988), phenol toxicity could be enhanced, as well as diminished, by increasing temperature, depending on which parameter was influenced most.

Several biological factors also influence the response of the biota to phenol, e.g., strain type, nutritional status, size, embryonal or developmental stage, crowding and physiological adaptation (Dowden & Benett, 1965; Alexander & Clarke, 1978; Birge *et al.*, 1979; Flerov, 1979; De Graeve *et al.*, 1980; Kordylewska,

1980; Gupta *et al.*, 1982b; Mayes *et al.*, 1982; Black *et al.*, 1983; Lewis, 1983).

Comparison of 48-h LC_{50} values from Table 11 shows that, in general, fish are the most sensitive freshwater species with respect to phenol toxicity. The 48-h LC_{50} values for some selected fish species ranged from 7 to 64 mg/litre. For crustaceans, this range was 3.1-200, and for molluscs it was 200-205 mg/litre; for insects, it was 19-720 mg/litre and for worms 200-870 mg/litre. Upon simultaneous testing of eight species at concentrations up to 51 mg phenol/litre, no toxicity was observed for larvae of the amphibian *Xenopus laevis,* for the snail *Aplexa hypnorum* or the insect *Tanytarsus dissimilis.* Where toxicity was observed, LC_{50} values were included in Table 11 (Holcombe *et al.,* 1987). The data presented in Table 11 are in good agreement with the order of increasing tolerance to phenol proposed by Alekseyev & Antipin (1976): fish-crustaceans-tolerant insects-worms-molluscs-highly tolerant insects.

9.2.1.2 Long-term studies

Most long-term studies with freshwater species have concerned growth, reproduction and/or mortality; these studies are discussed below. Studies considered to be adequately performed and reported are included in Table 12.

A few long-term studies with freshwater fish have been designed to detect sublethal effects of phenol exposure. Increased proteolysis as a result of stress, mild kidney damage, and an inhibitory effect on the development and maturation of the ovary, secondary to a liver dysfunction, were some of the effects reported (Dangé, 1986; Gupta & Dalela, 1987; Kumar & Mukerjee, 1988).

In a life-cycle test using *Daphnia magna,* the maximum acceptable tolerance concentration (MATC) proved to be 1.5-6.3 mg phenol/litre (US EPA, 1980). These results are comparable with the no-observed-effect concentration (NOEC) values for growth and reproduction (both 3.2 mg phenol/litre) found by Hermens (1984) and Oris *et al.* (1991). De Neer *et al.* (1988), however, found a considerably lower NOEC value of 0.16 mg phenol/litre for growth of *Daphnia magna* under similar experimental conditions.

Exposure of adult *Brachydanio rerio* to 2.2, 4.9 or 24 mg phenol/litre for 3 months resulted in 67% mortality at the highest concentration; the no-observed-lethal concentration (NOLC) was 4.9 mg phenol/litre. At 24 mg phenol/litre, only immature oocytes were found in surviving fish; at the two lower concentrations both immature and mature oocytes were observed, whereas spawning was delayed. In subsequent embryo-larval tests, starting with the eggs of exposed adults, mortality appeared to be maximal during embryonic development and the initial larval stage. All larvae died within 12 days at 4.9 mg phenol/litre. At 2.2 mg phenol/litre, larval mortality was still slightly increased, but surviving animals showed normal growth and development (Razani *et al.,* 1986b).

In two embryo-larval bioassays on *Pimephales promelas,* growth proved to be the most sensitive criterion: the NOEC values were 0.75 and 1.83 mg phenol/litre (De Graeve *et al.,* 1980; Holcombe *et al.,* 1982).

The results of the embryo-larval test on *Salmo gairdneri* given by Birge *et al.* (1979) (LC_1:0.2 µg/litre) and Black *et al.* (1983) (NOEC:9 µg/litre) are much lower than those obtained by De Graeve *et al.* (1980) ($NOEC_{growth}$: 0.1 mg/litre), probably because the latter test was started with eyed eggs, whereas the

former two tests were started with just-fertilized eggs.

In addition, Birge *et al.* (1979) studied the influence of phenol in an embryo-larval test on *Carassius auratus* and found a LC_1 of 2.0 µg phenol/litre.

Dumpert (1987) reported a NOLC value of 10 mg phenol/litre for larvae of the amphibian *Xenopus laevis;* larval mortality was 100% within 3 weeks at 50 mg phenol/litre. Larval growth was slightly, but not significantly, retarded at 5 and 10 mg phenol/litre. Hatching was normal at all tested concentrations. However, the results may not be reliable because test solutions were renewed only once a week, whereas aeration may also have contributed to undetected loss of phenol. In other embryo-larval bioassays on five amphibian species, *Rana ripiens* and *Rana catesbeiana* were the least tolerant. These species exhibited about equal sensitivity to phenol (LC_1: 1.0 and 1.1 mg phenol/litre, respectively; LC_{10}: 5.2 and 8.5 mg phenol/litre, respectively (Birge *et al.,* 1980).

9.2.2 Marine organisms

9.2.2.1 Short-term studies

In acute toxicity studies on some marine organisms (crustaceans, worms, snails and fish), the LC_{50} values ranged from 8.8-330 mg phenol/litre (see Table 11). In general, the sensitivities of marine and freshwater organisms for phenol were similar.

At a sublethal phenol concentration, activities of some enzymes appeared to be decreased in the brain, liver and muscle tissue of *Sarotherodon mossambicus;* this effect was independent of salinity (Ravichandran & Anantharaj, 1984).

9.2.2.2 Long-term studies

No adequate data are available on long-term toxicity to marine organisms.

9.2.3 Accumulation

The bioconcentration factor of phenol may be calculated, using a log P_{ow} value of 1.46 (pH not stated, see Table 1) and the formula log BCF = 0.79 log P_{ow} -0.40 (Veith & Kosian, 1983). This yields a bioconcentration factor of 5.7, which is very low and does not indicate any potential for bioaccumulation.

The experimental bioconcentration factors, reported by Hardy *et al.* (1985) for algae, by Erben (1983) for flatworms, by Erben (1982) for snails, by Key & Scott (1986) for crabs, and by Call *et al.* (1980) and Kobayashi & Akitake (1975) for fish, are in agreement with the calculated value. Other studies, however, reported higher values. The bioconcentration factor for *Daphnia magna,* as assessed from ^{14}C measurements, was reported to be 1375 after 24 h, with an estimated half-life upon depuration of 8 h. A lower bioconcentration factor (277) was calculated from uptake and depuration rate constants (Dauble *et al.,* 1986). The bioconcentration factors for phenol, as determined by ^{14}C measurements in a 5-day experiment with activated sludge, in a 24 h-experiment with the alga *Chlorella fusca,* and a 3-day experiment with the fish *Leuciscus idus melanotus,* were 2200, 200 and 20, respectively (Freitag *et al.,* 1985).

Uptake was usually complete (the equilibrium level reached)

within 1-2 days. Initially, excretion was also rapid, but it usually slowed down after some hours, and depuration was reported to be incomplete. The amount of unchanged phenol still present after 24 h in the alga *Scenedesmus quadricauda,* for example, was 22% (Hardy *et al.,* 1985), whereas radioactivity from ^{14}C showed a retention of 80% after 96 h of depuration in the mud crab *Panopeus herbstii* (Key & Scott, 1986).

Based on reported and estimated bioconcentration factors for aquatic organisms, phenol is not expected to bioaccumulate significantly.

9.2.4 Metabolism

The metabolism of phenol in fish yields the known phenyl conjugates (phenyl sulfate and phenyl glucuronide) and quinol sulfate (Kobayashi *et al.,* 1976; Layiwola & Linnecar, 1981; Nagel, 1983; Nagel & Urich, 1983; Kasokat *et al.,* 1987). In the excreta of the frog *Rana temporaria,* the same metabolites were found after phenol injection, together with catechol, catechol sulfate and traces of resorcinol. *Xenopus laevis,* another amphibian, appeared to be unable to glucuronidate phenol, but compensated this by increasing the production of other metabolites compared to *Rana temporaria* (more quinol sulfate and phenyl sulfate, and, in addition, resorcinol sulfate) (Beyer & Frank, 1985; Görge *et al.,* 1987).

Phenol metabolism may be induced by prior exposure to phenol or phenol derivatives, as was observed for sulfate conjugation in the clam *Ruditapes phillippinarum* (Kobayashi *et al.,* 1987).

9.3 Terrestrial organisms

Phenol may be taken up by, and stored in, the cuticle membranes of various plants, such as tomatoes and green pepper fruits, and rubber leaves (Shafer & Schönherr, 1985). Labelled phenol was demonstrated to be taken up by soybean roots. The label stayed in the roots, and was not transported to the shoot, which was attributed to the metabolism of phenol by the plant into immobile compounds (McFarlane *et al.,* 1987). Millet seeds appeared to be more sensitive to the toxicity of phenolic compounds than lettuce and cucumber seeds. The 120-h EC_{50} value for root elongation inhibition in millet was determined to be 120-170 mg phenol/litre (Wang, 1986).

The toxicity of phenols for four earthworm species (Neuhauser *et al.,* 1986) was compared with those of other chemicals using two standardized tests developed by the EEC, the 2-day contact test and the 14-day artificial soil test. Of ten classes of chemicals, phenol was the most toxic in the contact test, with LC_{50} values of 2.4-10.6 µg/cm^2, regardless of species. A lower relative toxicity was reported by the same authors using the artificial soil test.

10. EVALUATION OF HUMAN HEALTH RISKS AND EFFECTS ON THE ENVIRONMENT

10.1 Evaluation of human health risks

10.1.1 Exposure

The main way in which the general population can be exposed, on a long-term basis, to phenol present in ambient air is as a result of industrial emissions and various combustion processes. Other inhalation sources include the decomposition of organic materials,

liquid manure, and the atmospheric degradation of benzene. Inhalation and dermal exposure may arise from contact with contaminated water or consumer products containing phenol. Indirect exposure of man through the food chain is not likely to add significantly to long-term inhalation exposure, in view of the short life-time of the compound in the environment (section 10.2.1.). Individuals may ingest phenol via drinking-water from contaminated surface water or ground water. Repeated oral exposure may arise from the consumption of smoked food items. Endogenous production of phenol may be influenced by the diet and exposure to certain drugs and other xenobiotics.

The exposure data available are inadequate to determine the degree of exposure of the general population or of specific groups at risk, including workers.

An upper-limit estimate of the daily intake can be made for long-term exposure of the general population. In this hypothetical case, it is assumed that an individual will be maximally exposed to phenol through continuous inhalation of air from a heavily industrialized area, with frequent consumption of smoked food items with a high phenol content, and of drinking-water containing phenol up to the taste threshold. The estimate is summarized in the table below:

Source	Quantity of source	Phenol concentration	Phenol intake
Air	20 m^3/day	200 µg/m^3	4 mg/day
Smoked food items	200 g/week	70 mg/kg	2 mg/day
Drinking-water	2 litres/day	300 µg/litre	0.6 mg/day

Assuming an average body weight of 70 kg, the total daily intake of this maximally exposed individual will be 0.1 mg/kg body weight per day. The daily intake by the general population can be expected to be much less than this figure.

10.1.2 Toxicity

Phenol has moderately acute toxicity for animals. The oral LD_{50} for various animal species range from 300 to 600 mg phenol/kg body weight, and the LC_{50} for rats by inhalation is more than 900 mg phenol/m^3.

In humans, the lowest acutely lethal oral dose was reported to be 4.8 g, which is approximately 70 mg/kg body weight. Local, as well as systemic, effects have been reported in humans, consisting of irritation, necrosis, cardiovascular effects, metabolic acidosis, neurological effects and methaemoglobinaemia. Several fatal cases have been reported after oral or dermal intoxication. No documented cases of death by inhalation of phenol have been found.

Solutions of phenol are corrosive to the skin and eyes. Phenol vapours can irritate the respiratory tract. Phenol is not a skin sensitiser in guinea-pigs or humans.

The most important effects reported in short-term animal

studies were neurotoxicity, liver and kidney damage, respiratory effects and growth retardation. Toxic effects in rat kidney have been reported to occur at oral dose levels of 40 mg/kg per day or more. Liver toxicity was evident in rats administered at least 100 mg/kg per day. In a limited 14-day study on rats, an oral NOAEL of 12 mg/kg per day was reported based on kidney effects. In this experiment, miosis (an iris response to light) was inhibited at 4 mg/kg per day (the lowest dose tested). However, the health significance of this finding is not clear. Some biochemical changes have been reported to occur in the intestinal mucosa and kidneys of mice at dose levels below 1 mg/kg per day. The toxicological value of these insufficiently reported biochemical observations is not known.

There have been no long-term general toxicity studies in animals or adequate epidemiological studies.

No adequate studies on the reproductive toxicity of phenol have been reported. Phenol has been identified as a developmental toxicant in studies with rats and mice. In two multiple-dose rat studies, NOAELs of 40 mg/kg per day (the LOAEL was 53 mg/kg per day) and 60 mg/kg per day (the LOAEL was 120 mg/kg per day) have been reported. For the mouse, the NOAEL was 140 mg/kg per day (the LOAEL was 280 mg/kg per day).

There is some evidence that phenol is genotoxic to mammalian cells *in vitro.* Based on the induction of bone marrow micronuclei in several studies with mice, phenol may have genotoxic potential.

Oral (drinking-water) animal carcinogenicity bioassays did not give evidence of a carcinogenic potential of phenol. No animal inhalation or adequate dermal carcinogenicity studies are available. Two-stage carcinogenicity studies with mice showed that phenol applied to the skin does have tumour-promoting activity. Adequate human data on carcinogenicity are not available.

10.1.3 Evaluation

Accidental high exposure to phenol may cause severe local effects, systemic intoxications and even death. The available data do not suggest a strong potential for cumulative health effects from chronic exposure.

The lowest NOAELs identified are for kidney and developmental effects, and in rats are in the range of 12-40 mg/kg body weight per day. The Task Group decided to derive a tolerable daily intake (TDI), taking into consideration this range. An uncertainty factor of 200 (including factors of 10 for interspecies variation, 10 for intraspecies variation, and 2 to account for the limited data base on the toxicity of phenol in animals) was considered appropriate. A range of 60-200 µg/kg per day was recommended as the upper limit of the TDI by the Task Group. As the Task Group's upper-limit estimate of human daily intake is 100 µg/kg body weight per day (section 10.1.1), it can be concluded that the average general population exposure to phenol from all sources will be well below this range.

There remain, however, two reasons for concern. The available data suggest that phenol may be genotoxic, and there is insufficient data to discount the possibility that phenol is carcinogenic. For these reasons, it is particularly important that this evaluation of phenol be kept under periodic review.

10.2 Evaluation of effects on the environment

10.2.1 Environmental levels

Once released into the environment, intercompartmental transport of phenol may occur by wet deposition from air to sea water and surface water and soil, and, as the compound can be expected to be highly mobile in soil, by leaching through soil. Evaporation will be slow from water and can only be expected following contamination of relatively dry soil.

Phenol, however, is generally not likely to persist in either air, sea or surface water, soil or sewage. It readily reacts photochemically and is rapidly biodegraded aerobically, mainly to carbon dioxide. Anaerobic degradation to carbon dioxide or methane also occur. Half-lives will be in the range of several hours for photodegradation and in the range of hours to days for aerobic biodegradation. Anaerobic biodegradation also occurs, albeit at a slower rate. Low removal rates of phenol in ground water and soil may occur, e.g., following spills, with subsequent inhibition of the microbial populations.

The scarce environmental exposure data available give some support for the above conclusions:

* reported ambient air levels are low ($\leq$ 8 µg/m^3 for urban areas; < 200 µg/m^3 for heavily industrialized areas);
* phenol has been detected in rain water;
* reported surface water levels are low ($\leq$ 24 µg/litre);
* levels in ground water have only been found at highly contaminated sites.

10.2.2 Toxicity

Based on reported and estimated bioconcentration factors for aquatic organism, phenol is not expected to bioaccumulate significantly. The data base on aquatic toxicity is considered adequate for evaluation. Phenol is toxic to aquatic organisms: the lowest EC_{50} for water organisms is estimated to be 3.1 mg/litre (48-h LC_{50} for *Ceriodaphnia dubia)*. The lowest chronic NOEC is estimated to be 0.2 µg/litre (8-day LC_1 for *Salmo gairdneri)*. Applying the modified US EPA method, an Environmental Concern Level of 0.02 µg/litre can be derived for water. In general, fish are the most sensitive species and the sensitivities of marine and freshwater organisms are similar. Adequate data on plants and terrestrial organisms are not available.

10.2.3 Evaluation

The scarce exposure data available do not allow any firm conclusions with regard to the degree of risk from phenol to either aquatic or terrestrial ecosystems. However, in view of the derived Environmental Concern Level of phenol for aquatic organisms, it is reasonable to assume that these organisms may be at risk in any surface or sea water subject to phenol contamination, in spite of the rapid degradation of this compound.

11. FURTHER RESEARCH

There is a need for the following items:

a) further investigation of the *in vivo* genotoxicity of phenol;

b) more animal toxicology studies, including 90-day oral and inhalation studies, carcinogenicity bio-assays by the

inhalation route, and neurotoxicity and multigeneration reproductive toxicity studies (including evaluation in offspring);

c) assessment of environmental and occupational exposures and evaluation of health effects in occupational populations;

d) further evaluation of the dose-duration-effect relationships, reversibility/persistence and health significance of the reported phenol-induced inhibition of the pupillary response to light;

e) further data on the toxicity of phenol for plants and terrestrial organisms.

12. PREVIOUS EVALUATIONS BY INTERNATIONAL BODIES

The carcinogenic risk of phenol was evaluated in 1989 by the International Agency for Research on Cancer (IARC, 1989). The summary evaluation from the IARC Monograph is reproduced here.

"Exposures

Phenol is a basic feedstock for the production of phenolic resins, bisphenol A, caprolactam, chlorophenols and several alkylphenols and xylenols. Phenol is also used in disinfectants and antiseptics. Occupational exposure to phenol has been reported during its production and use, as well as in the use of phenolic resins in the wood products industry. It has also been detected in automotive exhaust and tobacco smoke.

Experimental carcinogenicity data

Phenol was tested for carcinogenicity by oral administration in drinking-water in one strain of mice and one strain of rats. No treatment-related increase in the incidence of tumours was observed in mice or in female rats. In male rats, an increase in the incidence of leukaemia was observed at the lower dose, but not at the higher dose. Phenol was tested extensively in the two-stage mouse skin model and showed promoting activity.

Human carcinogenicity data

In one case-control study of workers in various wood industries, an increased risk was seen for tumours of the mouth and respiratory tract in association with exposure to phenol; however, the number of cases was small and confounding exposures were inadequately controlled.

Other relevant data

In humans, phenol poisoning can occur after skin absorption, inhalation of vapours or ingestion. Acute local effects are severe tissue irritation and necrosis. At high doses, the most prominent systemic effect is central nervous system depression. Phenol causes irritation, dermatitis, central nervous system effects and liver and kidney toxicity in experimental animals.

Phenol induced micronuclei in female mice and sister chromatid exchange in cultured human cells. It did not inhibit intercellular communication in cultured animal cells. It induced mutation but not DNA damage in cultured animal cells. It did not induce recessive lethal mutation in Drosophila. It had a weak effect in inducing mitotic segregation in *Aspergillus nidulans.* Phenol did not induce

mutation in bacteria.

Evaluation

There is inadequate evidence for the carcinogenicity of phenol in humans.

There is inadequate evidence for the carcinogenicity of phenol in experimental animals.

Overall evaluation

Phenol is not classifiable as to its carcinogenicity to humans (Group 3)".

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RESUME

1. Identité, propriétés physiques et chimiques et méthodes d'analyse

Le phénol se présente sous la forme d'un solide cristallin blanc qui fond à 43 °C et se liquéfie par contact avec l'eau. Il dégage une odeur âcre caractéristique et possède une saveur forte et piquante. Il est soluble dans la plupart des solvants organiques; sa solubilité dans l'eau est limitée à la température ambiante; au-dessus de 68 °C il est entièrement soluble dans l'eau. Le phénol est modérément volatil à la température ambiante. C'est un acide faible, et, sous sa forme ionisée, il est très sensible aux réactions de substitution électrophile et à l'oxydation.

On peut recueillir le phénol dans des échantillons prélevés dans l'environnement par absorption dans une solution de soude ou par adsorption sur un solide. La désorption s'effectue par acidification, entraînement à la vapeur et extraction à l'éther (à partir des solutions) ou par voie thermique ou en phase liquide (lorsqu'il est adsorbé sur un solide). Les méthodes d'analyse les plus importantes sont la chromatographie en phase gazeuse avec détection par ionisation de flamme ou capture d'électrons ou encore la chromatographie liquide à haute performance avec détection en lumière ultra-violette. La limite de détection la plus basse qui ait été signalée dans l'air est de 0,1 µg par m^3. On peut doser le phénol dans le sang et les urines; dans les échantillons d'urine, on

a fait état d'une limite de détection de 0.5 µg/litre.

2. Sources d'exposition humaine et environnementale

Le phénol est un constituant du goudron de houille et il se forme au cours de la décomposition naturelle des substances organiques. La majeure partie du phénol présent dans l'environnement provient cependant de l'activité humaine. Les sources potentielles en sont la production et l'utilisation, tel quel ou sous forme de dérivés, en particulier de résines phénoliques et de caprolactame, les gaz d'échappement, la combustion de bois de construction et la fumée de cigarette. Une autre source potentielle est constituée par la dégradation atmosphérique du benzène sous l'action de la lumière, la présence de phénol dans le purin pouvant également fortement contribuer à sa concentration dans l'atmosphère. Les dérivés du benzène et du phénol peuvent, par conversion *in vivo,* constituer une source d'exposition humaine endogène.

La production de phénol dans le monde s'est montrée relativement constante pendant les années 1980, les Etats-Unis d'Amérique en étant le premier producteur. Il est principalement utilisé pour la fabrication des résines phénoliques, du bisphénol A et de la caprolactame. On en connaît également un certain nombre d'applications médicales et pharmaceutiques.

3. Transport, distribution et transformation dans l'environnement

Les principales émissions de phénol se produisent dans l'air. La majeure partie du phénol présent dans l'atmosphère finit par être dégradée par voie photochimique en dihydroxybenzènes, nitrophénols et dérivés résultant de l'ouverture du cycle, avec une demi-vie estimative de 4 à 5 heures. Une petite quantité est éliminée de l'air par dépôt humide (pluie). Le phénol devrait présenter une forte mobilité dans le sol mais son transport et sa réactivité peuvent être affectés par le pH.

Le phénol présent dans l'eau et le sol peut être décomposé par des réactions abiotiques ainsi que par l'activité microbienne en un certain nombre de produits, dont les plus importants sont le dioxyde de carbone et le méthane. La part des réactions biologiques dans la décomposition globale du phénol dépend de nombreux facteurs tels que la concentration, l'acclimatation, la température et la présence d'autres composés.

4. Concentrations dans l'environnement et exposition humaine

On ne possède aucune donnée sur la concentration atmosphérique du phénol. La concentration de fond est vraisemblablement inférieure à 1 ng/m^3. Les valeurs en milieu urbain et suburbain varient de 0,1 à 8 µg/m^3 alors que dans les zones où prédominent les sources de phénol (zones industrielles) les concentrations signalées peuvent être jusqu'à 100 fois plus élevées. On a décelé du phénol dans l'eau de pluie, les eaux superficielles et les eaux souterraines mais les données sont très rares. On a fait état de concentrations élevées de phénol dans des sédiments et des eaux souterraines par suite de pollution industrielle.

Il peut y avoir exposition professionnelle au phénol lors de la production de ce produit et de ses dérivés, lors de l'enduction avec des résines phénoliques (industrie du bois et métallurgie) et lors d'un certain nombre d'autres activités industrielles. La concentration la plus élevée qui ait été signalée (jusqu'à 88 mg/m^3) concernait des ouvriers de l'ex-URSS employés à l'extinction du coke avec des eaux usées contenant du phénol. La

plupart des autres concentrations évoquées ne dépassaient 19 mg/m^3.

En ce qui concerne la population dans son ensemble, c'est la fumée de cigarette et les aliments fumés qui constituent les plus importantes sources d'exposition au phénol, si l'on excepte l'exposition par voie atmosphérique. L'exposition par l'eau de boisson ou la consommation par inadvertance de produits alimentaires contaminés devraient rester faibles; le phénol a en effet une odeur et une saveur désagréables, ce qui dans la plupart des cas devrait alarmer le consommateur.

5. Cinétique et métabolisme

Le phénol est facilement absorbé par toutes les voies d'exposition. Après absorption, il se répartit rapidement dans l'ensemble des tissus.

Une fois résorbé, il forme essentiellement des conjugués avec l'acide glucuronique et l'acide sulfurique, et, dans une moindre mesure, des hydroxylates avec le catéchol et l'hydroquinone. Il y a également conjugaison avec les phosphates. La formation de métabolites réactifs (4,4-biphénol et diphénoquinone) a été mise en évidence lors d'études *in vitro* portant sur des neutrophiles et des leucocytes humains activés.

La proportion relative de glucuronides et de sulfo-conjugués varie avec la dose et l'espèce animale. Chez le rat, on a observé qu'en augmentant la dose de phénol, la formation de sulfo-conjugués l'emportait sur celle de glucuro-conjugués.

C'est essentiellement dans le foie, les poumons et au niveau de la muqueuse gastro-intestinale que le phénol est métabolisé. Le rôle relatif joué par ces divers tissus dépend de la voie d'administration et de la dose.

Des études *in vivo* et *in vitro* ont montré que le phénol se fixait aux protéines tissulaires et plasmatiques par liaison covalente. Certains métabolites du phénol se lient également aux protéines.

C'est principalement par la voie urinaire que la phénol est excrété chez l'animal et l'homme. Le taux d'excrétion urinaire varie selon la dose, la voie d'administration et l'espèce. Une faible proportion est excrétée dans les matières fécales et l'air expiré.

6. Effets sur les animaux d'expérience et les systèmes d'épreuve in vitro

Le phénol présente une toxicité aiguë modérée pour les mammifères. La DL_{50} par voie orale varie chez les rongeurs de 300 à 600 mg de phénol/kg de poids corporel. La DL_{50} dermique varie respectivement de 670 à 1400 mg/kg de poids corporel chez le rat et le lapin et pour le rat, la CL_{50} à 8h. par voie respiratoire est supérieure à 900 mg de phénol/m^3. Après exposition aiguë, les symptômes cliniques sont une hyperexcitabilité neuromusculaire, des convulsions graves, une nécrose de la peau et des muqueuses de la gorge et l'on note également des effets au niveau des poumons, des fibres nerveuses, des reins, du foie et de la pupille (réflexe photomoteur).

Les solutions de phénol sont agressives pour la peau et les yeux. A l'état de vapeur, le phénol peut irriter les voies

respiratoires. On est fondé à croire que le phénol n'agit pas comme sensibilisateur cutané.

Les effets les plus importants relevés lors d'études à court terme sur l'animal consistaient en neurotoxicité, lésions hépatiques et rénales, troubles respiratoires et retard de croissance. A des doses orales quotidiennes de 40 mg/kg ou davantage on a observé des effets néphrotoxiques chez le rat. Chez la même espèce, il y avait une évidente hépatotoxicité aux doses supérieures ou égales à 100 mg/kg/jour. Lors d'une étude limitée de 14 jours sur des rats, on a obtenu, pour la dose par voie orale sans effets nocifs observables, une valeur de 12 mg/kg/jour, le critère retenu étant les effets sur le rein. Dans cette expérience, il y avait encore inhibition du myosis (réaction de l'iris à un stimulus lumineux) à la dose quotidienne de 4 mg/kg; toutefois, l'importance médicale de cette observation demeure incertaine. On a signalé la présence de certaines altérations biologiques au niveau de la muqueuse intestinale et des reins chez des souris recevant des doses quotidiennes inférieures à 1 mg/kg, observation dont l'importance toxicologique n'est pas non plus bien claire.

Il n'y a pas eu d'études satisfaisantes sur la toxicité du phénol pour la fonction de reproduction. Toutefois, la toxicité du phénol paraît se manifester par son action délétère sur le développement du rat et de la souris. Lors de deux études au cours desquelles des rats ont reçu des doses multiples de phénol, on a obtenu, pour la dose sans effets nocifs observables, une valeur de 40 mg/kg/jour (pour la dose la plus faible sans effets nocifs observables, cette valeur était de 53 mg/kg/jour) et de 60 mg/kg/jour respectivement (dans ce cas, la dose la plus faible sans effets nocifs observables était de 120 mg/kg/jour). Chez la souris, la dose sans effets nocifs observables était de 140 mg/kg/jour (dose minimale sans effets nocifs observables: 280 mg/kg/jour).

La plupart des tests de mutagénicité bactérienne ont donné des résultats négatifs. Cependant, des épreuves effectuées *in vitro* sur des cellules mammaliennes ont révélé la présence de mutations, de lésions chromosomiques et d'effets sur l'ADN. Le phénol est sans effet sur la communication intercellulaire (mesurée par la coopération métabolique) dans des cultures de cellules mammaliennes. Un certain nombre d'études ont mis en évidence l'induction de micro-noyaux dans des cellules de moelle osseuse murine. Toutefois, les études sur la souris n'ont pas révélé la présence de micro-noyaux à doses plus faibles.

Deux études de cancérogénicité ont été effectuées sur des rats et des souris mâles et femelles à qui l'on administrait du phénol mêlé à leur eau de boisson. On n'a observé d'affections malignes (à savoir cancers médullaires de la thyroïde, leucémies) que chez les rats mâles soumis à de faibles doses. On n'a pas effectué d'études de cancérogénicité en bonne et due forme utilisant la voie

percutanée ou la voie respiratoire. Des études de cancérogénicité en deux phases ont montré que le phénol pouvait se comporter comme un agent tumoro-promoteur lorsqu'on l'appliquait à plusieurs reprises sur la peau de la souris.

7. Effets sur l'homme

Des cas bien documentés d'exposition humaine au phénol par la voie percutanée, buccale ou intraveineuse, ont donné lieu à l'observation d'effets indésirables très divers. Il a été fait état d'une irritation des voies gastro-intestinales après ingestion de phénol. Après exposition de la peau, les effets observés localement

vont d'un blémissement cutané indolore ou d'un érythème à la corrosion et à la nécrose profonde. Parmi les effets généraux, on a noté les troubles suivants: arythmies cardiaques, acidose métabolique, hyperventilation, détresse respiratoire, insuffisance rénale aiguë, lésions rénales, urines foncées, méthémoglobinémie, troubles neurologiques (notamment des convulsions), choc cardio-vasculaire, coma et mort. La dose orale la plus faible qui ait entraîné un décès humain était de 4,8 g; la mort est survenue dans les 10 minutes.

Le risque d'intoxication par inhalation de vapeurs de phénol est connu depuis longtemps, mais on n'a pas signalé de décès consécutif à ce type d'accident. Les symptômes produits par l'inhalation de phénol consistent notamment en anorexie, perte de poids, maux de tête, vertiges, salivation et coloration foncée des urines.

Le phénol n'est pas un agent sensibilisateur.

Le seuil olfactif pour l'homme serait 0,021 à 20 mg/m^3 d'air. Pour le phénol en solution aqueuse, on a fait état d'un seuil olfactif de 9 mg/litre, le seuil gustatif étant de 0,3 mg/litre d'eau.

On ne dispose pas de données suffisantes sur le pouvoir cancérogène du phénol.

8. Effets sur les êtres vivants dans leur milieu naturel

Lors d'études portant sur une seule espèce de bactéries, on a obtenu, pour la CE_{50} relative à l'inhibition de la croissance, des valeurs allant de 244 à 1600 mg de phénol/litre. On a constaté que le seuil de toxicité se situait à 64 mg de phénol/litre. Pour les protozoaires et les champignons, les valeurs étaient du même ordre que pour les bactéries; pour les algues elles étaient un peu inférieures. Le phénol est toxique pour les organismes dulçaquicoles supérieurs. Pour les crustacés et les poissons, les valeurs les plus faibles de la CL_{50} ou de CE_{50} se situent entre 3 et 7 mg de phénol/litre. Les données concernant la toxicité aiguë du phénol

pour les organismes marins sont comparables à celles dont on dispose au sujet des organismes d'eau douce. Des études à long terme sur des crustacés et diverses espèces de poissons ont révélé des différences de sensibilité remarquables; c'est ainsi que les valeurs de la CL_1 provenant d'épreuves sur des embryons et des larves de *Salmo* et de *Carassius* se sont révélées très inférieures (respectivement 0,2 et 2 µg de phénol/litre) aux valeurs correspondantes pour d'autres espèces de poissons (concentration sans effet létal observable, 2,2-6,1 mg/litre) et d'amphibiens, ou tirées d'études sur la reproduction des crustacés (concentration sans effet létal observable, 10 mg de phénol/litre). On ne dispose pas de données sur des épreuves à long terme qui auraient été pratiquées sur des organismes marins.

En général le facteur de bioconcentration du phénol chez les divers types d'organismes aquatiques est très bas (<1-10) encore qu'on ait signalé parfois des valeurs plus élevées (jusqu'à 2200). Il est donc vraisemblable que le phénol ne subit pas d'accumulation biologique importante.

Les données dont on dispose au sujet de la destinée et des effets du phénol chez les organismes terrestres sont très peu nombreuses. La CE_{50} à 120 h. est de 120 à 170 mg/litre pour le millet et lors d'une épreuve par contact, on a obtenu pour la CL_{50}

chez le lombric, une valeur comprise entre 2,4 et 10,6 µg/cm^3.

9. Résumé de l'évaluation

9.1 Santé humaine

La population dans son ensemble est essentiellement exposée au phénol par la voie respiratoire. Par voie orale, il peut y avoir exposition répétée par suite de la consommation d'eau de boisson contaminée ou d'aliments fumés.

On ne dispose pas de données suffisantes pour déterminer l'ampleur de l'exposition de la population générale, mais on peut donner une limite estimative supérieure de l'absorption quotidienne. En mettant les choses au pire, on peut considérer que l'exposition maximale se produit chez un individu qui inhale en permanence de l'air fortement contaminé et consomme souvent des aliments fumés ou de l'eau de boisson qui contient du phénol à des concentrations atteignant le seuil gustatif. On a calculé que la dose quotidienne ingérée maximale totale estimative pour un individu de ce genre pesant 70 kg était de 0,1 mg/kg de poids corporel.

Les valeurs de la dose sans effets nocifs observables obtenues par expérimentation animale en prenant comme critères les troubles rénaux et les effets sur le développement étaient, chez le rat, de l'ordre de 12 à 40 mg/kg de poids corporel et par jour. En utilisant un coefficient d'incertitude de 200, on peut recommander comme

limite supérieure de la dose journalière totale une valeur située entre 60 et 200 µg/kg de poids corporel. En prenant pour l'homme une dose quotidienne limite de 100 µg/kg de poids corporel, on peut conclure que l'exposition de toutes origines au phénol de la population dans son ensemble se situe en-dessous de ces valeurs.

On peut être préoccupé par le fait que, selon certaines données, le phénol pourrait être génotoxique et que d'autre part, on ne possède pas suffisamment de résultats pour écarter avec certitude l'éventualité que le phénol soit cancérogène. L'évaluation de ce composé doit être revue périodiquement.

9.2 Environnement

Le phénol ne subit probablement pas d'accumulation biologique importante. Il est toxique pour les organismes aquatiques; en appliquant la méthode modifiée de l'Agence de protection de l'environnement des Etats-Unis, on peut considérer que la concentration préoccupante de cette substance dans l'environnement est de 0,02 µg/litre. On manque de données suffisantes sur son action chez les plantes et les organismes terrestres.

Il peut y avoir transport du phénol d'un compartiment à l'autre de l'environnement par dépôt humide ou par lessivage du sol. En général, ce composé ne devrait pas persister dans l'environnement. Les rares données dont on dispose sur l'exposition ne permettent pas d'évaluer le risque qu'il présente pour les écosystèmes aquatiques ou terrestres. Toutefois, en tenant compte de la valeur de sa concentration préoccupante pour l'environnement aquatique, il est raisonnable de considérer qu'en cas de contamination par le phénol des eaux de surface ou des eaux marines, il y a un risque pour les organismes aquatiques.

RESUMEN

1. Identidad, propiedades físicas y químicas, métodos analíticos

El fenol es un sólido cristalino, blanco, que funde a 43 oC y se licúa al contacto con el agua. Posee un olor acre característico y un sabor ardiente fuerte. Es soluble en la mayor parte de los disolventes orgánicos. A temperatura ambiente, su solubilidad en agua es limitada; por encima de 68 oC es completamente hidrosoluble. El fenol es moderadamente volátil a temperatura ambiente. Es un ácido débil y, en su forma ionizada, muy sensible a las reacciones de sustitución electrofílica y a la oxidación.

El fenol se puede obtener a partir de muestras ambientales por absorción en una solución de NaOH o en contacto con sorbentes sólidos. La desorción se lleva a cabo por acidificación, destilación al vapor y extracción con éter (a partir de soluciones) o mediante desorción térmica o líquida (a partir de sorbentes sólidos). Las técnicas analíticas más importantes son la cromatografía de gases en combinación con la detección de ionización por conductor y de captura de electrones, y la cromatografía en fase líquida, de alta presión, en combinación con la detección por luz ultravioleta. En el aire, el límite de detección más bajo que se haya notificado es de 0,1 µg/m^3. Se puede determinar la presencia de fenol en la sangre y la orina; en muestras de orina se ha registrado un límite de detección de 0,5 µg/litro.

2. Fuentes de exposición humana y ambiental

El fenol es uno de los componentes del alquitrán de hulla y se forma durante la descomposición natural de materiales orgánicos. No obstante, la mayor parte del fenol presente en el medio ambiente es de origen antropogénico. Algunas fuentes potenciales son la producción y el uso de fenol y de sus productos, especialmente plásticos fenólicos y caprolactama, los gases de escape, la quema de leña y el humo de los cigarrillos. Otra fuente potencial es la degradación atmosférica del benceno por la influencia de la luz, si bien la presencia del fenol en los purines puede asimismo tener considerable influencia en sus niveles atmosféricos. Los derivados del benceno y del fenol pueden, mediante una conversión *in vivo,* constituir una fuente de exposición humana endógena a fenol.

Según parece, la producción mundial de fenol fue bastante regular a lo largo del decenio de 1980, en que los Estados Unidos fueron el productor más importante. Se usa principalmente como materia básica de las resinas fenólicas, del bisfenol A y de la caprolactama. También se le conocen algunas aplicaciones médicas y farmacéuticas.

3. Transporte, distribución y transformación en el medio ambiente

Las principales emisiones de fenol van al aire. La mayor parte del fenol existente en la atmósfera se degradará mediante reacciones fotoquímicas frente a los dihidroxibencenos, los nitrofenoles y los productos de rotura del anillo, con una semivida, estimada en 4 a 5 hs. Una parte menor desaparecerá del aire por deposición hídrica (lluvia). Se piensa que el fenol es móvil en el suelo, pero el pH puede influir en el transporte y la reactividad.

El fenol presente en el agua y el suelo puede degradarse por reacciones abióticas, así como por la actividad microbiana, dando lugar a un número de compuestos, los más importantes de los cuales son el dióxido de carbono y el metano. La proporción entre la biodegradación y la degradación general del fenol está determinada por múltiples factores, como la concentración, la aclimación, la temperatura y la presencia de otros compuestos.

4. Niveles ambientales y exposición humana

No se dispone de datos sobre los niveles atmosféricos de fenol. Se supone que los niveles básicos son inferiores a 1 ng/m^3. Los niveles urbanos y suburbanos oscilan entre 0,1 y 8 µg/m^3, mientras que se ha notificado que las concentraciones en las zonas próximas al foco de emisión (industria) alcanzan magnitudes cien veces superiores. Se ha detectado fenol en la lluvia y en las aguas superficiales y subterráneas, pero los datos son muy escasos. En sedimentos y aguas subterráneas se han notificado niveles elevados de fenol debidos a la contaminación industrial.

La exposición profesional al fenol puede tener lugar durante la producción del mismo y de sus derivados, la aplicación de resinas fenólicas (industrias maderera y siderúrgica) y algunas otras actividades industriales. La concentración más alta (hasta 88 mg/m^3) se ha notificado en relación con trabajadores de la antigua Unión Soviética que apagaban el coque con aguas residuales que contenían fenol. La mayor parte de las restantes concentraciones notificadas no rebasan los 19 mg/m^3.

Para la población en general, el humo de cigarrillo y los alimentos ahumados constituyen las fuentes más importantes de exposición al fenol, aparte de la exposición a través del aire. La exposición a través del agua potable y de los alimentos contaminados por inadvertencia probablemente sea baja; el fenol tiene un olor y un sabor desagradables, que en la mayor parte de los casos provocan el rechazo del consumidor.

5. Cinética y metabolismo

El fenol se absorbe fácilmente por todas las vías de exposición. Tras la absorción, la sustancia se distribuye rápidamente a todos los tejidos.

El fenol absorbido se conjuga principalmente con el ácido glucurónico y el ácido sulfúrico y, en menor medida, se hidroxila en pirocatequina e hidroquinona. También se conjuga con los fosfatos. La formación de metabolitos reactivos (4,4-bifenol y difenoquinona) se ha demostrado en estudios *in vitro* con neutrófilos y leucocitos humanos activados.

Las cantidades relativas de glucurono y sulfoconjugados varían según la dosis y la especie animal. Tras aumentar la dosis de fenol, se observó en las ratas un cambio de la sulfatación a la glucuronidación.

El hígado, los pulmones y la mucosa gastrointestinal constituyen los sitios más importantes del metabolismo fenólico. La función relativa desempeñada por esos tejidos depende de la vía de administración y de la dosis.

Estudios *in vivo* e *in vitro* han demostrado la unión covalente del fenol con las proteínas tisulares y plasmáticas. Algunos metabolitos fenólicos se unen asimismo a las proteínas.

La excreción por la orina es la principal vía de eliminación del fenol en los animales y en los seres humanos. La tasa de excreción urinaria varía en función de la dosis, de la vía de administración y de la especie. Una parte menor se excreta a través de las heces y del aire espirado.

6. Efectos en mamíferos de laboratorio y en sistemas de prueba in vitro

El fenol tiene una toxicidad aguda moderada en los mamíferos. En los roedores, los valores de la DL_{50} por vía oral oscilan entre 300 y 600 mg de fenol/kg de peso corporal. Los valores de la DL_{50}por vía cutánea para ratas y conejos oscilan entre 670 y 1400 mg/kg de peso corporal, respectivamente, y el valor de la CL_{50} por inhalación a las 8 horas en las ratas es superior a los 900 mg de fenol/m^3. Los síntomas clínicos después de la exposición aguda son hiperexcitabilidad neuromuscular y convulsiones graves, necrosis de la piel y de las mucosas de la garganta y efectos en los pulmones, fibras nerviosas, riñones, hígado y en la respuesta pupilar a la luz.

Las soluciones de fenol son corrosivas para la piel y los ojos. Los vapores de fenol pueden irritar las vías respiratorias. Existen pruebas de que el fenol no produce sensibilización cutánea.

Los efectos más importantes notificados a partir de estudios de corta duración en animales fueron neurotoxicidad, lesiones hepáticas y renales, trastornos respiratorios y retraso del crecimiento. Se han notificado efectos tóxicos en el riñón de las ratas con dosis por vía oral de 40 mg/kg al día o más. La toxicidad en el hígado resultó evidente en las ratas a las que se habían administrado al menos 100 mg/kg diarios. En un estudio limitado de 14 días de duración realizado en ratas se notificó un nivel sin efectos adversos observados (NOAEL) de 12 mg/kg al día por vía oral, basado en los efectos renales. En este experimento, la miosis (respuesta del iris a la luz) se mantuvo inhibida con 4 mg/kg al día; sin embargo, no está claro el significado médico de este hallazgo. Se notificó la existencia de algunos cambios biológicos en la mucosa intestinal y los riñones de ratones con dosis inferiores a 1 mg/kg al día, dato de significado toxicológico incierto.

No hay estudios adecuados sobre la toxicidad reproductiva del fenol. En estudios con ratas y ratones el fenol ha sido identificado como tóxico del desarrollo. En dos estudios de dosis múltiples en ratas, se han notificado NOAEL de 40 mg/kg al día (el más bajo nivel sin efectos adversos observados (LOAEL) fue de 53 mg/kg al día) y de 60 mg/kg al día (el LOAEL fue de 120 mg/kg al día). En el ratón, el NOAEL fue de 140 mg/kg al día (el LOAEL fue de 280 mg/kg al día).

La mayor parte de las pruebas de mutagenicidad bacteriana han dado resultados negativos. En células *in vitro* de mamíferos se han observado mutaciones, lesiones cromosómicas y efectos en el ADN. El fenol no tiene efectos en la comunicación intercelular (medida como cooperación metabólica) en cultivos de células de mamíferos. En algunos estudios se ha observado la inducción de micronúcleos en células de médula ósea de ratones. Con dosis más bajas no se observaron micronúcleos en estudios con ratones.

Se han llevado a cabo dos estudios de carcinogenicidad con ratas y ratones machos y hembras a los que se administró fenol con el agua de beber. Sólo se observó malignidad (por ejemplo, carcinoma de células C de la tiroides y leucemia) en ratas macho con dosis bajas. No se han realizado estudios adecuados de carcinogenicidad por vía dérmica o por inhalación. Estudios de carcinogenicidad de dos fases han mostrado que el fenol, aplicado repetidamente a la piel del ratón, tiene efectos activadores.

7. Efectos en el ser humano

Se ha notificado una larga serie de efectos adversos en el ser humano resultantes de la exposición bien documentada al fenol por vía cutánea, oral o intravenosa. Se ha notificado irritación

gastrointestinal tras su ingestión. Los efectos locales de la exposición cutánea van desde el emblanquecimiento o el eritema indoloros hasta la corrosión y la necrosis profunda. Entre los efectos sistémicos cabe citar disritmias, acidosis metabólica, hiperventilación, disnea, insuficiencia renal aguda, lesiones renales, orinas oscuras, metahemoglobinemia, trastornos neurológicos (incluidas convulsiones), choque cardiovascular, coma y muerte. La dosis mínima reportada como causante de muerte en el ser humano es de 4,8 g por ingestión; la muerte se produjo en menos de 10 minutos.

Durante mucho tiempo se ha reconocido la posibilidad de envenenamiento por inhalación de los vapores de fenol, pero no se han reportado casos mortales relacionados con esta vía de exposición. Los síntomas que se asocian a la inhalación de fenol consisten, entre otros, en anorexia, pérdida de peso, dolor de cabeza, vértigo, salivación y orinas oscuras.

El fenol no es un agente sensibilizante.

El umbral de percepción del fenol por el olfato humano oscila entre 0,021 y 20 mg/m^3 en el aire. Se ha notificado un umbral de percepción del fenol en el agua de 7,9 mg/litro, y un umbral de percepción por el gusto de 0,3 mg/litro en el agua.

No se dispone de datos adecuados sobre la carcinogenicidad del fenol en el ser humano.

8. Efectos en los seres vivos del medio ambiente

En estudios con bacterias de especie única, los valores de la CE_{50} con inhibición del crecimiento oscilaron entre 244 y 1600 mg de fenol/litro. Se comprobó un umbral de toxicidad de 64 mg de fenol/litro. Los valores para los protozoarios y los hongos fueron de la misma cuantía que para las bacterias, mientras que para las algas fueron ligeramente inferiores.

El fenol es tóxico para los organismos superiores de agua dulce. Los valores más bajos de la CL_{50} o la CE_{50}, para crustáceos y peces se sitúan entre 3 y 7 mg de fenol/litro. Los datos sobre la toxicidad aguda para organismos marinos son comparables a los correspondientes a organismos de agua dulce. En estudios de larga duración sobre especies de crustáceos y de peces se han observado notables diferencias de sensibilidad; los valores de la CL_1 en pruebas con embriones y larvas de *Salmo* y *Carassius* resultaron mucho más bajos (0,2 y 2 µg de fenol/litro, respectivamente) que los valores correspondientes a otras especies de peces (NOLC de 2,2-6,1 mg/litro) y anfibios, o que los obtenidos en pruebas de reproducción en crustáceos (NOLC de 10 mg de fenol/litro). No se dispone de datos acerca de pruebas de larga duración realizadas en organismos marinos.

Los factores de bioconcentración del fenol en diversos tipos de organismos acuáticos son en general muy bajos (< 1-10), aunque se han notificado también algunos valores más altos (hasta 2200). Así pues, no se prevé que la bioacumulación del fenol sea significativa.

Los datos sobre el destino y los efectos del fenol en organismos terrestres son muy escasos. En el mijo se determinó una CE_{50} a las 120 horas de 120-170 mg/litro mientras que, en una prueba de contacto, la CL_{50} para especies de lombrices resultó ser de 2,4-10,6 µg/cm^2.

9. Resumen de la evaluación

9.1 Salud humana

La población en general está expuesta al fenol principalmente por inhalación. La exposición repetida por vía oral puede producirse por el consumo de alimentos ahumados o de agua potable.

No existen datos suficientes para determinar el grado de exposición de la población en general, pero se puede calcular la cantidad máxima ingerida diariamente. Basándose en "la peor de las hipótesis" se puede realizar una estimación suponiendo que un individuo estará expuesto en grado máximo al fenol mediante la inhalación continua de aire intensamente contaminado acompañada de un consumo frecuente de productos alimenticios ahumados y de agua que contenga fenol hasta niveles de percepción por el gusto. En total, la ingesta máxima diaria de fenol en un individuo de 70 kg se calcula en 0,1 mg/kg de peso corporal al día.

Los valores de NOAEL más bajos identificados en experimentos con animales se refieren a efectos en el riñón y en el desarrollo, y en las ratas se sitúan dentro de un margen de variación de 12-40 mg/kg de peso corporal al día. Utilizando un factor de incertidumbre de 200, se recomienda como límite máximo de la ingesta diaria total (IDT) entre 60 y 200 µg/kg de peso corporal al día. Teniendo en cuenta que el límite máximo de la ingesta diaria en seres humanos se calcula en 100 µg/kg de peso corporal al día, se llega a la conclusión de que la exposición media de la población en general al fenol, sea cual fuere la fuente, se encuentra por debajo de este intervalo.

Son motivo de preocupación algunas indicaciones de que el fenol podría ser genotóxico y el hecho de que no haya datos suficientes para descartar con seguridad la posible carcinogenicidad del compuesto. La evaluación debe mantenerse sujeta a revisión periódica.

9.2 Medio ambiente

No se prevé una bioacumulación importante del fenol. Este compuesto es tóxico para los organismos acuáticos; mediante la aplicación del método modificado de la Agencia de los EE.UU. para la Protección del Medio Ambiente, se puede determinar un nivel en medio ambiente de preocupación de 0,02 µg/litro. Se carece de datos adecuados sobre plantas y organismos terrestres.

El transporte de fenol entre compartimientos se produce principalmente por deposición hídrica y filtración a través del suelo. En general, es poco probable que el compuesto persista en el medio ambiente. La escasez de datos sobre la exposición no permiten evaluar el riesgo que representa el fenol para los ecosistemas tanto acuáticos como terrestres. Sin embargo, habida cuenta del nivel de preocupación ambiental que se ha establecido en relación con el agua, es razonable suponer que los organismos acuáticos pueden correr riesgo en cualquier agua superficial o marina contaminada con fenol.

See Also:
- Toxicological Abbreviations
- Phenol (HSG 88, 1994)
- Phenol (ICSC)
- PHENOL (JECFA Evaluation)
- Phenol (PIM 412)
- Phenol (IARC Summary & Evaluation, Volume 71, 1999)