Contaminants in soil: updated collation of toxicological data and intake values for humans

Phenol

Better Regulation science programme
Science report: SC050021 / TOX 9
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4) CLEA Software version 1.04 (2009)
5) Toxicological reports and Soil Guideline Value briefings

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Steve Killeen

Head of Science
Executive summary

This report, one of a number on the assessment of risks to human health from contaminants in soil, presents key data and expert opinions on the toxicology and intake of phenol. It provides an update to a report by the Department for Environment, Food and Rural Affairs (Defra) and the Environment Agency published in October 2003.

The report is based on findings from a series of literature searches, the latest of which was undertaken in November 2008. These findings together with evaluations of national, European and international expert groups are used to recommend Health Criteria Values (HCVs) and estimate mean daily intakes (MDIs) for phenol in the UK.

Chemical overview

Phenol is a colourless to pink crystalline solid which is water soluble and a weak acid. Phenol occurs naturally in coal tar and is formed during the natural decomposition of organic materials; however, most of the phenol in the environment comes from anthropogenic sources. Phenol can be rapidly biodegraded in soil under both aerobic and anaerobic conditions. However, it does persist in contaminated soils and coal tar wastes, suggesting that optimal degradation conditions are not always achieved, primarily because of its ecotoxicity. Volatilisation from environmental water and soils appears to be slow.

Pharmacokinetics

Phenol is efficiently absorbed via both the pulmonary and gastrointestinal tracts, and is readily absorbed through the skin. Once absorbed, it is rapidly metabolised – mainly in the liver, gut and kidney – to phenyl sulphate and phenyl glucuronide. Excretion is primarily in the urine.

Toxicity

Lethal oral doses of phenol in humans may be as low as 1–15 g – equivalent to about 14–214 mg kg$^{-1}$ bodyweight (bw) – though higher doses have been survived. Signs and symptoms of acute toxicity in humans and laboratory animals are similar following dermal and oral absorption. Toxicity targets are the nervous system, kidneys, heart and lungs. The very limited information on the impact of repeated inhalation exposure of humans to phenol indicates possible liver toxicity. Phenol is a powerful skin irritant in man, and skin necrosis has been produced by contact with 1% solutions.

In laboratory animal studies, phenol clearly exhibits a higher degree of toxicity when it is given by stomach tube than when it is administered in the drinking-water. Liver and kidney damage (and spleen or thymus abnormalities) occurred in rats that received repeated doses of 40 mg kg$^{-1}$ bw day$^{-1}$ by stomach tube. Neurotoxicity has been reported in rodents similarly treated with 40–70 mg kg$^{-1}$ bw day$^{-1}$. The administration of phenol in drinking-water to two generations of rats for up to 13 weeks produced no effects at 70–93 mg kg$^{-1}$ bw day$^{-1}$. Doses of 300–380 mg kg$^{-1}$ bw day$^{-1}$ produced, at worst, only a mild degree of toxicity both in this study and in rats and mice given doses of a similar order for two years.

Changes in some blood parameters indicative of liver toxicity were found in a group of workers occupationally exposed to average atmospheric phenol concentrations of 21 mg m$^{-3}$ for about 13 years. Continuous exposure to air containing about 20 mg m$^{-3}$ phenol for 13 weeks may have produced some organ pathology in monkeys, rats and mice, while exposure to 100–200 mg m$^{-3}$ for seven hours per day, five days a week for
6–13 weeks caused effects on the respiratory system, heart, liver and kidney in guinea pigs and mice, and additionally neurological effects and mortality in the guinea pigs.

Experimental studies show phenol to be mutagenic. While the evidence indicates that, for ingested phenol, this mutagenic activity may demonstrate a threshold, no such assumption can be made for inhalation or dermal exposure.

**Health Criteria Values and risk assessment**

The drinking-water studies with their more protracted period of treatment and more detailed examination of the treated animals provide the best insights into phenol’s likely oral toxic potential in humans. The no-observed adverse effect level (NOAEL) of 70–93 mg kg\(^{-1}\) bw day\(^{-1}\) is the basis of the oral tolerable daily intake (TDI\(_{\text{oral}}\)) of 700 µg kg\(^{-1}\) bw day\(^{-1}\) recommended here.

The inhalation toxicity database for phenol is very limited. In view of the potential for non-threshold mutagenicity, derivation of an inhalation Index Dose (ID\(_{\text{inh}}\)) would be appropriate. However, there are no suitable data from which an ID\(_{\text{inh}}\) can be derived.

Despite the significant limitations in the available inhalation data, it does appear that, aside from potential mutagenic effects, phenol is more potent when inhaled than when ingested – probably due to efficient first-pass metabolism following ingestion. Deriving Soil Guideline Values (SGVs) based on the recommended TDI\(_{\text{oral}}\) alone might therefore be insufficiently protective of the threshold effects of inhaled phenol in addition to the potential mutagenic effects. Based on limited occupational epidemiology data, it is concluded that an inhalation tolerable daily intake (TDI\(_{\text{inh}}\)) of 10 µg kg\(^{-1}\) bw day\(^{-1}\) represents the most suitable empirically-based inhalation value for use in deriving SGVs at the present time. The potential mutagenic (and thus assumed carcinogenic) risks at this dose are unknown, but likely to be small.

No authoritative assessments of dermal toxicity (based on either mutagenicity or threshold toxicity) were identified, but phenol can be absorbed through the skin in toxic amounts. Due to the first-pass metabolism of phenol following ingestion, it would seem most appropriate to compare dermal exposure with the TDI\(_{\text{inh}}\). It is also noted that phenol is a powerful skin irritant in man, and skin necrosis has been produced by contact with 1% solutions.

Since both inhaled and ingested phenol cause similar (threshold) systemic toxic effects, this should be considered in an assessment where exposure is via both routes. In view of the potential non-threshold mutagenic risks from inhalation and dermal contact, it would be prudent to assume that the ALARP principle (to reduce exposures to ‘as low as reasonably practicable’) applies in risk management considerations.

**Mean daily intakes from non-soil sources**

The adult oral mean daily intake of phenol from its presence in food and drinking-water (MDI\(_{\text{oral}}\)) is estimated to be 350 µg day\(^{-1}\); the adult inhalation mean daily intake (MDI\(_{\text{inh}}\)) from its presence in ambient air is estimated to be 40 µg day\(^{-1}\).
HCV and MDI values for phenol

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Units</th>
<th>Oral</th>
<th>Inhalation</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDI</td>
<td>µg day⁻¹</td>
<td>350</td>
<td>40</td>
</tr>
<tr>
<td>MDI for 70-kg adult</td>
<td>µg kg⁻¹ bw day⁻¹</td>
<td>5</td>
<td>0.6</td>
</tr>
<tr>
<td>MDI for 20-kg child</td>
<td>µg kg⁻¹ bw day⁻¹</td>
<td>13 a</td>
<td>1.5 a</td>
</tr>
<tr>
<td>TDI</td>
<td>µg kg⁻¹ bw day⁻¹</td>
<td>700</td>
<td>10 b</td>
</tr>
</tbody>
</table>

- The TDI inh does not account for phenol’s mutagenic potential, which for inhalation is assumed to have no threshold.

Summary of changes to HCV recommendations

The TDI oral of 700 µg kg⁻¹ bw day⁻¹ is the same as was recommended in the previous TOX report published in 2003; an inhalation HCV was not previously proposed.
Acknowledgements

This document was initially written by RPS Group plc and was subsequently updated by the MRC Institute for Environment and Health and Toxicology Advice & Consulting Ltd before being published in 2003. The 2003 document was updated in 2009 with the assistance of bibra toxicology advice & consulting.

The Environment Agency is also grateful for the valuable inputs from various government agencies and departments, particularly the Health Protection Agency and Food Standards Agency.
## Contents

1  Introduction 1  
1.1  Update to R&D Publication TOX 9 1  
1.2  Background 1  
1.3  Advice on using this report 2  

2  Chemical overview 4  

3  Toxicity 6  
3.1  Literature sources 6  
3.2  Pharmacokinetics 6  
3.3  Acute toxicity 7  
3.4  Repeated dose toxicity 8  
3.5  Reproductive and developmental toxicity 11  
3.6  Genotoxicity 11  
3.7  Carcinogenicity 12  
3.8  Summary 13  

4  Derivation of Health Criteria Values 15  
4.1  UK Committees on Toxicity and Mutagenicity of Chemicals in Food,  
     Consumer Products and the Environment 15  
4.2  Joint FAO/WHO Expert Committee on Food Additives 15  
4.3  WHO guidelines for drinking-water quality 16  
4.4  International Programme on Chemical Safety 16  
4.5  EU Risk Assessment Report 16  
4.6  US Environmental Protection Agency 17  
4.7  US Agency for Toxic Substances and Disease Registry 17  
4.8  Dutch National Institute for Public Health and the Environment 17  
4.9  Discussion 18  

5  Background intake 20  
5.1  Food 20  
5.2  Water 20  
5.3  Air 20  
5.4  Other sources 20  
5.5  Estimation of mean daily intakes 21  

6  Conclusions 22  

7  References 23  

List of abbreviations 28  

Contaminants in soil: updated collation of toxicological data and intake values for humans. Phenol
1 Introduction

1.1 Update to R&D Publication TOX 9

This report presents key data and expert opinion on the human toxicology and non-soil intakes of phenol. It updates and replaces R&D Publication TOX 9 published in 2003 (Defra and Environment Agency, 2003), taking into account:

- updates to the toxicological framework document that describes how the human toxicity of chemical soil contaminants is assessed (Environment Agency, 2009)
- further review of the scientific literature on the toxicology of phenol and the findings and opinion of national, European, and international expert groups up to November 2008 (see Appendix).

1.2 Background

The main purpose of this report is to provide technical guidance to regulators and their advisors in support of the statutory regimes addressing land contamination, particularly Part 2A of the Environmental Protection Act 1990 and development control under the Town and Country Planning Acts.

Part 2A defines the term contaminated land according to whether or not it poses a significant risk to human health and/or the environment.

In relation to health effects not attributable to radioactivity, it considers land to be contaminated land where it:

"... appears to the local authority in whose area the land is situated to be in such a condition by reason of substances in, on or under the land that (a) significant harm [to human health] is being caused or there is a significant possibility of such harm being caused."

Statutory guidance (Defra, 2006) explains that significant harm to a person would include such health effects as death, disease, serious injury, genetic mutation, birth defects or the impairment of reproductive function. The definition of significant harm therefore encompasses a broad range of possible health outcomes from chemical exposure.

Land contamination is a material consideration within the planning regime. A planning authority has to consider the potential implications of contamination both when it is developing structure or local plans (or unitary development plans) and when it is considering applications for planning permission. Planning Policy Statement 23: Planning and Pollution Control (PPS 23) (ODPM, 2004) explains the relationship between planning and Part 2A. In the granting of planning permission for new development including permission to carry out remediation, PPS 23 states that remediation must remove unacceptable risk to human health and make the site suitable for its intended use. As a minimum, after carrying out a development and

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1 For the purpose of the Statutory Guidance, disease is taken to mean an unhealthy condition of the body or part of it and can include, for example, cancer, mental dysfunction, liver dysfunction or extensive skin ailments.
commencement of its use, the land should not be capable of being determined as contaminated land under Part 2A.

1.3 Advice on using this report

This report reviews the key toxicological literature and expert opinion on health effects arising from exposure to phenol. It has been prepared by the Environment Agency with the support of the Health Protection Agency (HPA) and the Food Standards Agency (FSA).

This report recommends one or more Health Criteria Values (HCVs) for use in assessing the risks to health from long-term human exposure to phenol in soil. HCVs are an important part of the risk assessment process. They are used subsequently in the derivation of Soil Guideline Values (SGVs), which are scientifically-based generic assessment criteria used to simplify the screening of land contamination (Defra and Environment Agency, 2004). HCVs can also be used to derive site-specific assessment criteria for soil as part of any Detailed Quantitative Risk Assessment.

The HCVs set out in this report represent levels of minimal or tolerable risk from long-term human exposure to chemicals in soil. They represent a baseline and health protective position to minimise risks of significant harm. They do not represent thresholds above which there is an unacceptable intake or a significant possibility of significant harm in the context of Part 2A, but they can be a useful starting point for such an assessment (Defra, 2008). Science alone cannot answer the question of whether or not a given possibility of significant harm is significant, since what is either significant or unacceptable is a matter of socio-political judgment and the law entrusts decisions on this to the enforcing authorities (Defra, 2008).

In the context of Part 2A, an assessor using the HCVs in this report can conclude that (Defra, 2008):

- human exposure at or below the HCV is unlikely to represent a significant possibility of significant harm;
- human exposure above the HCV might represent a significant possibility of significant harm, with the significance linked to the margin of exceedance, the duration and frequency of exposure, and other factors that the enforcing authority may wish to take into account.

The information presented in this report is intended for technical professionals familiar with assessment of the risks posed to human health by land contamination. It should be read in conjunction with Science Report SC050021/SR2 Human Health Toxicological Assessment of Contaminants in Soil (Environment Agency, 2009), which introduces and describes the terms and general technical approaches used in this review of phenol.

Although HCVs are an important quantitative tool for judging the health risks associated with a particular level of human exposure, they should not be used in isolation from the rest of the information presented in this report. Further understanding of the mechanisms of toxicity and the range of potential health effects are important to assessing the risks posed by phenol at any level of exposure both individually and when combined with other chemicals present.

The remainder of this report is separated into the following sections:

- Section 2 provides a short overview of the chemistry of phenol, its main uses and its behaviour in the environment with particular reference to soils.
Section 3 presents information obtained from the literature search on the toxicity of phenol (pharmacokinetics, acute toxicity, repeated dose toxicity, reproductive and developmental toxicity, genotoxicity and carcinogenicity).

Section 4 sets out the HCVs derived by various expert groups worldwide.

Section 5 gives estimates of exposure to background levels of phenol in food and water, air and other sources.

Section 6 presents the conclusions drawn from the literature review including the recommendations for HCVs.
2 Chemical overview

The structure of phenol is provided in Figure 2.1. It is essentially a benzene molecule in which one hydrogen atom is replaced by a hydroxyl group. The word “phenol” is, however, not only the name of this specific compound but also of a class of compounds. A member of this class may have other functional groups in addition to the hydroxyl moiety directly bonded to its benzene ring. Only phenol itself is considered in this review.

![Figure 2.1 The structure of phenol](image)

Phenol (Chemical Abstracts Service Registry Number 108-95-2) is colourless to light pink crystalline solid at room temperature and ambient pressure although it readily absorbs moisture and liquefies (EC, 2006). It is water soluble and a weak acid. Table 2.1 lists some of the physical-chemical properties of phenol.

Phenol occurs naturally in coal tar and is formed during the natural decomposition of organic materials. However, most of the phenol present in the environment comes from anthropogenic sources. Among these are the production and use of phenol and its derivatives, waste incineration, motor vehicle exhausts, wood burning and cigarette smoking (IPCS, 1994).

The major use of phenol is in the production of phenolic resins and bisphenol A (an intermediate in the manufacture of epoxy resins). Other important uses include the production of caprolactam (an intermediate in the manufacture of nylon), aniline and other organic chemicals (IPCS, 1994). Phenol is also used as a general disinfectant but this use appears to be in decline in European countries (EC, 2006). It is used in a limited number of medicines today including antiseptics, lotions, salves, and ointments (ATSDR, 1998; EC, 2006).

Although volatile in a pure form at room temperature, phenol partitions strongly to water and its volatilisation from water and soil appears to be a slow process and is not a significant source of atmospheric contamination (ATSDR, 1998).

Phenol can be rapidly biodegraded in soil under both aerobic and anaerobic conditions (EC, 2006; ATSDR, 2008). However, phenol does persist in contaminated soils and coal tar wastes, suggesting that optimal degradation conditions are not always achieved, primarily because of its ecotoxicity.

Where studies have reported atmospheric phenol levels in parts per million (ppm), a conversion factor of 1 ppm = 3.84 mg m⁻³ (IPCS, 1994) has been used to ensure consistency in units throughout this report.
### Table 2.1 Physical-chemical properties of phenol (Environment Agency, 2008)

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical formula</td>
<td>C₆H₅OH</td>
</tr>
<tr>
<td>Molecular weight (g mol⁻¹)</td>
<td>94.11</td>
</tr>
<tr>
<td>Physical state at room temperature</td>
<td>Solid</td>
</tr>
<tr>
<td>Melting point (pure) (°C)</td>
<td>41</td>
</tr>
<tr>
<td>Boiling point (°C)</td>
<td>182</td>
</tr>
<tr>
<td>Water solubility (mg L⁻¹, at 25°C)</td>
<td>84,100</td>
</tr>
<tr>
<td>Octanol-water partition coefficient (log KOW)</td>
<td>1.48</td>
</tr>
<tr>
<td>Vapour pressure (Pa, at 10°C)</td>
<td>11.5</td>
</tr>
<tr>
<td>Henry’s law constant (Pa m³ mol⁻¹, at 25°C)</td>
<td>0.065</td>
</tr>
</tbody>
</table>
3 Toxicity

3.1 Literature sources

Major reviews of the literature on the toxicology of phenol have been published by:

- International Programme on Chemical Safety (IPCS, 1994; 1999);
- International Agency for Research on Cancer (IARC, 1999);
- European Commission (EC, 2006);
- UK Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT, 2002);
- Dutch National Institute for Public Health and the Environment (RIVM, 2001);
- US Agency for Toxic Substances and Disease Registry (ATSDR, 1998, 2008);

This section is largely based on the major conclusions of these reviews; in general, the primary literature has not been consulted. Particular mention is made of those studies used in deriving HCVs.

3.2 Pharmacokinetics

3.2.1 Absorption

Human and laboratory animal data show that phenol is efficiently absorbed via both the inhalation and ingestion routes. In eight volunteers exposed to varying concentrations of phenol vapour (6–20 mg m⁻³) for a period of eight hours, 60–88% of the inhaled dose was retained (Piotrowski, 1971). A study in which three volunteers received a single oral dose of 0.01 mg kg⁻¹ bodyweight (bw) showed a mean 24-hour urinary recovery of 90% (Capel et al., 1972). An EU risk assessment assumed that any oral or inhalation dose was totally systemically absorbed (EC, 2006).

Phenol vapour and phenol in solution are also readily absorbed through the skin (Piotrowski, 1971; Baranowska-Dutkiewicz, 1981; Hansen, 1993; Skowronski et al., 1994).

3.2.2 Distribution

No reports were found regarding the distribution of phenol after intake by humans. Laboratory animal data show that distribution was rapid after oral exposure in rabbits (given 500 mg kg⁻¹ bw) (IPCS, 1994) and in rats (given 207 mg kg⁻¹ bw) (USEPA, 2002b), with peak tissue concentrations of total phenol (free plus conjugated) occurring within an hour of dosing. The highest peak concentrations were found in the liver, but phenol or its metabolites were also detected in the central nervous system (CNS) and lungs of the rabbits, and the spleen, kidney, adrenal gland, lungs and thyroid of rats.
3.2.3 Metabolism and excretion

Absorbed phenol is metabolised rapidly (mainly to phenyl sulphate and phenyl glucuronide) and eliminated primarily in the urine. The major tissues in which metabolism appears to occur are the liver, gut and kidney. The ratio of sulphate/glucuronide conjugates excreted in urine is species and dose-dependent (EC, 2006). At higher phenol doses an oxidised hydroquinone metabolite is formed. Its glutathione conjugate can undergo redox cycling, which may cause toxicity (IARC, 1999). A lack of first-pass metabolism following skin absorption may contribute to phenol’s dermal toxicity (Skowronski et al., 1994).

For humans who have absorbed a single dose of phenol, the amounts of total phenol (free plus conjugated) excreted in the urine during the first 24 hours are about 99%, 90% and 80% for the inhalation, oral and dermal routes respectively (ATSDR, 1998).

Phenol is a normal product of protein metabolism, but the concentration of total phenol in urine does not usually exceed 20 mg L⁻¹ (ATSDR, 2008).

3.3 Acute toxicity

A wide range of adverse effects has been reported following human exposure to phenol by the dermal or oral route. Gastrointestinal irritation occurs following ingestion. Systemic effects from either route 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 (IPCS, 1994).

Most recent data are in the form of case histories of accidental or deliberate exposures. In a five-year retrospective review of all exposures to a high concentration of phenol disinfectant reported to a regional poison centre, 96 cases (mostly oral exposure) were located. The most frequently recorded symptoms were burns, depression of the CNS, coughing and vomiting (Spiller et al., 1997). Lethal doses in humans may be as low as 1–15 g (equivalent to about 14–214 mg kg⁻¹ bw) (Reynolds, 1993), though other sources report survival at higher doses (ATSDR, 2008). A very old case study (Anderson, 1869) reported that ingestion of 4.8 g (equivalent to about 70 mg kg⁻¹ bw) was fatal after 10 minutes in one person. The variability in the reported lethal doses in these case reports, and the limited information and uncertainty as to whether corrosivity could have been a factor in addition to systemic toxicity, makes it difficult to interpret whether humans are more sensitive than experimental animals (see below) to phenol’s acute toxicity.

Human fatalities have also commonly resulted from the absorption of phenol through the skin (Kania, 1981; EC, 2006). In these case reports, the concentration of phenol, the area of skin exposed and the contact times have varied, and the information available is limited. Local effects following dermal exposure range from painless blanching or erythema to corrosion and deep necrosis (IPCS, 1994). Skin necrosis has been produced by contact with solutions as dilute as 1% (EC, 2006).

Single inhalation exposures are irritating to the respiratory tract and may also lead to headache, vertigo, salivation and indications of kidney toxicity (HPA, 2007).

Oral LD₅₀ values in rodents range from 340 to 620 mg kg⁻¹ bw (EC, 2006), with signs of neurotoxicity occurring within minutes of an oral dose of 120 mg kg⁻¹ bw (HPA, 2007). Dermal LD₅₀ values for 24-hour covered skin contact of 660 and 850 mg kg⁻¹ bw have been reported for rats and rabbits respectively (EC, 2006). The eight-hour LC₅₀ for rats by inhalation was more than 900 mg m⁻³ (IPCS, 1994). 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, and liver (IPCS, 1994).

3.4 Repeated dose toxicity

3.4.1 Humans

Oral

An accident in the USA in which about 40 tonnes of phenol were spilt from an overturned railway tank car in a rural area resulted in the contamination of local drinking-water wells (Baker et al., 1978). The local population was divided into two groups: those for whom at least one water test had shown a concentration in excess of 0.1 mg L⁻¹, and those for whom no water test had shown a concentration in excess of 0.1 mg L⁻¹. Mouth sores, diarrhoea and dark urine – symptoms consistent with classic phenol poisoning – were noted in 17 individuals in the first group. Their average daily phenol intakes from the contaminated water over the period of concern (a few weeks) were estimated to be in the range 10–240 mg day⁻¹. Examination six months after exposure did not show any residual toxicity.

Inhalation

Compared to unexposed controls, a group of 20 Egyptian workers occupationally exposed for long periods (mean exposure time 13.5 years +/- 6.55 years) to airborne levels of phenol had significantly higher levels of serum alanine aminotransferase and aspartate aminotransferase, longer blood clotting times, lower serum creatinine levels, and various haematological changes. The effects on the serum transaminases and blood clotting were thought to be indicative of possible liver toxicity. The time weighted average atmospheric concentration of phenol was reported to be 21 mg m⁻³ (Shamy et al., 1994).

No ill effects were recorded in workers at a factory manufacturing Bakelite who were exposed to airborne concentrations of phenol of up to 12.5 mg m⁻³ (Ohtsuji and Ikeda, 1972).

There were indications of an increased death rate from ischaemic heart disease in a US group of phenol-exposed workers (Wilcosky and Tyroler, 1983). In a second US study, phenol exposure was associated with reduced mortality rates for arteriosclerotic heart disease, emphysema, disease of the digestive system and cirrhosis of the liver, but these reductions were not statistically significant (Dosemeci et al., 1991).

Gastrointestinal effects such as anorexia, muscle pain and weakness have also been reported in workers chronically exposed to phenol liquid and vapour (HPA, 2007).
3.4.2 Experimental animals

Oral Administration in the drinking-water

Rats and mice were given drinking-water containing 2,500 or 5,000 parts per million (ppm) phenol for 103 weeks (NCI, 1980). According to USEPA (2002b), these correspond to doses of about 260–280 or 585–630 mg kg\(^{-1}\) bw day\(^{-1}\) for rats, and 450 or 660 mg kg\(^{-1}\) bw day\(^{-1}\) for mice.\(^2\) Detailed histopathological evaluations of a wide range of tissues revealed no treatment-related abnormalities. The only unequivocal effect found in either species was a reduction in bodyweight gain, which was associated with a depressed water intake. This occurred in both species at the higher tested doses and also in the male rats in the lower dose group. A reduced bodyweight gain (and reduced water intake) was also the only sign of possible toxicity reported in a study of two generations of rats receiving doses of the order of 300–380 mg kg\(^{-1}\) bw day\(^{-1}\) in drinking-water for up to 13 weeks. Bodyweights were unaffected in the group given 70–93 mg kg\(^{-1}\) bw day\(^{-1}\) (Ryan et al., 2001).

An immunotoxicity screening of male rats that had been exposed to phenol in their drinking-water for 13 weeks providing doses of up to 300 mg kg\(^{-1}\) bw day\(^{-1}\) found no evidence of any treatment-related changes. Spleen weight and cellularity, and antibody responses were among the endpoints examined. A comprehensive haematological examination of these animals revealed no abnormalities (IITRI, 1999; Ryan et al., 2001).

Groups of five male mice were exposed to phenol in drinking-water at three dose levels (about 1.8, 6.3 and 34 mg kg\(^{-1}\) bw day\(^{-1}\)) for 28 days (Hsieh et al., 1992). Decreases in the concentrations of various neurotransmitters and their metabolites were found in different parts of the brain. The levels of noradrenaline in the hypothalamus (mid- and high-dose groups), and of dopamine in the corpus striatum (all dose groups) were the most obviously affected; the magnitude of the decreases was statistically significant and dose-related. The functional significance of these biochemical changes is unknown.

In this same mouse study, effects on the blood (a reduced red blood cell count and haematocrit) were also seen throughout the tested dose range of 1.8–34 mg kg\(^{-1}\) bw day\(^{-1}\) (Hsieh et al., 1992). A reduced antibody response was detected in the groups receiving 6.3 and 34 mg kg\(^{-1}\) bw day\(^{-1}\). USEPA expressed uncertainty over what degree of immunological impairment constituted a true toxicological effect and described the 6.3 mg kg\(^{-1}\) bw dose as a no-observed adverse effect level (NOAEL) (USEPA, 2002a). The UK Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) was even more doubtful over the value of the study in defining phenol’s toxic potential. COT noted that the paper of Hsieh et al. “provided no information on impurities in the reagent grade phenol used in the study, and did not indicate that any precautions had been taken to minimise oxidation and degradation of the test substance.” As the dose–response of the effects on the blood was “not consistent with the absence of comparable or related findings in other well-conducted studies at higher doses and longer periods of exposure to ingested phenol” the data generated by Hsieh et al. were not influential in COT’s derivation of an oral health criteria value (COT, 2002) (see Section 4.1).

\(^2\) ATSDR (2008) estimated the lowest tested doses to be 322 mg kg\(^{-1}\) bw day\(^{-1}\) in the rats and 590 mg kg\(^{-1}\) bw day\(^{-1}\) in the mice.
Administration by stomach tube

A much more severe degree of toxicity was seen in a rat study involving the administration of phenol by gavage (Schlicht et al., 1992; Berman et al., 1995). Groups of eight females were given 0, 4, 12, 40 or 120 mg kg\(^{-1}\) bw day\(^{-1}\) for up to 14 days. All the rats in the highest dose group died within 11 days. Kidney pathology occurred at 40 mg kg\(^{-1}\) bw day\(^{-1}\). Necrosis or atrophy of the thymus or spleen (not defined more specifically) was also reported in two of the rats given 40 mg kg\(^{-1}\) bw day\(^{-1}\) and in one given 12 mg kg\(^{-1}\) bw day\(^{-1}\), but in none of the low-dose (4 mg kg\(^{-1}\) bw day\(^{-1}\)) or untreated control animals. Liver pathology (hepatocyte necrosis and vacuolation) was present in one of the rats that had received 14 doses of 40 mg kg\(^{-1}\) bw day\(^{-1}\) (and in rats treated with a single dose of 40 mg kg\(^{-1}\) bw).

More overt signs of neurotoxicity have been seen in pregnant mice given repeated gavage doses of 70 mg kg\(^{-1}\) bw day\(^{-1}\) (EC, 2006). An increase in “rearing behaviour” was reported in female rats that had received 14 daily doses of 40 mg kg\(^{-1}\) bw by gavage (Moser et al., 1995). In the same study, single doses of 120 mg kg\(^{-1}\) bw produced mild-to-severe whole-body tremors and decreased motor activity. There was decreased motor activity in female rats that had received 360 mg kg\(^{-1}\) bw day\(^{-1}\) of phenol in their drinking-water for 13 weeks (CTB, 1998). The behaviour of the females was unaffected at 107 mg kg\(^{-1}\) bw day\(^{-1}\). Male rats were unaffected by the highest dose (308 mg kg\(^{-1}\) bw day\(^{-1}\)).

Dermal

Overt signs of toxicity (tremors) were reported in rabbits receiving 18 dermal applications of a 2.4% aqueous solution of phenol. The liquid was essentially in contact with the skin for five hours daily, and the animals were treated five days per week. No toxic effects were recorded in four rabbits treated similarly with a 1.2% solution (about 130 mg kg\(^{-1}\) bw day\(^{-1}\)). For two of these, the phenol was in occluded contact with the skin (Deichmann et al., 1950).

Inhalation

There is only a very limited database on the repeated inhalation toxicity of phenol. Clinical signs indicative of possible mild respiratory tract irritation were recorded in male rats exposed six hours per day, five days per week for two weeks to about 20 mg m\(^{-3}\) and above. A microscopic examination of the tissues from the liver, kidney and respiratory tract of 10 males and 10 females exposed similarly to 100 mg m\(^{-3}\) revealed no treatment-related abnormalities (Hoffman et al., 2001).

An earlier study (US Air Force, 1961) in which rhesus monkeys, rats and mice were exposed continuously to about 5 ppm (19.2 mg m\(^{-3}\)) phenol, apparently found no significant adverse effects; however, ATSDR (2008) noted that incomplete reporting of this study was suggestive of possible lung, liver and kidney pathology, and data to support the assertion that there were no effects on some other parameters such as haematology and blood chemistry were also incomplete.

Another study (Deichmann et al., 1944) in which rats, mice and guinea pigs were exposed for seven hours per day, five days per week for 6–13 weeks to atmospheres containing 100–200 mg m\(^{-3}\) phenol found guinea pigs to be the most sensitive and rats the least sensitive to exposure. In addition to neurological effects and mortality in the guinea pigs, effects on the respiratory system, heart, liver and kidney were seen in guinea pigs and rabbits; no effects were seen in rats (USEPA, 2002b; HPA, 2007; ATSDR, 2008).
3.5 Reproductive and developmental toxicity

Maternal toxicity (excess salivation, rapid breathing and death) and foetotoxicity (reduced bodyweights and a possible lower degree of bone ossification) occurred when phenol was administered by stomach tube to female rats three times daily on days 6–15 of pregnancy at total daily doses of 360 mg kg$^{-1}$ bw. The suspicions of mild maternal toxicity seen at 120 mg kg$^{-1}$ bw day$^{-1}$ were not present at 60 mg kg$^{-1}$ bw day$^{-1}$ (ARL, 1997).

In earlier studies (Jones-Price et al., 1983a, 1983b), phenol was administered to pregnant rats and mice on days 6–15 of pregnancy by a single gavage dose each day. For both species, the most pronounced effect was a reduction in foetal bodyweights in the highest dose group: 120 mg kg$^{-1}$ bw day$^{-1}$ in the rats, which was not associated with any overt signs of maternal toxicity; 280 mg kg$^{-1}$ bw day$^{-1}$ in the mice, which was maternally toxic (inducing neurotoxicity). No convincing signs of foetotoxicity were seen at 60 and 140 mg kg$^{-1}$ bw day$^{-1}$ in rats and mice respectively. In the mice, but not in the rats, there was a slight increase in the incidence of cleft palate in the foetuses of the highest dose group.

There were some litter losses and overt signs of maternal toxicity (“severe respiratory signs”) in rats given 40 or 53 mg kg$^{-1}$ bw day$^{-1}$ of phenol by gavage on days 6–15 of pregnancy. The three dams (one in the low-dose and two in the high-dose group) that fully absorbed their litters all had severe respiratory effects (Narotsky and Kavlock, 1995). As no similar signs of a respiratory action have been reported in other studies, it has been suggested that these may have reflected a problem with the gavaging technique rather than the administered phenol. RIVM selected 40 mg kg$^{-1}$ bw day$^{-1}$ as a no-effect level for this study (RIVM, 2001).

Foetal toxicity was observed in a two-generation rat study in which phenol was administered in the drinking-water. Both generations, which were treated for around 10 weeks prior to mating, and during mating, gestation and lactation, were affected (Ryan et al., 2001). A reduced litter survival as well as a slight delay in the development of the offspring was seen at the maximum tested concentration of 5,000 ppm, which produced a dose in the order of 300–380 mg kg$^{-1}$ bw day$^{-1}$. Reduced adult bodyweight gain was also observed at this dose. The investigators identified the 1,000 ppm concentration as the NOAEL. This would have delivered a dose of 70 mg kg$^{-1}$ bw day$^{-1}$ in the males and 93 mg kg$^{-1}$ bw day$^{-1}$ in the females. At this concentration and the lowest tested concentration of 200 ppm, there were reduced (absolute) uterus and prostate weights. Tissues from the reproductive and other major organs were microscopically examined. In the case of the reproductive organs, they were taken from 20 rats in each dose group from each generation, and with the other organs (which included the liver, kidney, thymus and spleen) from 10 rats per sex in the high-dose and control groups. No pathological changes were identified. In view of this, and in the absence of a dose–response relationship or functional effects on reproduction, the investigators did not consider the organ weight changes as adverse (Ryan et al., 2001).

3.6 Genotoxicity

Phenol has given no evidence of mutagenic activity in the majority of bacterial Ames tests conducted. Treatment-related increases in gene mutation, and chromosomal and DNA damage occur in mammalian cells in culture, and increases in sister chromatid exchange have been recorded in human lymphocytes exposed in vitro (IPCS, 1994). Phenol induced chromosomal damage (micronuclei) in the bone marrow cells of mice given intraperitoneal doses of 40–300 mg kg$^{-1}$ bw (COM, 2000, 2008; Li et al., 2005; Spencer et al., 2007). In the corresponding oral studies, there was at worst only a
minimal increase in chromosome damage at doses close to the maximum tolerated dose (Ciranni et al., 1988; EC, 2006).

The UK Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment (COM) considered that phenol administered by intraperitoneal injection was a somatic cell mutagen (COM, 2000). COM concluded in 2003 and 2008 that there was potential for a threshold of activity by the oral route because of the rapid metabolism and detoxification of phenol in humans via the glutathione pathway or catalase activity, but that there was insufficient evidence to support a threshold approach to risk assessment for inhalation and dermal exposure (COM, 2003, 2008).

A 2008 assessment by the US Agency for Toxic Substances and Disease Registry (ATSDR) noted that “under certain conditions, especially at higher doses, phenol has the potential to be genotoxic. However, at the exposure levels likely to occur near hazardous waste sites, phenol is not anticipated to be genotoxic” (ATSDR, 2008).

The EC Risk Assessment Report (RAR) issued in 2006 confirmed the 2001 EU decision to classify phenol as a Category 3 mutagen. The RAR noted that “the high-dose positive micronuclei results being secondary to phenol-induced hypothermia [was] a plausible hypothesis”, but that no definite conclusions about this mechanism could be drawn because of the limited nature of the available data (EC, 2006). A similar opinion has been expressed by COM (COM, 2003, 2008).

### 3.7 Carcinogenicity

Both USEPA in an assessment based on a 1999 literature review (USEPA, 2002a, 2002b) and the International Agency for Research on Cancer (IARC) in a 1998 meeting (IARC, 1999) did not consider there to be adequate evidence for the carcinogenicity of phenol in humans and in experimental animals. Both organisations put phenol into the group of substances that, on present evidence, cannot be classified as to their human carcinogenicity.

Four cancer epidemiological studies were considered by IARC (1999), leading to its conclusion that “the pattern of results fails to demonstrate a risk of cancer due to phenol exposure”. In a case-control study of about 7,000 men in the US rubber industry, an increased risk of stomach cancer was associated with exposure to phenol, but the reported Odds Ratio was not raised to a statistically significant extent (Wilcosky et al., 1984). In a case-control study of 136 patients with respiratory cancer and about 400 controls nested within a cohort of about 7,300 men in the Finnish plywood industry, exposure to phenol per se was found to be associated with a three-fold increased risk of lung cancer. The excess risk, though, was stronger in short-term than in long-term workers (Kauppinen et al., 1993). A cohort of about 15,000 workers from five US companies occupationally exposed to phenol was followed for a number of years and mortality rates compared with those of the general population (Dosemeci et al., 1991). Increased mortality ratios were observed for some cancers (e.g. oesophagus, kidney and Hodgkin’s disease), whereas reduced ratios were observed for others (buccal cavity and pharynx, stomach and brain). None of these changes in mortality ratios was dose-related and none was statistically significant. In a population-based case-control study of cancer in Montreal (Siemiatycki, 1991), phenol exposure (reported by 1% of the study population) was associated with an increased pancreatic cancer risk (Odds Ratio of 4.8) based on only four cases.

In carcinogenicity studies in rodents (NCI, 1980), phenol was administered in the drinking-water for 103 weeks at dose levels of 450 and 660 mg kg\(^{-1}\) bw day\(^{-1}\) for the

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Substances that cause concern for man owing to possible mutagenic effects. There is evidence from appropriate mutagenicity studies, but this is insufficient to place the substance in Category 2.
mice and 260–280 and 585–630 mg kg\(^{-1}\) bw day\(^{-1}\) for the rats. Matched controls received tap water. The increased incidence of phaeochromocytomas and leukaemia or lymphomas seen in the male rats of the low-dose group was not present in the high-dose group. There was no significant tumour increase in any tissues in the female rats. There was no dose-related increase of tumours in any tissues in mice of either sex. The US National Cancer Institute (NCI) concluded that, under the conditions of this study, phenol was not carcinogenic in mice or rats — a conclusion supported by the 2006 EC risk assessment (EC, 2006).

Two-stage carcinogenicity studies have been conducted in which phenol was applied to mouse skin previously given an initiating dose of either a polycyclic aromatic hydrocarbon (PAH) compound or phenol, or in which both compounds were applied simultaneously (IARC, 1989; IPCS, 1994). The tested concentrations of phenol were typically 5–20%. Results from these studies are ambiguous, with phenol exhibiting both promoting and inhibiting activity. In some of the studies, simultaneous application of both agents showed a reduction in the number of carcinomas compared with mice treated with the PAH compound alone. In others, an inhibitory effect was observed when phenol treatment preceded the application of the PAH compound (compared with the effect of both agents being applied simultaneously).

3.8 Summary

Phenol is well absorbed via the gastrointestinal tract, respiratory tract and skin. Signs and symptoms of acute toxicity in humans and laboratory animals are similar for dermal and oral exposure, and can occur within minutes of exposure. Toxicity targets include the nervous system, kidney, heart and lung.

Lethal oral doses in humans may be as low as 1–15 g (equivalent to about 14–214 mg kg\(^{-1}\) bw), though higher doses have been survived. Human deaths have also occurred from skin contact. Oral LD\(_{50}\) values in laboratory animals (340–620 mg kg\(^{-1}\) bw day\(^{-1}\)) are of a similar order to the 24-hour dermal LD\(_{50}\) value reported in rats. The eight-hour inhalation LC\(_{50}\) in rats was in excess of 900 mg m\(^{-3}\). Phenol is a powerful skin irritant in man, and skin necrosis has been produced by contact with 1% solutions.

Liver and kidney damage (and spleen or thymus abnormalities) occurred in rats that received repeated doses of 40 mg kg\(^{-1}\) bw day\(^{-1}\) by stomach tube. Neurotoxicity has been reported in rodents similarly treated with 40–70 mg kg\(^{-1}\) bw day\(^{-1}\). Drinking-water studies, however, found only a mild degree of toxicity either in two generations of rats given doses of 300–380 mg kg\(^{-1}\) bw day\(^{-1}\) for up to 13 weeks, or in rats and mice given doses of a similar order for two years. It is possible that the higher degree of apparent toxicity seen in the gavage studies was due to a bolus effect; other reasons, including possible impurities in the test agents used in the gavage studies, have also been postulated (COT, 2002).

Testing of a group of workers exposed occupationally to average phenol concentration of 21 mg m\(^{-3}\) for around 13 years showed effects on some haematological and clinical chemistry parameters indicative of possible liver toxicity. Incompletely described inhalation studies in rodents and monkeys indicated that repeated exposure to 20 mg m\(^{-3}\) produced lung, liver and kidney abnormalities. Higher exposures of rabbits and guinea pigs affected the same target organs, as well as the heart and, in the guinea pigs only, the nervous system.

Mutations, chromosomal damage and DNA effects have been observed in mammalian cells in culture. Phenol induced micronuclei in the bone marrow cells of mice treated by intraperitoneal injection. Oral doses produced little or no similar genotoxic effect. This may be due to efficient first-pass metabolism following ingestion.
Long-term administration of phenol in drinking-water at the maximum tested doses of 600 mg kg$^{-1}$ bw day$^{-1}$ or more in rats and mice produced no convincing evidence of carcinogenic potential. USEPA and IARC have concluded that, overall, phenol cannot currently be classified as to its human carcinogenicity.

Foetal toxicity has been seen only in rats and mice receiving oral doses above those known to be toxic to the adult animals.
4 Derivation of Health Criteria Values

4.1 UK Committees on Toxicity and Mutagenicity of Chemicals in Food, Consumer Products and the Environment

In 2002, the UK Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) concluded that the critical study for the assessment of the risks posed by all toxicological endpoints other than mutagenicity was a two-generation reproductive and developmental toxicity study in rats (Ryan et al., 2001). Standard uncertainty factors (UFs) of 10 for extrapolation from rodent data and 10 for variability within the human population were applied to the NOAEL of 70 mg kg\(^{-1}\) bw day\(^{-1}\) to produce a tolerable daily intake (TDI) for ingested phenol of 700 µg kg\(^{-1}\) bw day\(^{-1}\).

COT was aware that several studies (Hsieh et al., 1992; Narotsky and Kavlock, 1995) had reported effects at lower doses, but noted that the results were not consistent with the absence of comparable or related findings in other well-conducted investigations involving higher doses and longer periods of phenol ingestion. COT noted that “[t]he reasons for the apparent discrepancies between studies are unclear, but may be related to factors such as manner of exposure (abnormal findings reported at lower doses when phenol is administered as bolus doses by gavage than in studies using administration via drinking-water) and impurities, including oxidation and degradation products, in the test agent” (COT, 2002).

COT noted the conclusion of the Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment (COM) reported in 2000 that “by the oral route, there was potential for a threshold of activity” for the mutagenicity of phenol (see Section 3.7). This earlier opinion was based mainly on the fact that orally administered phenol was subject to rapid conjugation and detoxification via the glutathione pathway. COT also noted that catalase activity could protect against any mutagenic potential, and that the actual systemic exposure levels in humans would be very much lower than the doses that had demonstrated a mutagenic action in rodents (which at that time were intraperitoneal injections of 100–160 mg kg\(^{-1}\) bw) (COT, 2002). In 2000, COM had concluded there was insufficient evidence to support a threshold approach to risk assessment for inhalation and dermal exposure to phenol. COM’s subsequent evaluations of phenol’s mutagenicity in 2003 and 2008 came to essentially the same conclusion (COM, 2003, 2008).

4.2 Joint FAO/WHO Expert Committee on Food Additives

The Joint FAO/WHO Expert Committee on Food Additives (JECFA) has assessed phenol only as a food flavouring. On the basis of an estimated intake as a flavouring of 6 µg day\(^{-1}\), it concluded that phenol posed “no safety concern” (JECFA, 2001).
4.3 WHO guidelines for drinking-water quality

Phenol is not one of the contaminants discussed in the latest World Health Organization (WHO) guidelines on drinking-water quality (WHO, 1993, 1996, 2006). When it was considered in earlier publications (WHO, 1984a, 1984b), WHO had suggested that “typical criterion levels” based on toxicity, an odour threshold and a taste threshold would be 3, 1 and 0.1 mg L\(^{-1}\) respectively.

4.4 International Programme on Chemical Safety

An International Programme on Chemical Safety (IPCS) Task Group that met in 1993 derived a TDI from the results of a 14-day study in which rats were administered phenol by gavage dosing. The lowest cited NOAELs were for kidney and developmental effects, and were reported to be in the range 12–40 mg kg\(^{-1}\) bw day\(^{-1}\). There is no clear identification in the resulting Environmental Health Criteria document (IPCS, 1994) of the studies that generated these NOAELs, but it seems likely that the 12–40 mg kg\(^{-1}\) bw day\(^{-1}\) comes from the findings described in a study abstract (Schlicht et al., 1992) that was subsequently published as Berman et al. (1995). IPCS used an UF of 200 (factors of 10 each for interspecies and intraspecies variations, and a factor of 2 for the limited database), and so arrived at a range of 60–200 µg kg\(^{-1}\) bw day\(^{-1}\), which was described as “an upper limit for the TDI”. The Task Group noted that there was some evidence that phenol might be genotoxic and expressed concern over the fact that there were insufficient data to discount with certainty the possible carcinogenicity of phenol.

4.5 EU Risk Assessment Report

Phenol has undergone an in-depth risk assessment at European Union level\(^4\) (EC, 2006). The objective was to estimate margins of safety by comparing toxic effect levels with estimates of occupational and consumer exposure, and indirect human exposure via the environment. No HCVs were explicitly derived. The report was based on key toxicity studies identified in a literature search undertaken in 2003 and was reviewed by technical experts in the Member States in 2005.

The critical data points for risk assessment purposes for systemic toxicity were an oral lowest-observed adverse effect level (LOAEL) of 1.8 mg kg\(^{-1}\) bw day\(^{-1}\) for the reduced blood cell count in mice given phenol in drinking-water for 28 days (Hsieh et al., 1992), an inhalation LOAEC of 21 mg m\(^{-3}\) for possible liver injury in exposed workers (Shamy et al., 1994), and a dermal NOAEL of 1.18% (said to be equivalent to about 130 mg kg\(^{-1}\) bw day\(^{-1}\)) from a 18-day dermal study in rabbits (Deichmann et al., 1950). The NOAEL for developmental toxicity was 93 mg kg\(^{-1}\) bw day\(^{-1}\) from the two-generation rat study (Ryan et al., 2001).

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\(^4\) Phenol is a priority substance covered by Council Regulation (EEC) 793/93 on the evaluation and control of the risks of “existing” substances.
4.6 US Environmental Protection Agency

In 2002, USEPA published an oral Reference Dose (RfD) based on the developmental study in which phenol was administered by gavage in divided doses to pregnant rats (ARL, 1997). The NOAEL was 60 mg kg\(^{-1}\) bw day\(^{-1}\). Key signs of toxicity present at higher doses involved effects on maternal bodyweight. A detailed statistical analysis of the dose–response relationship for this endpoint generated a benchmark dose of 93 mg kg\(^{-1}\) bw day\(^{-1}\). The application of an overall UF of 300 (two factors of 10 to take account of possible inter- and intra-species variations, and a factor of 3 for database deficiencies) and rounding produced an RfD of 300 µg kg\(^{-1}\) bw day\(^{-1}\) (USEPA, 2002a, 2002b).

Uncertainties over the database (the assessment relied on the results of a 1999 literature search) were driven by the report of Hsieh et al. (1992) which found evidence of immunotoxicity in mice given phenol in their drinking-water. This prompted concerns over the validity of the current choice of effects on maternal weight gain in pregnant rats as the appropriate starting point in the development of the RfD.

4.7 US Agency for Toxic Substances and Disease Registry

In 2008, the US Agency for Toxic Substances and Disease Registry (ATSDR) could not derive either chronic or intermediate oral or inhalation Minimum Risk Levels (MRLs) for phenol because of the inadequacy of the database (ATSDR, 2008). There was a reluctance to use the LOAEL of 322 mg kg\(^{-1}\) bw day\(^{-1}\) of the two-year rat study (NCI, 1980) in the development of a chronic oral guideline because the reported indication of toxicity (a reduced final bodyweight) may have been due to a decreased water intake – in which case it would not represent a toxicological effect. ATSDR was also concerned that the immunosuppression seen in mice in a shorter duration study (Hsieh et al., 1992) could indicate that the immune system is the most sensitive target of phenol’s toxic potential. The two-year studies, which included no investigation of immunocompetence, might therefore not have had the desired degree of sensitivity. Uncertainty over the relevance of the study of Hsieh et al. was the main impediment to the derivation of an intermediate oral MRL (ATSDR, 2008).

4.8 Dutch National Institute for Public Health and the Environment

In a 2000 assessment, the Dutch National Institute for Public Health and the Environment (RIVM) described phenol as a tumour promoter and “not to be genotoxic” (RIVM, 2001). The NOAEL of 40 mg kg\(^{-1}\) bw day\(^{-1}\) from a study in which rats were

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5 The RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of non-cancer deleterious effects during a lifetime.

6 A benchmark dose (BMD) is a dose of a substance that produces a predetermined change in response rate of an adverse effect. In this instance it was the 95% lower confidence limit of the dose producing a one standard deviation decrease in maternal bodyweight gain.

7 An ATSDR MRL is an estimate of the human exposure to a hazardous substance that is likely to be without appreciable risk of adverse non-cancer health effects over a specified duration of exposure. A chronic MRL applies to life-time human exposures, whereas an intermediate MRL is applicable to human exposures of up to one year.
treated orally on days 6–19 of pregnancy (Narotsky and Kavlock, 1995) was the foundation of an oral TDI. Foetotoxicity was seen at 53 mg kg\(^{-1}\) bw day\(^{-1}\). Application of UFs of 100 for inter- and intra-species variations, 3 for the limited duration of the study (a reduced figure from the usual default of 10 because "phenol is rapidly eliminated") and 3 for the limited nature of the database to the NOAEL produced, after rounding, an oral TDI of 40 µg kg\(^{-1}\) bw (RIVM, 2001).

A Tolerable Concentration in Air (TCA)\(^8\) was based on an overall no-observed adverse effect concentration (NOAEC) of 20 mg m\(^{-3}\) reported in “semi-chronic” inhalation studies in rhesus monkeys, rats and mice (as described in a 1998 ATSDR review\(^9\)). Division of this by an UF of 1,000 – consisting of factors of 100 for possible inter- and intra-species differences and 10 for extrapolation of a semi-chronic study to lifetime exposure – generated a TCA of 20 µg m\(^{-3}\). As the database was poor, this was described as a “provisional” value.

4.9 Discussion

Phenol has demonstrated mutagenic potential in rodents. In 2000, however, COM noted that there is potentially a dose threshold for any mutagenic action arising from the ingestion of phenol.

An IPCS Task Group suggested in 1993 that the upper limit for the oral TDI for phenol lay within the range of 60–200 µg kg\(^{-1}\) bw (IPCS, 1994). The derivation, which was only briefly described, was based on the view that the critical effect was kidney toxicity. The NOAEL for this endpoint was said to lie within the dose range of 12–40 mg kg\(^{-1}\) bw day\(^{-1}\), which was probably generated by a 14-day gavage study in rats (Schlicht et al., 1992; Berman et al., 1995). As well as the usual UF of 100, to take account of interindividual variations and an interspecies extrapolation, an additional UF of 2 was applied to the NOAEL range to compensate for the limited nature of the database.

Although benefiting from several more years of data (its foundation being a literature survey conducted in 1999), a USEPA assessment in 2002 also relied on a very short-term gavage study in rats. The derived oral RfD of 300 µg kg\(^{-1}\) bw day\(^{-1}\) was based on reduced adult weight gains seen in a developmental study (ARL, 1997). Doses of 120 mg kg\(^{-1}\) bw day\(^{-1}\) produced effects on the bodyweight of pregnant rats and the NOAEL was 60 mg kg\(^{-1}\) bw day\(^{-1}\). The RfD arose from the application of an UF of 300 to a benchmark dose of 93 mg kg\(^{-1}\) bw day\(^{-1}\) from what was essentially only a 10-day toxicity study. Database deficiencies triggered a constituent UF of 3 out of the overall 300.

In 2000, RIVM also based its oral HCV on a gavage developmental study in rats (Narotsky and Kavlock, 1995). An UF of 900, which similarly included a factor of 3 for the inadequacy of the database, was applied to the selected NOAEL of 40 mg kg\(^{-1}\) bw day\(^{-1}\) for developmental effects to produce (with rounding) an oral TDI of 40 µg kg\(^{-1}\) bw.

In laboratory animal studies, phenol has exhibited a higher degree of toxicity when given by stomach tube than when administered in the drinking-water. The two-year drinking-water studies (NCI, 1980) found evidence of, at worst, mild and non-specific toxicity in rats given about 260 mg kg\(^{-1}\) bw day\(^{-1}\), whereas 14 gavaged doses of only

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8 The TCA is the concentration of a substance in the atmosphere that any human individual can be exposed to continuously during a full lifetime without significant health risk.

9 The studies, which involved the continuous exposure of monkeys, rats and mice to 0 or 5 ppm phenol for 90 days (US Air Force 1961), were also described in the 2008 ATSDR report. ATSDR noted that "incomplete reporting of the results suggests that there may have been some lung, liver, and kidney pathology".
40 mg kg\(^{-1}\) bw produced kidney and liver damage (Schlicht et al., 1992; Berman et al., 1995). Similarly with developmental toxicology, the two-generation rat studies involving administration in drinking-water (Ryan et al., 2001) identified mild foetotoxicity at doses in the order of 300–380 mg kg\(^{-1}\) bw day\(^{-1}\), whereas gavaged doses of 53 mg kg\(^{-1}\) bw day\(^{-1}\) may have produced total litter loss in rats (Narotsky and Kavlock, 1995).

The two-generation rat study by Ryan et al. (2001) was considered by COT to be critical in its 2002 assessment of the risks posed by ingested phenol. With its more protracted treatment period of 13 weeks, its drinking-water administration, and its more detailed examination of the animals, COT considered it provided a superior basis to deriving an HCV than the shorter-term gavage studies favoured by USEPA, IPCS and RIVM. An UF of 100 (for possible interspecies and intraspecies differences) applied to the NOAEL of 70 mg kg\(^{-1}\) bw day\(^{-1}\) produced a TDI of 700 µg kg\(^{-1}\) bw. This value is recommended here as the oral TDI for the purposes of deriving SGVs.

A single expert group, RIVM in 2000, has proposed an inhalation HCV, and this was only a provisional TCA of 20 µg m\(^{-3}\). Its basis was an NOAEC of 20 mg m\(^{-3}\) from a series of limited studies in monkeys, rats and mice summarised in a 1998 ATSDR report. In a 2008 report, ATSDR notes that the “incomplete reporting of the results [of these same studies] suggests that there may have been some lung, liver, and kidney pathology”. IPCS in 1993, USEPA in 2002 and ATSDR in a 2008 each considered that there are no reliable data on the effects of inhaled phenol from which a TDI\(_{inh}\) could be derived.

The critical effect arising from inhalation (or dermal) exposure to phenol is, in fact, likely to be its mutagenic potential. In 2000, COM concluded that there was no evidence to support a threshold approach to the risk assessment of inhalation or dermal exposure, and that it was not possible to quantify the mutagenic risk. COM reached similar conclusions in 2003 and 2008.

An HCV recommended for the inhalation of phenol based on mutagenic (and thus carcinogenic) potential for which it is assumed there is no threshold would take the form of an Index Dose (ID\(_{inh}\)), with the associated requirement to reduce exposure to a level as low as reasonably practicable (ALARP). However, no evaluations that would be appropriate to adopt as a basis for such an Index Dose are currently available.

Despite the significant limitations in the available inhalation data, it does appear that, aside from potential mutagenic effects, phenol is more potent when inhaled that when ingested. Deriving SGVs based on the recommended TDI\(_{oral}\) alone might therefore be insufficiently protective of the threshold (non-mutagenic) effects of phenol. In addition to the old 90-day laboratory animal studies, which formed the basis of the RIVM provisional TCA of 20 µg m\(^{-3}\), the study of Egyptian workers occupationally exposed for an average of 13.5 years to reported atmospheric phenol concentrations of 21 mg m\(^{-3}\) also provides a basis for an inhalation TDI (TDI\(_{inh}\)). The RAR considered this level of 21 mg m\(^{-3}\) to be the critical LOAEL for inhalation risk assessment. The RAR concludes that an UF of 3 should be applied for use of a LOAEL and a further factor of 2 to account for uncertainty in the true level of exposure. Application of a factor of 10 to allow for the conversion of occupational to continuous exposure, and a further factor of 10 to allow for sensitive individuals in the population, would produce a value of 35 µg m\(^{-3}\). Based on the default 70-kg adult inhaling 20 m\(^{3}\) of air per day, this is equivalent to an inhalation dose of 10 µg kg\(^{-1}\) bw day\(^{-1}\) and is considered to represent the most suitable empirical inhalation value for use in deriving SGVs at the present time.
5 Background intake

5.1 Food

Phenol is found in smoked meat and fish products. The total content of all phenols is usually reported and the concentration of phenol itself is not always stated explicitly.

In evaluating the acceptability of phenol as a flavouring, JECFA (2001) concluded that the annual volume of phenol used as a food additive in Europe was 71.6 kg (estimated from the reported volume of 43 kg and the assumption that only 60% of the true volume was identified in the surveys) and that the annual volume in naturally occurring foods was 41,193 kg. Based on the reported population of $320 \times 10^6$, the average annual intake of total dietary phenol would have been 129 mg per person. This is equivalent to approximately 350 µg day$^{-1}$.

5.2 Water

The Water Supply (Water Quality) Regulations 1989 included a limit of 0.5 µg L$^{-1}$ for total phenols. However, the Water Supply (Water Quality) Regulations 2000 do not include a standard for phenol or total phenols. Assuming that drinking-water concentrations of phenol are equal to 0.5 µg L$^{-1}$, for an adult drinking two litres of water each day, this would give rise to a daily phenol intake of 1 µg, i.e. intake from water would not add significantly to that ingested in food.

5.3 Air

Phenol and other volatile organic compounds (VOCs) were measured in the air of 50 homes and apartments in Finland. The average and maximum concentrations were found to be about 1 and 3 µg m$^{-3}$ respectively (Kostiainen, 1995).

A review by IPCS of the reported measurements of phenol in urban air found concentrations to be within the range 0.1–8 µg m$^{-3}$ (IPCS, 1994).

It seems unlikely that the mean value to which the public is exposed is greater than about 2 µg m$^{-3}$. This corresponds to a daily intake of 40 µg day$^{-1}$ for the default 70-kg adult breathing 20 m$^3$ of air per day.

5.4 Other sources

Phenol is used in a variety of consumer products including soaps, shampoos, paints, polishes and floor waxes. Dermal exposure from phenol-containing soaps and shampoos has been estimated to be around 21 µg kg$^{-1}$ bw day$^{-1}$ (EC, 2006). The EC risk assessment for phenol (EC, 2006) considered that inhalation exposure from the use of other phenol-containing consumer products such as polishes will not exceed 480 µg kg$^{-1}$ bw day$^{-1}$ for an adult (equivalent to approximately 33,600 µg day$^{-1}$).

However, this estimate, based on modelled scenarios, is very much higher than would be predicted from the measured indoor air concentrations from Kostiainen (1995) and IPCS (1994). The EC risk assessment additionally estimated dermal exposures of
approximately 440 µg kg\(^{-1}\) bw per event for use of waxes and 900 µg kg\(^{-1}\) bw per event for use of disinfectants (EC, 2006).

Phenol is also present in some pharmaceutical preparations, including those for injection as well as those for topical application (EC, 2006).

Cigarette smoke contains phenol, and figures of 60–400 µg per cigarette have been quoted (IARC, 1989; IPCS, 1994; ATSDR, 2008). For an individual smoking 20 cigarettes per day, the resulting additional daily intake could therefore be 8,000 µg. Similar estimates were produced by Kuwata et al. (1980) who calculated that, in a non-ventilated 50 m\(^3\) room, the smoke from 10 cigarettes would result in a phenol concentration of 60–80 µg m\(^{-3}\) and an exposure of about 20 µg kg\(^{-1}\) bw day\(^{-1}\) (equivalent to about 1,400 µg day\(^{-1}\) for a 70-kg adult). It has also been estimated that non-smokers who live with smokers are exposed to atmospheric concentrations of up to 1.1 µg m\(^{-3}\). This would account for a daily inhalation of 6–14 µg day\(^{-1}\) (Nazaroff and Singer, 2004).

### 5.5 Estimation of mean daily intakes

The adult oral mean daily intake (MDI\(_{oral}\)) of phenol from food and drinking-water combined is estimated to be about 350 µg day\(^{-1}\).

The adult inhalation mean daily intake (MDI\(_{inh}\)) of phenol from its presence in ambient air is estimated to be about 40 µg day\(^{-1}\).

The total adult MDI of phenol from its presence in food, drinking-water and ambient air is thus expected to be about 390 µg day\(^{-1}\). This value lies between the 2006 EC risk assessment estimation of a local worst-case total exposure scenario from environmental sources (food, drinking-water and air) of 46.4 µg kg\(^{-1}\) bw day\(^{-1}\) (equivalent to approximately 3,200 µg day\(^{-1}\) for a 70-kg adult) and its estimation of total exposure from regional background concentrations of 0.15 µg kg\(^{-1}\) bw day\(^{-1}\) (equivalent to approximately 10.5 µg day\(^{-1}\) for a 70-kg adult) (EC, 2006).
6 Conclusions

Experimental data demonstrate phenol is mutagenic. By the oral route, there is likely to be an activity threshold for this mutagenic potential; however, no such assumption can be made for inhalation or dermal exposure.

In laboratory animal studies, phenol has exhibited a higher degree of toxicity when administered by stomach tube as a bolus dose than when administered in the drinking-water. A TDI_{oral} of 700 µg kg⁻¹ bw day⁻¹ is recommended here, based on the results of a study in which phenol was administered via the drinking-water to two generations of rats.

The inhalation toxicity database for phenol is very limited. In view of the potential for non-threshold mutagenicity, derivation of an IDI_{inh} would be appropriate; however, there are no suitable data from which an IDI_{inh} can be derived.

Despite the significant limitations in the available inhalation data, it does appear that, aside from potential mutagenic effects, phenol is more potent when inhaled than when ingested – probably due to efficient first-pass metabolism following ingestion. Deriving SGVs based on the recommended TDI_{oral} alone might therefore be insufficiently protective of the threshold effects of inhaled phenol in addition to the potential mutagenic effects. Based on limited occupational epidemiology data, it is concluded that an inhalation dose of 10 µg kg⁻¹ bw day⁻¹ represents the most suitable empirically-based value for use as a TDI_{inh} in deriving SGVs at the present time. The potential mutagenic (and thus assumed carcinogenic) risks at this dose are unknown, but likely to be small.

Phenol can potentially be absorbed through the skin in toxic amounts, but no authoritative assessments of dermal toxicity (based on either mutagenicity or threshold toxicity) were identified. In view of the first-pass metabolism of phenol following ingestion, it would seem most appropriate to compare dermal exposure with the TDI_{inh} when deriving SGVs. It is also noted that phenol is a powerful skin irritant in man, and skin necrosis has been produced by contact with 1% solutions.

Since both inhaled and ingested phenol cause similar (threshold) systemic toxic effects, this should be considered in an assessment where exposure is via both routes. In view of the potential non-threshold mutagenic risks from inhalation and dermal contact, it would be prudent to assume that the ALARP principle (to reduce exposures to a level ‘as low as reasonably practicable’) applies in risk management considerations.

The adult MDI_{oral} is estimated to be 350 µg day⁻¹; the adult MDI_{inh} is estimated to be 40 µg day⁻¹ (see Table 6.1).

### Table 6.1  HCV and MDI values for phenol

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Units</th>
<th>Oral</th>
<th>Inhalation</th>
</tr>
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<tbody>
<tr>
<td>MDI</td>
<td>µg day⁻¹</td>
<td>350</td>
<td>40</td>
</tr>
<tr>
<td>MDI for 70-kg adult</td>
<td>µg kg⁻¹ bw day⁻¹</td>
<td>5</td>
<td>0.6</td>
</tr>
<tr>
<td>MDI for 20-kg child</td>
<td>µg kg⁻¹ bw day⁻¹</td>
<td>13</td>
<td>1.5⁻¹</td>
</tr>
<tr>
<td>TDI</td>
<td>µg kg⁻¹ bw day⁻¹</td>
<td>700</td>
<td>10⁻¹</td>
</tr>
</tbody>
</table>

⁻¹ See Environment Agency (2009) for details of MDI conversion factors.
⁻² The TDI_{inh} does not account for phenol’s mutagenic potential, which for inhalation is assumed to have no threshold.
7 References


ANDERSON, W., 1869. Fatal misadventure with carbolic acid. Lancet, 1, 179 [cited in IPCS, 1999].


Contaminants in soil: updated collation of toxicological data and intake values for humans. Phenol 25


<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATSDR</td>
<td>Agency for Toxic Substances and Disease Registry [USA]</td>
</tr>
<tr>
<td>bw</td>
<td>bodyweight</td>
</tr>
<tr>
<td>CNS</td>
<td>central nervous system</td>
</tr>
<tr>
<td>COM</td>
<td>Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment [UK]</td>
</tr>
<tr>
<td>COT</td>
<td>Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment [UK]</td>
</tr>
<tr>
<td>Defra</td>
<td>Department for Environment, Food and Rural Affairs [UK]</td>
</tr>
<tr>
<td>EC</td>
<td>European Commission</td>
</tr>
<tr>
<td>FSA</td>
<td>Food Standards Agency [UK]</td>
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<tr>
<td>HCV</td>
<td>Health Criteria Value</td>
</tr>
<tr>
<td>HPA</td>
<td>Health Protection Agency [UK]</td>
</tr>
<tr>
<td>IARC</td>
<td>International Agency for Research on Cancer</td>
</tr>
<tr>
<td>IPCS</td>
<td>International Programme on Chemical Safety</td>
</tr>
<tr>
<td>JECFA</td>
<td>Joint FAO/WHO Expert Committee on Food Additives</td>
</tr>
<tr>
<td>L</td>
<td>litre</td>
</tr>
<tr>
<td>LC&lt;sub&gt;50&lt;/sub&gt;</td>
<td>atmospheric concentration killing 50 per cent of treated animals</td>
</tr>
<tr>
<td>LD&lt;sub&gt;50&lt;/sub&gt;</td>
<td>dose killing 50 per cent of treated animals</td>
</tr>
<tr>
<td>LOAEL</td>
<td>lowest-observed-adverse effect level</td>
</tr>
<tr>
<td>MDI</td>
<td>mean daily intake</td>
</tr>
<tr>
<td>MRL</td>
<td>Minimal Risk Level</td>
</tr>
<tr>
<td>NOAEC</td>
<td>no-observed adverse effect concentration</td>
</tr>
<tr>
<td>NOAEL</td>
<td>no-observed-adverse effect level</td>
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<tr>
<td>NTP</td>
<td>National Toxicology Program [USA]</td>
</tr>
<tr>
<td>PAH</td>
<td>polycyclic aromatic hydrocarbon</td>
</tr>
<tr>
<td>ppm</td>
<td>parts per million</td>
</tr>
<tr>
<td>RAR</td>
<td>Risk Assessment Report [EU]</td>
</tr>
<tr>
<td>RfD</td>
<td>Reference Dose</td>
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<tr>
<td>RIVM</td>
<td>National Institute for Public Health and the Environment [Netherlands]</td>
</tr>
<tr>
<td>SGV</td>
<td>Soil Guideline Value</td>
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<tr>
<td>TCA</td>
<td>Tolerable Concentration in Air</td>
</tr>
<tr>
<td>TDI</td>
<td>tolerable daily intake</td>
</tr>
<tr>
<td>UF</td>
<td>uncertainty factor</td>
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</table>
Appendix – Literature search

The literature search that formed the basis of this update report was undertaken using a proprietary database – the TRACE database developed and managed by bibra toxicology advice & consulting. The database was most recently searched in November 2008 for comprehensive reviews and evaluations of phenol. A search for salient primary literature published during 2005–2008, i.e. since the most recent expert group evaluation, was also conducted.

TRACE includes information from peer-reviewed toxicology and nutrition journals as well as secondary sources (websites, official publications and evaluations by authoritative groups) including:

- UK government agency (Defra and the Environment Agency, FSA, HPA) and advisory committee (COT, COM, COC, ACAF, ACNFP and ACP) reports and evaluations
- EU Risk Assessment Reports
- EU expert committees (EU scientific committees, EFSA scientific panels)
- WHO/IPCS reports and evaluations (including CICADs and EHCs, and IARC, JECFA and JMPR monographs), and the WHO Air Quality and Drinking-Water Quality Guidelines
- US government agency reports and evaluations (EPA, ATSDR, FDA, NTP, OSHA, NCEA, CFSAN, CERHR, NIEHS and OEHHA)
- OECD SIDS dossiers/SIARS
- ECETOC, ACGIH, BG Chemie and DFG reports and monographs
- IUCLID data sets
- NICNAS Priority Existing Chemical Assessments

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