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English only

2-Phenylphenol in Drinking-water

Background document for development of
WHO *Guidelines for Drinking-water Quality*

Preface

One of the primary goals of WHO and its member states is that "all people, whatever their stage of development and their social and economic conditions, have the right to have access to an adequate supply of safe drinking water." A major WHO function to achieve such goals is the responsibility "to propose ... regulations, and to make recommendations with respect to international health matters ...."

The first WHO document dealing specifically with public drinking-water quality was published in 1958 as *International Standards for Drinking-water*. It was subsequently revised in 1963 and in 1971 under the same title. In 1984–1985, the first edition of the WHO *Guidelines for Drinking-water Quality* (GDWQ) was published in three volumes: Volume 1, Recommendations; Volume 2, Health criteria and other supporting information; and Volume 3, Surveillance and control of community supplies. Second editions of these volumes were published in 1993, 1996 and 1997, respectively. Addenda to Volumes 1 and 2 of the second edition were published in 1998, addressing selected chemicals. An addendum on microbiological aspects reviewing selected microorganisms was published in 2002.

The GDWQ are subject to a rolling revision process. Through this process, microbial, chemical and radiological aspects of drinking-water are subject to periodic review, and documentation related to aspects of protection and control of public drinking-water quality is accordingly prepared/updated.

Since the first edition of the GDWQ, WHO has published information on health criteria and other supporting information to the GDWQ, describing the approaches used in deriving guideline values and presenting critical reviews and evaluations of the effects on human health of the substances or contaminants examined in drinking-water.

For each chemical contaminant or substance considered, a lead institution prepared a health criteria document evaluating the risks for human health from exposure to the particular chemical in drinking-water. Institutions from Canada, Denmark, Finland, France, Germany, Italy, Japan, Netherlands, Norway, Poland, Sweden, United Kingdom and United States of America prepared the requested health criteria documents.

Under the responsibility of the coordinators for a group of chemicals considered in the guidelines, the draft health criteria documents were submitted to a number of scientific institutions and selected experts for peer review. Comments were taken into consideration by the coordinators and authors before the documents were submitted for final evaluation by the experts meetings. A "final task force" meeting reviewed the health risk assessments and public and peer review comments and, where appropriate, decided upon guideline values. During preparation of the third edition of the GDWQ, it was decided to include a public review via the world wide web in the process of development of the health criteria documents.

During the preparation of health criteria documents and at experts meetings, careful consideration was given to information available in previous risk assessments carried out by the International Programme on Chemical Safety, in its Environmental Health Criteria monographs and Concise International Chemical Assessment Documents, the International Agency for Research on Cancer, the joint FAO/WHO Meetings on Pesticide Residues and the joint FAO/WHO Expert Committee on Food Additives (which evaluates contaminants such as lead, cadmium, nitrate and nitrite, in addition to food additives).

Further up-to-date information on the GDWQ and the process of their development is available on the WHO internet site and in the current edition of the GDWQ.

Acknowledgements

The first draft of 2-Phenylphenol in Drinking-water, Background document for development of WHO *Guidelines for Drinking-water Quality*, was prepared by Dr P. Toft, Canada, to whom special thanks are due.

The work of the following working group coordinators was crucial in the development of this document and others in the third edition:

Mr J.K. Fawell, United Kingdom (*Organic and inorganic constituents*)
Dr E. Ohanian, Environmental Protection Agency, USA (*Disinfectants and disinfection by-products*)
Ms M. Giddings, Health Canada (*Disinfectants and disinfection by-products*)
Dr P. Toft, Canada (*Pesticides*)
Prof. Y. Magara, Hokkaido University, Japan (*Analytical achievability*)
Mr P. Jackson, WRc-NSF, United Kingdom (*Treatment achievability*)

The contribution of peer reviewers is greatly appreciated. The draft text was posted on the world wide web for comments from the public. The revised text and the comments were discussed at the Final Task Force Meeting for the third edition of the GDWQ, held on 31 March to 4 April 2003, at which time the present version was finalized. The input of those who provided comments and of participants in the meeting is gratefully reflected in the final text.

The WHO coordinators were as follows:

Dr J. Bartram, Coordinator, Water Sanitation and Health Programme, WHO Headquarters, and formerly WHO European Centre for Environmental Health
Mr P. Callan, Water Sanitation and Health Programme, WHO Headquarters
Mr H. Hashizume, Water Sanitation and Health Programme, WHO Headquarters

Ms C. Vickers provided a liaison with the International Chemical Safety Programme, WHO Headquarters.

Ms Marla Sheffer of Ottawa, Canada, was responsible for the scientific editing of the document.

Many individuals from various countries contributed to the development of the GDWQ. The efforts of all who contributed to the preparation of this document and in particular those who provided peer or public domain review comment are greatly appreciated.

Acronyms and abbreviations used in the text

ADI	acceptable daily intake
CARB	California Air Resources Board
CAS	Chemical Abstracts Service
DNA	deoxyribonucleic acid
FAO	Food and Agriculture Organization of the United Nations
GEMS	Global Environment Monitoring System
IARC	International Agency for Research on Cancer
JMPR	Joint FAO/WHO Meeting on Pesticide Residues
LD_{50}	median lethal dose
NOAEL	no-observed-adverse-effect level
WHO	World Health Organization

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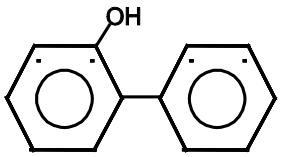
1. GENERAL DESCRIPTION

1.1 Identity

CAS No.:	90-43-7
Molecular formula:	$C_{12}H_{10}O$

The chemical structure of 2-phenylphenol is shown below:



1.2 Physicochemical properties (CARB, 1997)

Property	*Value*
Boiling point	280–284 °C
Melting point	55.5–57.5 °C
Density/specific gravity	1.213 at 25/4 °C
Vapour pressure	133 Pa at 100 °C
Solubility of 2-phenylphenol in water	<0.1 g/litre at 20 °C
Solubility of sodium 2-phenylphenate in water	122 g dissolve in 100 ml water

1.3 Major uses

2-Phenylphenol is used as a disinfectant, bactericide and virucide. In agriculture, it is used in disinfecting fruits, vegetables and eggs. 2-Phenylphenol is also used as a general surface disinfectant in hospitals, nursing homes, veterinary hospitals, poultry farms, dairy farms, commercial laundries, barbershops and food processing plants. It is also used to sterilize hospital and veterinary equipment (CARB, 1997).

1.4 Environmental fate

2-Phenylphenol is readily degraded in surface waters and municipal waste mixtures, and the degradation is biologically mediated. In river water, radiolabelled 2-phenylphenol at concentrations ranging from 1.2 to 120 µg/litre was degraded to about 50% of the initial concentration in 1 week. The addition of mercuric chloride to inhibit biological activity reduced the decrease to only 10% after 30 days. In activated sludge, radiolabelled 2-phenylphenol at 9.6 mg/litre was degraded to 50% of the initial concentration in 24 h. 2-Phenylphenol therefore meets the criteria to be classified as readily biodegradable (FAO/WHO, 1999).

Based on its vapour pressure, 2-phenylphenol can be expected to exist primarily in the gas phase in the ambient atmosphere, although a small percentage may be associated with the particulate phase. The calculated half-life and lifetime of 2-phenylphenol due to reaction with the hydroxyl radical are 10 h and 14 h, respectively (Atkinson, 1995).

2-Phenylphenol may also degrade very rapidly in night air by the reaction with nitrate radicals.

2. ANALYTICAL METHODS

Numerous methods exist for the determination of 2-phenylphenol and sodium 2-phenylphenate. A gas–liquid chromatographic method involves reflux distillation with hydrochloric acid and hexane. The distillate is extracted and analysed by gas–liquid chromatography with a flame ionization detector and a capillary column. The limit of detection is 0.1 mg/kg (FAO/WHO, 1999).

3. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

3.1 Air

In surveys carried out in the USA in 1986–1988, indoor concentrations of 2-phenylphenol were moderately elevated. The mean indoor concentrations of 2-phenylphenol for homes in Massachusetts for spring and winter were 22.8 and 44.5 ng/m^3, respectively. The mean indoor concentrations for homes in Florida over three seasons ranged from 59.0 to 96.0 ng/m^3. In contrast, outdoor concentrations of 2-phenylphenol were much lower and ranged from below 0.05 to 1.6 ng/m^3 (CARB, 1997).

3.2 Food

Median residues from supervised trials for one raw commodity and one processed commodity were used for a chronic dietary intake assessment. The International Estimated Daily Intakes for the five GEMS/Food regional diets, based on these trials, were all determined to be 0% of the ADI (see below). It was concluded that the intake of residues of 2-phenylphenol resulting from its uses that have been considered by JMPR is unlikely to present a public health concern (FAO/WHO, 1999).

4. KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS[1]

After oral administration to mice and rats, 2-phenylphenol and its sodium salt are rapidly and extensively absorbed (95%) and distributed. Excretion is also rapid in these species, being almost complete within 48 h, and occurs mainly in urine (about 90%) and in faeces (about 5%). Little radiolabel (<1%) is retained in organs and tissues, including the urinary bladder. After dermal application of 2-phenylphenol to humans, about 43% of the applied dose was absorbed through the skin, and about 58% was recovered in skin rinse and the protective enclosure. Most of the absorbed radiolabel was recovered in urine (99%), and only 1% was recovered in faeces. The absorption half-time was 10 h, and the elimination half-time was 0.8 h. The rapid excretion of the radiolabel into urine indicates that 2-phenylphenol is unlikely to

[1] This section is taken from FAO/WHO (2000).

accumulate in humans exposed repeatedly. The metabolic profiles of both compounds were similar in mice, rats and humans at the various doses tested. The main metabolic pathways are conjugation of 2-phenylphenol or hydroxylation at the 5 position of the phenol ring, followed by conjugation with glucuronide or sulfate. The parent compound was detected in only very small amounts (0.4%) in urine. The metabolic profile in plants raised no toxicological concern, since about 90% of the residue found in oranges and pears is 2-phenylphenol or its conjugates.

5. EFFECTS ON EXPERIMENTAL ANIMALS AND IN VITRO TEST SYSTEMS[2]

2-Phenylphenol and its sodium salt have low acute toxicity in mice and rats treated orally, the LD_{50} values ranging from 600 to 3500 mg/kg of body weight.

WHO (2001) has classified 2-phenylphenol as unlikely to present an acute hazard in normal use.

2-Phenylphenol and its sodium salt caused severe dermal irritation in rabbits, and the sodium salt caused severe dermal irritation in humans. 2-Phenylphenol irritated the eye of rabbits, whereas the sodium salt caused only moderate ocular irritation. Neither substance caused delayed contact hypersensitivity in guinea-pigs or humans.

In medium- and long-term tests for toxicity, the urinary bladder was regarded as the main toxicological target organ of both 2-phenylphenol and its sodium salt in male and female rats. At doses of 200 mg/kg of body weight per day and above, hyperplasia, papillomas and transitional cell carcinomas were seen with both compounds in male rats. Increased mitosis was observed in the bladder epithelium 3 days after the start of dosing, and thickening (i.e., simple hyperplasia) was seen at 14 days. In female rats, hyperplasia and papillomas were observed, but to a far lower degree than in males. In male and female mice, the liver was the primary target organ. Increased relative liver weights and an increased incidence of hepatocellular adenomas were seen with 2-phenylphenol at doses of 500 mg/kg of body weight per day and above. Reduced body weight gain was a common finding in mice and rats. In 90-day studies, the NOAELs for 2-phenylphenol were 6300 mg/kg, equal to 760 mg/kg of body weight per day, in rats and 300 mg/kg of body weight per day (the highest dose tested for up to 1 year) in dogs. The NOAEL for the sodium salt was 5000 mg/kg, equivalent to 550 mg/kg of body weight per day, in mice and 2500 mg/kg, equal to 180 mg/kg of body weight per day, in rats. In a 1-year study of toxicity, the NOAEL for 2-phenylphenol was 800 mg/kg, equal to 39 mg/kg of body weight per day, in rats. In 2-year studies of carcinogenicity, the NOAEL for 2-phenylphenol was 250 mg/kg of body weight per day in mice and 800 mg/kg, equal to 39 mg/kg of body weight per day, in rats. In 2-year carcinogenicity studies with the sodium salt, the NOAEL for carcinogenicity was 20 000 mg/kg, equal to 3000 mg/kg of body weight per day, in mice and 2500 mg/kg, equivalent to 95 mg/kg of body weight per day, in rats. The Meeting concluded that both 2-phenylphenol and its

[2] This section is taken from FAO/WHO (2000).

sodium salt are carcinogenic in male rats and that 2-phenylphenol is carcinogenic in male mice.

2-Phenylphenol has been more extensively tested for genotoxic activity than its sodium salt. Within that limitation, the results for the two compounds were similar. Data regarding covalent binding to DNA in the urinary bladder of rats dosed with either compound were conflicting. 2-Phenylphenol induced chromosomal aberrations in cultured mammalian cells, but negative results were obtained *in vivo.* The Meeting concluded that there are unresolved questions about the genotoxic potential of 2-phenylphenol.

Several studies have been conducted to elucidate the mechanism of the carcinogenic action of 2-phenylphenol and its sodium salt on the male rat urinary bladder, since neither compound has a carcinogenic effect on the urinary bladder of female rats or in mice, guinea-pigs or hamsters of either sex. No clear mechanisms have been found, although raising the urinary pH or sodium concentration has a promoting effect. There was some evidence from studies with the sodium salt that initial irritation followed by hyperplasia might be involved in the bladder carcinogenicity in male rats. In addition, ^{32}P-postlabelling showed binding of 2-phenylphenol and its sodium salt to DNA in the male rat urinary bladder in some studies, but not in others. The genotoxicity of the metabolites phenylhydroquinone and dihydroxybiphenyl appears to be similar to that of the parent molecules.

The Meeting concluded that the urinary bladder tumours observed in male rats and the liver tumours observed in male mice exposed to 2-phenylphenol are threshold phenomena that are species- and sex-specific, and that 2-phenylphenol is therefore unlikely to represent a carcinogenic risk to humans. In coming to this conclusion, the Meeting was aware that a working group convened by IARC had classified 2-phenylphenol, sodium salt, in Group 2B (possibly carcinogenic to humans) and 2-phenylphenol in Group 3 (not classifiable as to its carcinogenicity to humans). The Meeting noted, however, that the IARC classification is based on hazard identification, not on risk assessment, and is furthermore limited to published literature, with the exclusion of unpublished studies on toxicity and carcinogenicity.

In two two-generation studies of reproductive toxicity in rats, 2-phenylphenol had no reproductive toxicity, even at 460 mg/kg of body weight per day, the highest dose tested. The overall NOAEL for carcinogenicity was 92 mg/kg of body weight per day, since urinary bladder tumours were found in male rats at doses of 120 mg/kg of body weight per day and above.

In a study of developmental toxicity in mice with 2-phenylphenol and its sodium salt, the NOAELs for 2-phenylphenol were below 1500 mg/kg of body weight per day (lowest dose tested) for maternal toxicity and fetotoxicity and 2100 mg/kg of body weight per day (highest dose tested) for teratogenicity. The NOAELs for the sodium salt were below 100 mg/kg of body weight per day (lowest dose tested) for maternal toxicity, 100 mg/kg of body weight per day for fetotoxicity and 400 mg/kg of body weight per day (highest dose tested) for teratogenicity. In two studies of

developmental toxicity in rats, the overall NOAELs for 2-phenylphenol were 150 mg/kg of body weight per day for maternal toxicity, 300 mg/kg of body weight per day for fetotoxicity and 700 mg/kg of body weight per day (highest dose tested) for teratogenicity. In two studies of developmental toxicity in rabbits, the overall NOAELs for 2-phenylphenol were 100 mg/kg of body weight per day for maternal toxicity, 500 mg/kg of body weight per day for fetotoxicity and 750 mg/kg of body weight per day (highest dose tested) for teratogenicity.

6. CONCLUSIONS

The Meeting established an ADI of 0.4 mg/kg of body weight for 2-phenylphenol, on the basis of the NOAEL of 39 mg/kg of body weight per day in the 2-year study of toxicity (based on decreased body weight gain and hyperplasia of the urinary bladder) and carcinogenicity of the urinary bladder in male rats and a safety factor of 100.

A health-based value of 1 mg/litre (rounded value) can be calculated from the ADI of 0.4 mg/kg of body weight, based on an allocation of 10% of the ADI to drinking-water. However, 2-phenylphenol usually occurs at concentrations in drinking-water well below those at which toxic effects can be expected to be observed. Under usual conditions, therefore, the presence of 2-phenylphenol in drinking-water is unlikely to represent a hazard to human health. For this reason, the establishment of a numerical guideline value for 2-phenylphenol is not deemed necessary.

7. REFERENCES

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