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English only

Parathion 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 Parathion 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
CAS	Chemical Abstracts Service
FAO	Food and Agriculture Organization of the United Nations
JMPR	Joint FAO/WHO Meeting on Pesticide Residues
LC_{50}	median lethal concentration
LD_{50}	median lethal dose
NOAEL	no-observed-adverse-effect level
USA	United States of America
WHO	World Health Organization

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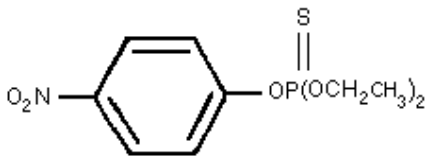
1. GENERAL DESCRIPTION

1.1 Identity

CAS No.:	56-38-2
Molecular formula:	$C_{10}H_{14}NO_5PS$

The chemical name of parathion is *O,O*-diethyl-*O*-(4-nitrophenyl) phosphorothioate. Its chemical structure is shown below:



1.2 Physicochemical properties (WHO, 1992)

Property	*Value*
Boiling point	157–162 °C at 80 Pa
Vapour pressure	5.0 mPa at 20 °C
Water solubility	24 mg/litre at 25 °C; 77 mg/litre at 40 °C
Hydrolysis in aqueous solution	1% in 62 days at pH 5.0–6.0 (25 °C)
Log octanol–water partition coefficient	3.15

1.3 Major uses

Parathion is a non-systemic insecticide that controls numerous insects by contact and stomach action. It is used in many countries throughout the world. It has some fumigant as well as acaricidal activity. Parathion is used as a pre-harvest soil and foliage treatment on a wide variety of crops, both outdoors and in greenhouses. The usual application rate is 0.2–1 kg/ha. Parathion is non-phytotoxic, except to some sensitive ornamentals, apples and pears (WHO, 1992).

1.4 Environmental fate

Parathion released to the environment will adsorb strongly to the top layer of soil and is not likely to leach significantly. Parathion disappears from surface waters in about a week (Health Canada, 1991).

Parathion is degraded quite rapidly in the environment, mainly by hydrolysis, but to a certain extent also by reduction of the nitro group as well as conversion to the oxon. The half-life of the oxon is much shorter than that of parathion itself, and the oxon does not accumulate. The other degradation products are *p*-nitrophenol, *p*-aminophenol, diethyl thiophosphoric acid and diethyl phosphoric acid (WHO, 1992).

2. ANALYTICAL METHODS

Parathion in water may be determined by extracting into dichloromethane, drying the extract, redissolving in hexane and analysing by gas–liquid chromatography, phosphorus mode. The detection limit is 0.1 µg/litre (Health Canada, 1991).

3. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

3.1 Water

Parathion was not detected in surveys of municipal and private drinking-water supplies conducted in Canada between 1971 and 1986 (Health Canada, 1991).

3.2 Food

Analysis of fruit and vegetables entering commerce in Germany showed that only 14 out of 228 samples contained measurable amounts of parathion (more than 0.01 mg/kg). In most of these cases, the residue was less than 0.1 mg/kg, but two samples of lettuce contained residue levels of 0.15 and 1.5 mg/kg, respectively. One sample of parsley contained 0.4 mg of parathion per kg (WHO, 1992). Detectable concentrations of parathion and its oxygen analogue were found in only 50 of 6391 domestic food samples in the USA; in 86% of the samples, levels were 0.5 mg/kg or less (Hundley et al., 1988).

Total diet studies in the USA in 1965–1966 showed that only very low residues (0–0.001 mg/kg) were present in vegetables and fruits, as consumed (WHO, 1992). Market basket surveys in the USA in 1980–1982 indicated that the actual average daily intake was 0.166 µg (Gartrell et al., 1986).

3.3 Estimated total exposure and relative contribution of drinking-water

The general population is not usually exposed to parathion from air or water, parathion residues in food being the main source of exposure (WHO, 1992).

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

Parathion is readily absorbed from the respiratory and digestive tracts and is excreted primarily in the urine. Two hypotheses have been proposed for its metabolism; however, the metabolic spectrum is the same in both. Parathion is metabolized to paraoxon and diethyl phosphorothioic acid. Paraoxon is further metabolized; following its oral administration to rats, diethyl phosphate, diethyl phosphorothioate, de-ethyl paraoxon and *p*-nitrophenol were identified in the urine. In cattle, ruminal microorganisms are believed to be responsible for the production of aminoparathion and aminoparaoxon.

[1] This section is taken from FAO/WHO (1996).

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

Parathion is extremely hazardous when given orally (LD_{50} = 2 mg/kg of body weight) or by inhalation (4-h LC_{50} = 0.03 mg/litre) and moderately hazardous when given dermally (LD_{50} = 73 mg/kg of body weight). The compound has been characterized in studies in laboratory animals as a mild dermal and ocular irritant and as a non-sensitizing agent. When it was administered with other organophosphate pesticides, its toxic effects were not potentiated. WHO has classified parathion as "extremely hazardous."

In a 3-week study in rabbits treated dermally, the NOAEL was 0.1 mg/kg of body weight per day on the basis of depression of plasma, erythrocyte and brain cholinesterase activities at 2 mg/kg of body weight per day. In a 3-week study by inhalation in rats, the NOAEL was 0.9 mg/litre on the basis of decreases in brain, plasma and erythrocyte cholinesterase activity. In a 14-day study in dogs, parathion was administered orally at doses of 0, 1.5, 3 or 6 mg/kg of body weight per day. There was no NOAEL, as clinical cholinergic signs were observed at the lowest dose tested. Cholinesterase activity was not monitored in this study. In a 90-day study in dogs at doses of 0, 0.3, 1 or 3 mg/kg of body weight per day, the NOAEL was 3 mg/kg of body weight per day. Cholinesterase activity was not measured.

In a 29-day study in mice at doses of 0, 100, 200 or 400 mg/kg (equivalent to 15, 30 and 60 mg/kg of body weight per day), clinical signs of toxicity were reported in all groups. Cholinesterase activity was not determined, and there was no NOAEL. In a 90-day study in mice at dietary concentrations of 0, 15, 50 or 100 mg/kg, the NOAEL was 50 mg/kg (equivalent to 7.5 mg/kg of body weight per day) on the basis of decreased body weights of males. Cholinesterase activity was not monitored. When parathion was administered to rats for 90 days at dietary concentrations of 0, 2.5, 25 or 75 mg/kg, the NOAEL was 2.5 mg/kg (equal to 0.2 mg/kg of body weight per day), on the basis of depression of brain acetylcholinesterase.

In a 2-year study in rats, parathion was not associated with carcinogenicity when administered at dietary concentrations of 0, 0.5, 5 or 50 mg/kg. The NOAEL for systemic toxicity was 5 mg/kg (equivalent to 0.25 mg/kg of body weight per day) on the basis of decreased brain, plasma and erythrocyte cholinesterase activity, retinal atrophy and increased severity of degenerative changes in the sciatic nerve. In another study in rats given dietary levels of 0, 2, 8 or 32 mg/kg for 2 years, there was again no evidence of carcinogenicity. The NOAEL for systemic toxicity was 8 mg/kg (equivalent to 0.4 mg/kg of body weight per day) on the basis of decreases in brain acetylcholinesterase activity and retinal atrophy. No effects on sciatic nerves were reported at the highest dose tested.

[2] This section is taken from FAO/WHO (1996).

In mice receiving dietary concentrations of parathion at 0, 60, 100 or 140 mg/kg for 18 months, there was no NOAEL, as cholinergic signs were seen at all doses.

Two studies of developmental toxicity were conducted in rats. In the first study, parathion was administered by gavage at doses of 0, 0.25, 1 or 1.5 mg/kg of body weight on gestation days 6–19. The NOAEL for maternal toxicity was 1 mg/kg of body weight per day on the basis of increased mortality, and the NOAEL for developmental toxicity was 1.5 mg/kg of body weight per day. In the second study, parathion was administered by gavage at doses of 0, 0.1, 0.3 or 1 mg/kg of body weight per day on gestation days 6–15. The NOAEL for developmental toxicity was 1 mg/kg of body weight per day and that for maternal toxicity was 0.3 mg/kg of body weight per day on the basis of increased mortality and clinical signs of toxicity.

Two studies of developmental toxicity were conducted in rabbits. In the first study, parathion was administered by gavage on gestation days 7–19 at 1, 4 or 16 mg/kg of body weight per day. The NOAEL for developmental toxicity was 16 mg/kg of body weight per day, and the NOAEL for maternal toxicity was 4 mg/kg of body weight per day on the basis of decreased body weight gain. In the second study, parathion was administered by gavage on days 6–18 of gestation at 0, 0.03, 0.1 or 0.3 mg/kg of body weight per day. The NOAEL for both maternal and developmental toxicity was 0.3 mg/kg of body weight per day.

In a two-generation study of reproductive toxicity in rats, doses of 0, 0.5, 5 or 25 mg/kg were administered in the diet. Dams at the highest dose had tremors, and a reduction in body weight was seen during pre-mating, gestation and lactation. The NOAEL for reproductive toxicity was 25 mg/kg (equivalent to 1.2 mg/kg of body weight per day); the NOAEL for maternal toxicity was 5 mg/kg (equivalent to 0.25 mg/kg of body weight per day) on the basis of the observation of tremors in F_0 and F_1 females. In the second study, parathion was administered at dietary concentrations of 0, 1, 10 or 20 mg/kg. The NOAEL for reproductive toxicity was 20 mg/kg (equivalent to 1 mg/kg of body weight per day); the NOAEL for perinatal toxicity was 10 mg/kg (equivalent to 1 mg/kg of body weight per day) on the basis of reduced body weights; and the NOAEL for maternal toxicity was 1 mg/kg (equivalent to 0.05 mg/kg of body weight per day) on the basis of decreased brain acetylcholinesterase activity.

Special studies were conducted to assess the ocular toxicity of parathion. When parathion was administered to dogs at doses of 0, 0.002, 0.008 or 0.8 mg/kg of body weight per day for 6 months, no functional impairment of the eye was observed. The NOAEL was 0.008 mg/kg of body weight per day on the basis of depression of brain and retinal acetylcholinesterase activity. In a 3-month study of toxicity in female rats, parathion was administered at levels of 0, 0.04, 0.4 or 4 mg/kg of body weight per day. The NOAEL was 0.4 mg/kg of body weight per day on the basis of depression of brain acetylcholinesterase activity. No significant effects on ocular toxicity were reported at any dose.

Parathion was not associated with organophosphorus-induced delayed neurotoxicity in hens, but it induced demyelination in the peripheral nerves of rats at a dietary level

of 50 mg/kg (equivalent to 2.5 mg/kg of body weight per day). The NOAEL was 0.25 mg/kg of body weight per day.

Parathion has been adequately tested for genotoxicity in a range of tests *in vitro* and *in vivo*. JMPR concluded that parathion is not genotoxic.

6. EFFECTS ON HUMANS[3]

In a study conducted in humans, a NOAEL of 7.5 mg/day (0.1 mg/kg of body weight per day) was determined on the basis of lack of effect on erythrocyte acetylcholinesterase.

7. CONCLUSIONS

An ADI of 0.004 mg/kg of body weight was established on the basis of a NOAEL of 0.4 mg/kg of body weight per day in the 2-year study in rats for retinal atrophy and inhibition of brain acetylcholinesterase at the higher dose. A safety factor of 100 was used. Lower NOAELs in animals, based only on inhibition of erythrocyte or brain acetylcholinesterase, were not considered relevant because of the availability of a NOAEL for erythrocyte acetylcholinesterase inhibition in humans, which was 0.1 mg/kg of body weight per day.

A health-based value of 10 µg/litre (rounded figure) can be derived based on an allocation of 10% of the ADI of 0.004 mg/kg of body weight to drinking-water. As the health-based value is much higher than parathion concentrations likely to be found in drinking-water, the presence of parathion in drinking-water under usual conditions is unlikely to represent a hazard to human health. For this reason, the establishment of a numerical guideline value for parathion is not deemed necessary.

8. REFERENCES

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WHO (1992) *Parathion*. Geneva, World Health Organization (Health and Safety Guide No. 74).

[3] This section is taken from FAO/WHO (1996).