

Fenitrothion in Drinking-water

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

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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

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

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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:

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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
a.i.	active ingredient
CAS	Chemical Abstracts Service
FAO	Food and Agriculture Organization of the United Nations
IUPAC	International Union of Pure and Applied Chemistry
JMPR	Joint FAO/WHO Meeting on Pesticide Residues
LC ₅₀	median lethal concentration
LD ₅₀	median lethal dose
LOAEC	lowest-observed-adverse-effect concentration
NOAEC	no-observed-adverse-effect concentration
NOAEL	no-observed-adverse-effect level
WHO	World Health Organization

Table of contents

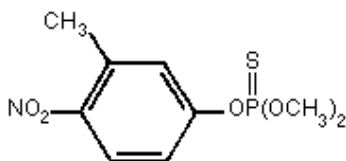
1. GENERAL DESCRIPTION	1
1.1 Identity	1
1.2 Physicochemical properties	1
1.3 Major uses	1
1.4 Environmental fate.....	1
2. ANALYTICAL METHODS	2
3. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE.....	2
3.1 Air	2
3.2 Water.....	2
3.3 Food	2
4. KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS	2
5. EFFECTS ON EXPERIMENTAL ANIMALS AND <i>IN VITRO</i> TEST SYSTEMS.	3
6. EFFECTS ON HUMANS.....	5
7. CONCLUSIONS.....	6
8. REFERENCES	6

1. GENERAL DESCRIPTION

1.1 Identity

CAS No.:	122-14-5
Molecular formula:	C ₉ H ₁₂ NO ₅ PS

The IUPAC chemical name of fenitrothion is *O,O*-dimethyl *O*-(4-nitro-*m*-tolyl) phosphorothioate. Its chemical structure is shown below:



1.2 Physicochemical properties (IPCS, 1992)

Property	Value
Melting point	0.3 °C
Boiling point	140–145 °C (decomposes)
Vapour pressure	18 mPa at 20 °C
Log <i>n</i> -octanol/water partition coefficient	3.16
Solubility in water	14 mg/litre at 30 °C

1.3 Major uses

Fenitrothion is mainly used in agriculture for controlling chewing and sucking insects on rice, cereals, fruits, vegetables, stored grains and cotton and in forest areas. It is also used for the control of flies, mosquitos and cockroaches in public health programmes and/or indoor use (IPCS, 1992).

1.4 Environmental fate

Fenitrothion enters the air through volatilization from contaminated surfaces and may drift beyond the intended target area during spraying. It leaches very slowly from most soils, but some runoff can occur (IPCS, 1992).

Fenitrothion is degraded by photolysis and hydrolysis. In the presence of ultraviolet radiation or sunlight, the half-life of fenitrothion in water is less than 24 h. The presence of microflora may also accelerate degradation. Thus, fenitrothion is stable in water only in the absence of sunlight or microbial contamination. In soil, biodegradation is the primary route of degradation, although photolysis may also play a role (IPCS, 1992).

FENITROTHION IN DRINKING-WATER

2. ANALYTICAL METHODS

The common procedure for determining residues in foods and environmental media consists of extraction, partition, chromatographic separation (cleanup) and qualitative and quantitative analysis using gas chromatography with a flame photometric or a nitrogen-specific detector or using high-pressure liquid chromatography. The detection limit is 0.001 mg/litre (IPCS, 1992).

3. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

3.1 Air

Pesticide residue surveys were conducted in relation to the 1980 and 1981 spruce budworm spray programmes (210 g a.i./ha applied twice with a 3-day interval) in New Brunswick, Canada. Fenitrothion was detected occasionally in the air, the maximum level being 1.2 µg/m³ in 1980. In 1981, fenitrothion was detected only twice in the air at levels of 0.08 and 0.04 µg/m³ (IPCS, 1992).

3.2 Water

In the 1981 spruce budworm spray programme in Canada, the concentrations of fenitrothion residues detected in water were low (maximum 1.30 µg/litre), and post-spray samples did not contain detectable concentrations (<0.01 µg/litre) (Mallett & Cassista, 1984).

3.3 Food

Levels of fenitrothion residues in fruits, vegetables and cereal grains may range from 0.001 to 9.5 mg/kg immediately after treatment, but decline rapidly with a half-life of 1–2 days (IPCS, 1992).

4. KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS¹

After oral administration, fenitrothion is rapidly and extensively absorbed from the mammalian intestinal tract (about 90–100% of the dose) and eliminated, predominantly in the urine (up to about 93% of the dose) and faeces (6–15% of the dose), within 24 h. After dermal application, approximately 45% of an applied dose was absorbed within 24 h. Fenitrothion is rapidly metabolized by mixed-function oxidases to the highly reactive fenitrooxon by oxidative desulfuration. The oxon is then further metabolized by demethylation and hydrolysis to 3-methyl-4-nitrophenol and dimethylphosphate. A minor metabolic pathway involves further oxidation to 3-carboxyl-4-nitrophenol. After low oral doses, the urinary metabolites consisted mainly of conjugated phenolic compounds, such as the sulfate and glucuronide of 3-methyl-4-nitrophenol; at higher doses, demethylated compounds such as desmethyl

¹ This section has been taken from FAO/WHO (2001).

FENITROTHION IN DRINKING-WATER

fenitrothion and desmethyl fenitrooxon were excreted in increasing amounts. The tissue concentrations of residues of [¹⁴C]fenitrothion were very low (generally <1 mg/kg) within 48 h of dosing.

In volunteers, the time to maximal concentration in plasma after oral ingestion, 12 h apart, of two capsules containing fenitrothion at 0.09 or 0.18 mg/kg of body weight for 4 days was 1 h, and the elimination half-time ranged from 2 to 3 h, irrespective of dose. The integrated area under the curve of concentration–time and the maximum concentration, however, increased with frequency of dosing. The maximal concentration in plasma 1 day after a single dose of 0.09 mg/kg of body weight was 0.54 ng/ml, whereas on day 4 it was 0.84 ng/ml. At the higher dose, the maximal concentration increased from 1.8 ng/ml on day 1 to 7.7 ng/ml on day 4. In a man who attempted to commit suicide by ingesting a fenitrothion formulation, the elimination half-time of fenitrothion was 4.5 h.

5. EFFECTS ON EXPERIMENTAL ANIMALS AND IN VITRO TEST SYSTEMS²

The lowest oral LD₅₀ was 240 mg/kg of body weight (range 240–1700 mg/kg of body weight) in rats and 780 mg/kg of body weight (range 780–1400 mg/kg of body weight) in mice. Male rats were generally more sensitive than females to the acute effects of fenitrothion, and the vehicle used had a marked effect on the observed toxicity. The signs of acute intoxication with fenitrothion were consistent with cholinesterase inhibition. The lowest acute dermal LD₅₀ was 890 mg/kg of body weight (range 890–5000 mg/kg of body weight) in rats. The lowest acute LC₅₀ in rats after whole-body exposure to a fenitrothion aerosol was 2.2 mg/litre. Technical-grade fenitrothion with a purity above 95% was not irritating to the eye or skin of rabbits and did not sensitize the skin of guinea-pigs (Buehler test). WHO (1999) has classified fenitrothion as “moderately hazardous.”

In short-term studies of toxicity lasting less than 12 months, the NOAEL for inhibition of erythrocyte acetylcholinesterase activity was 0.6 mg/kg of body weight per day in rats, <3 mg/kg of body weight per day in rabbits and 0.3 mg/kg of body weight per day in dogs. The NOAEL for inhibition of brain cholinesterase activity was 2.5 mg/kg of body weight per day in rats, 3 mg/kg of body weight per day in rabbits and >1.6 mg/kg of body weight per day in dogs. The signs of toxicity in rats and rabbits were generally limited to cholinergic signs and decreased body weights and/or food consumption. The NOAEL for these effects in short-term studies was 4.8 mg/kg of body weight per day in rats and >10 mg/kg of body weight per day in rabbits. When fenitrothion was applied to the skin of rabbits for 21 days, the NOAEL for inhibition of cholinesterase activity in erythrocytes and brain was 3 mg/kg of body weight per day. No NOAEC was identified for inhibition of brain cholinesterase in rats exposed to an aerosol of fenitrothion for 90 days. The LOAEC was 0.2 µg/litre per day.

² This section has been taken from FAO/WHO (2001).

FENITROTHION IN DRINKING-WATER

In long-term studies of toxicity, inhibition of cholinesterase activity was again the main toxicological finding in all species. In mice, erythrocyte and brain cholinesterase activities were inhibited at 13 mg/kg of body weight per day, with a NOAEL of 1.5 mg/kg of body weight per day. Reductions in body weight gain and food consumption were reported only at the highest dietary concentration of 1000 mg/kg (equal to 130 mg/kg of body weight per day). Other treatment-related findings in mice were an elevated cholesterol concentration, with a NOAEL of 10 mg/kg (equal to 1.5 mg/kg of body weight per day), and a reduced glucose concentration, with a NOAEL of 100 mg/kg (equal to 13 mg/kg of body weight per day).

Technical-grade fenitrothion was administered to Sprague-Dawley rats in the diet at a concentration of 0, 10, 30 or 100 mg/kg, equal to 0, 0.5, 1.5 or 5 mg/kg of body weight per day for males and 0, 0.6, 1.9 or 6.5 mg/kg of body weight per day for females, for 104 weeks. There were no treatment-related deaths or clinical signs at any time during the study at doses up to 6.5 mg/kg of body weight per day in rats. The NOAEL was 0.5 mg/kg of body weight per day for inhibition of erythrocyte and brain cholinesterase activities; the NOAEL for a reduction in body weight gain was 1.9 mg/kg of body weight per day. Treatment did not increase the incidence of neoplastic lesions in long-term studies in mice and rats.

On the basis of testing in an adequate range of studies *in vitro* and *in vivo*, the Meeting concluded that fenitrothion is unlikely to be genotoxic. It also concluded that fenitrothion is unlikely to pose a carcinogenic risk to humans.

In multigeneration studies of reproductive toxicity in rats, the treatment-related effects of fenitrothion were cholinergic signs at high doses and reductions in food consumption and body weight gain. These effects were consistent with those seen in short- and long-term studies of toxicity. Pups had reduced body weight, viability and lactation indices. The NOAEL for reduced food consumption and body weight gain in dams was 0.65 mg/kg of body weight per day. The NOAEL for toxicity in offspring was 3.1 mg/kg of body weight per day, the effects being seen at maternally toxic doses.

In studies of developmental toxicity in rats and rabbits, the maternal effects were cholinergic signs and reduced body weight gain (NOAEL = 8 mg/kg of body weight per day in rats and 10 mg/kg of body weight per day in rabbits). No fetal toxicity was observed at the highest dose tested (NOAEL = 25 mg/kg of body weight per day in rats and 30 mg/kg of body weight per day in rabbits); there was no evidence of treatment-induced malformations in any of the studies.

In studies of delayed neurotoxicity, fenitrothion was given to chickens as a single acutely toxic dose. There was no evidence that it caused delayed neurotoxicity, and the incidence of histopathological lesions in the nerve tissues of birds treated once at 500 mg/kg of body weight was not increased. In rats given single doses of fenitrothion of up to 200 mg/kg of body weight by gavage or as repeated doses of up to 18 mg/kg of body weight per day in the diet for 13 weeks, there were no treatment-related neurological lesions or effects on cognition and no inhibition of neuropathy

target esterase activity, although cholinergic signs and significant inhibition of erythrocyte and brain cholinesterase activity were seen at a number of doses. In these studies, which included a functional observational battery of tests, clinical signs of intoxication were observed. However, cholinergic signs were observed only when brain cholinesterase activity was inhibited by more than 58% or when erythrocyte acetylcholinesterase activity was inhibited by more than 38%.

Fenitrothion did not induce immunotoxicity in a series of immunological tests.

Although a published report on ocular effects indicated that a single oral dose of 14 mg/kg of body weight administered to male rats caused significant electroretinographic changes after 2 days, this could not be confirmed in rats given either a single dose of up to 400 mg/kg of body weight by gavage or repeated daily doses of 2.0 mg/kg of body weight in the diet for 13 weeks. In this latter study, the NOAEL for inhibition of brain and erythrocyte acetylcholinesterase activity was 10 mg/kg, equal to 0.57 mg/kg of body weight.

6. EFFECTS ON HUMANS³

When fenitrothion was given to 24 volunteers as a single oral dose of 0.042–0.33 mg/kg of body weight, there were no cholinergic signs, and erythrocyte acetylcholinesterase activity was not significantly inhibited. However, one person given 0.33 mg/kg of body weight showed a reduction of 28% in plasma cholinesterase activity. With repeated doses of 0.04–0.08 mg/kg of body weight per day for 4 days, the cholinesterase activities in erythrocytes and plasma were unchanged. In another study, fenitrothion given to 2–4 volunteers as a divided daily oral dose of 0.18 or 0.36 mg/kg of body weight per day for 4 days did not induce cholinergic signs or changes in cholinesterase activity in erythrocytes or plasma.

In a retrospective hospital-based study of 16 cases of poisoning with fenitrothion requiring extensive, aggressive antidotal therapy, 7 of 10 survivors had symptoms consistent with “intermediate syndrome” — namely, delayed onset (24–96 h) of muscular weakness affecting the muscles of the neck, proximal limb and respiratory system. No plasma cholinesterase activity was detectable at the time of admission of the patients, and the recovery time ranged from 5 to more than 10 weeks.

JMPR concluded that the existing database was adequate to characterize the potential hazard of fenitrothion to fetuses, infants and children. Although fenitrothion is known to be neurotoxic to adults, JMPR did not recommend that a study of developmental neurotoxicity be conducted, since there was no evidence of increased neurotoxicity in offspring exposed pre- or postnatally, when compared with adults in the same experiment.

³ This section has been taken from FAO/WHO (2001).

FENITROTHION IN DRINKING-WATER

7. CONCLUSIONS

JMPR affirmed the ADI of 0.005 mg/kg of body weight that was established by JMPR in 1988 (FAO/WHO, 1989), which was based on a NOAEL of 0.5 mg/kg of body weight per day for inhibition of brain and erythrocyte cholinesterase activity in a 2-year study of toxicity in rats and application of an uncertainty factor of 100. This was supported by a NOAEL of 0.57 mg/kg of body weight per day for inhibition of brain and erythrocyte cholinesterase activity in a 3-month study of ocular toxicity in rats and a NOAEL of 0.65 mg/kg of body weight per day for reduced food consumption and body weight gain in a study of reproductive toxicity in rats. The 4-day study in volunteers was not considered suitable for establishing an ADI because of its short duration and the associated absence of steady-state kinetics.

Intake of fenitrothion from all sources is generally low and well below the ADI. About 95% of the intake appears to be from food. A health-based value of 8 µg/litre can be calculated for fenitrothion, allocating 5% of the ADI of 5 µg/kg of body weight to drinking-water. However, as fenitrothion usually occurs in drinking-water at concentrations well below those at which toxic effects may be expected to occur, it is not considered necessary to derive a guideline value for fenitrothion in drinking-water.

8. REFERENCES

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