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Pendimethalin 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.

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GENERAL DESCRIPTION

Identity

CAS no.: 40487-42-1
Molecular formula: $C_{13}H_{19}N_3O_4$
Pendimethalin is the common name for *N*-(1-ethylpropyl)-2,6-dinitro-3,4-xylidine.

Physicochemical properties (1)

Property	*Value*
Physical state	Orange-yellow crystals
Melting point	54–58 °C
Vapour pressure	4.0×10^{-3} Pa at 25 °C
Water solubility	0.3 mg/litre at 20 °C
Log octanol–water partition coefficient	5.2

Major uses

Pendimethalin is a selective herbicide, applied before emergence to cereals, maize, and rice, and with shallow soil incorporation before seeding bean, cotton, soy beans, and groundnuts. In vegetable crops, it is applied before emergence or transplanting, and it is also used to control suckers on tobacco (*1*).

Environmental fate

Pendimethalin is stable under both alkaline and acidic conditions (*1*). It is a moderately persistent herbicide that can give rise to long-lasting metabolites, mainly by photodegradation (*2*). Three by-products of soil fungal degradation have been identified as the result of ring hydroxylation, nitro group reduction, and complete *N*-dealkylation (*3*). Both pendimethalin and its metabolites bind tightly to soil particles, and the leaching potential is negligible (*2*). A half-life in soil of 30–90 days has been estimated (*1*). Pendimethalin has a low affinity for the water compartment. However, under anaerobic conditions, more polar metabolites of greater mobility are formed, and these can potentially contaminate both groundwater and surface waters (*2*).

ANALYTICAL METHODS

Pendimethalin can be determined by capillary gas chromatography with a selective nitrogen–phosphorus detector following extraction with methylene chloride. Confirmation by a second capillary column of different polarity is recommended.

ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

Water

Pendimethalin was found at a concentration below 0.1 µg/litre in one of 76 drinking-water supplies examined in the Veneto Region in Italy in 1987–88 (*4*).

KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS

Pendimethalin appears to be both poorly absorbed and rapidly excreted. About 95% is excreted within 24 h after oral administration, 75% being found in the faeces and 20% in the urine. Maximum tissue concentrations were found in the liver and kidney. Although most parent compound is excreted unchanged, the metabolites identified suggest that oxidation of

the 4-methyl group on the phenyl moiety and the *N*-alkyl side chain of the dinitro-substituted aniline are the predominant metabolic pathways (*5*).

EFFECTS ON LABORATORY ANIMALS AND *IN VITRO* TEST SYSTEMS

Acute exposure

Pendimethalin is of low acute toxicity. LD_{50}s of 1050–1250 mg/kg of body weight in albino rats, 1340–1620 mg/kg of body weight in albino mice, and over 5000 mg/kg of body weight in beagle dogs have been reported (*1*).

Short-term exposure

In a study in which Charles River CD rats received pendimethalin in the diet at concentrations of 0, 100, 500, or 5000 mg/kg for 13 consecutive weeks, food intake and body weight gain were decreased only at 5000 mg/kg. A variety of indications of hepatotoxicity were also observed at this dose level. Absolute and relative kidney weights increased in males at 5000 mg/kg, and absolute and relative uterus and ovary weights decreased in females at 500 mg/kg (*6*).

Long-term exposure

CD-1 mice (75 per sex per dose) were given a diet containing the technical-grade compound at 0, 100, 500, or 2500 mg/kg for 18 months (dose doubled after 8 weeks) (*7*), and Long-Evans rats (60 per sex per dose) were fed a diet containing 0, 100, 500, or 2500 mg/kg for 2 years (highest dose doubled after 6 weeks) (*8*). At the highest doses, general toxic effects were observed both in the mouse (hyperglycaemia and increased thyroid and adrenal gland weights) and in the rat (increase in alkaline phosphatase levels, increased thyroid and kidney weights, hepatomegaly). Some toxic effects (hyperglycaemia in the mouse and hepatotoxicity in the rat) were present even at the lowest dose level of 100 mg/kg of diet (equivalent to 5 mg/kg of body weight per day). It was therefore not possible to establish a NOAEL.

Reproductive toxicity, embryotoxicity, and teratogenicity

Teratogenicity was not observed at the highest dose tested in rats (1000 mg/kg of body weight per day) (*9,10*) or rabbits (60 mg/kg of body weight per day) (*11*). In rats gavaged with pendimethalin on days 6–15 of gestation, embryotoxicity in the form of minor anomalies and reduced fetal weight was observed at 1000 mg/kg of body weight (*9*), and reduced ossification of the extremities was present at 250 and 500 mg/kg of body weight (*10*). Reproductive toxicity was not observed in a three-generation reproduction study in Long-Evans rats given pendimethalin in the diet at levels as high as 1000 mg/kg (*12*).

Mutagenicity and related end-points

Although genetic mutations were induced by pendimethalin with metabolic activation in *Salmonella typhimurium*, higher-purity technical material did not induce mutations in the same test system. Pendimethalin did not induce chromosomal aberrations, unscheduled DNA synthesis, or dominant lethal mutations (*13–17*).

Carcinogenicity

Neither CD-1 mice fed doses of pendimethalin up to 2500 mg/kg for 18 months (*7*) nor rats fed diets containing pendimethalin at up to 2500 mg/kg for 2 years showed evidence of carcinogenicity (*8*). However, these studies had important methodological limitations, including limited numbers of animals subjected to histological examinations.

GUIDELINE VALUE

Pendimethalin does not appear to have significant mutagenic activity. Long-term studies in mice and rats have not provided evidence of carcinogenicity; however, these studies have some important limitations.

The guideline value is based upon the LOAEL for liver toxicity (5 mg/kg of body weight per day) observed in the 2-year rat study (*8*). An uncertainty factor of 1000 (100 for intra- and interspecies variation and 10 for the use of a LOAEL instead of a NOAEL and for the limitations of the database) is used, giving a TDI of 5 µg/kg of body weight per day. An allocation of 10% of the TDI to drinking-water results in a guideline value of 20 µg/litre (rounded figure).

REFERENCES

1. Worthing CR, ed. *The pesticide manual*, 9th ed. Farnham, British Crop Protection Council, 1991.
2. *Drinking-water quality for selected herbicides*. Copenhagen, WHO Regional Office for Europe, 1987 (Environmental Health 27).
3. Barua AS et al. Degradation of pendimethalin by soil fungi. *Pesticide science*, 1990, 29:419-425.
4. Funari E, Sampaolo A. Erbicidi nelle acque potabili. [Herbicides in drinking-water.] *Annali dell'Istituto Superiore di Sanità*, 1989, 25:353-362.
5. American Cyanamid Co. *Toxicology report AX86-1, Doc. 13.* Wayne, NJ, 1986 (confidential information submitted to the Italian Ministry of Health).
6. American Cyanamid Co. *Toxicology report AX86-1 experiment L-2190. AC 92,553: A 13 week rat feeding study*. Wayne, NJ, 1986 (confidential information submitted to the Italian Ministry of Health).
7. Biodynamics Inc. *Report on project no. 72R-747*. Wayne, NJ, American Cyanamid, 1974 (confidential information submitted to the Italian Ministry of Health).
8. Biodynamics Inc. *Report on project no. 72R-746.* Wayne, NJ, American Cyanamid, 1974 (confidential information submitted to the Italian Ministry of Health).
9. American Cyanamid Co. *Report of December 12, 1972.* Wayne, NJ (confidential information submitted to the Italian Ministry of Health).
10. American Cyanamid Co. *Teratology study in rats.* Wayne, NJ, 1979 (confidential information submitted to the Italian Ministry of Health).
11. American Cyanamid Co. *Teratology study in rabbits. AC 92,553. Technical. Hazleton 362-164*. Wayne, NJ, 1986 (confidential information submitted to the Italian Ministry of Health).
12. Biodynamics Inc. *3 generation reproduction study in AC 92,553 in rats. Project 72R-748.* Wayne, NJ, American Cyanamid, 1974 (confidential information submitted to the Italian Ministry of Health).
13. American Cyanamid Co. *Project No. 0166.* Wayne, NJ, 1985 (confidential information submitted to the Italian Ministry of Health).
14. American Cyanamid Co. *Project No. S-0329.* Wayne, NJ, 1985 (confidential information submitted to the Italian Ministry of Health).
15. Pharmakon Research International Inc. *Study no. PH 320-AC-001-85*. Wayne, NJ, American Cyanamid, 1985 (confidential information submitted to the Italian Ministry of Health).
16. Pharmakon Research International Inc. *Study no. PH 311-AC-002-85*. Wayne, NJ, American Cyanamid, 1985 (confidential information submitted to the Italian Ministry of Health).
17. American Cyanamid Co. *Report of October 5, 1973.* Wayne, NJ (confidential information submitted to the Italian Ministry of Health).