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Metolachlor 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.: 51218-45-2
Molecular formula: $C_{15}H_{22}ClNO_2$
Metolachlor is the common name for 2-chloro-6'-ethyl-*N*-(2-methoxy-1-methylethyl) acet-*o*-toluidine.

Physicochemical properties (*1*)

Property	*Value*
Physical state	White to tan liquid
Vapour pressure	1.7×10^{-3} Pa at 20 °C
Water solubility	530 mg/litre at 20 °C
Octanol–water partition coefficient	2820

Organoleptic properties

Metolachlor is odourless.

Major uses

Metolachlor is a selective herbicide for pre-emergence and preplant weed control in corn, soy beans, peanuts, sorghum, pod crops, potatoes, cotton, safflower and woody ornamentals (*2*).

Environmental fate

Metolachlor photodegrades slowly in aqueous solution exposed to sunlight (*3*). Its hydrolysis half-life is over 200 days at 20 °C (*1*). Volatilization from silty loam and sand has been observed (*4*). Metolachlor leaching is affected by adsorption onto soil organic matter, soil texture, precipitation, and water application. It can leach beyond the root zone in detectable amounts. The half-life in soil has been reported to range from 47 to 107 days (*5*). It can be metabolized by microorganisms (*6*).

ANALYTICAL METHODS

Metolachlor may be determined by gas chromatographic methods applicable to the determination of certain nitrogen/phosphorus-containing pesticides in water samples. The estimated detection limit ranges from 0.75 to 0.01 µg/litre (*7*).

ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

Water

Metolachlor was found in 2091 of 4161 surface water samples and in 13 of 596 groundwater samples in the USA in 1988 (*8*). The 85th percentile of all non-zero samples was 12 µg/litre in surface water and 0.25µg/litre in groundwater. In another survey in the same country, metolachlor residues from agricultural use were detected in groundwater at levels ranging from 0.1 to 0.4µg/litre. In a survey of 160 water bodies in Italy, metolachlor was found, if at all, at levels of less than 0.1µg/litre (*9*).

KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS

Metolachlor is readily absorbed and excreted in the rat, male rats excreting 21.5% and 51.4% of the dose administered in the urine and faeces, respectively, within 48 h. It is metabolized via dechlorination, *O*-methylation, *N*-dealkylation, and side-chain oxidation. Urinary and faecal metabolites include 2-ethyl-6-methylhydroxyacetanilide and *N*-(2-ethyl-6-methylphenyl)-*N*-(hydroxyacetyl)DL-alanine. No unchanged chemical was isolated (*10*).

EFFECTS ON LABORATORY ANIMALS AND *IN VITRO* TEST SYSTEMS

Acute exposure

Metolachlor has a low oral acute toxicity. Oral LD_{50}s in the rat are over 2000 mg/kg of body weight. The dermal LD_{50} is over 10 000 mg/kg of body weight [Source: Registry of Toxic Effects of Chemical Substances (RTECS) file on line. Bethesda, MD, National Library of Medicine, National Institute for Occupational Safety and Health, 1977].

Short-term exposure

Beagle dogs given metolachlor at dose levels of 0, 50 (switched to 1000 mg/kg after 8 weeks), 150, or 500 mg/kg of diet for up to 15 weeks showed signs of toxicity only at the highest dose level (*11*).
In a 1-year study in beagle dogs, administration of metolachlor resulted in decreased kidney weight at the two highest dose levels. The NOAEL was determined to be 3.5 mg/kg of body weight per day (*12*).

Long-term exposure

In a 2-year study with albino mice fed diets containing metolachlor at levels of 0, 100, 300, or 1000 mg/kg, the only toxicological effects observed were decreased body weight gain and decreased survival in females at the highest dose level (*13*).

Albino Sprague-Dawley CD rats fed metolachlor for 2 years at dose levels of 0, 30, 300, or 3000 mg/kg showed decreased body weight gain and food consumption at the highest dose level (*14*).

Reproductive toxicity, embryotoxicity, and teratogenicity

Metolachlor was not teratogenic in gavage studies at daily dose levels up to and including 60 mg/kg of body weight in rats (*15*) and 360 mg/kg of body weight in rabbits (*16*). In a two-generation reproduction study, it decreased weight gain during lactation in pups at the highest dose level (equivalent to 14.7 mg/kg of body weight per day). The NOAEL in this study was 5 mg/kg of body weight per day (*17*).

Mutagenicity and related end-points

Metolachlor does not induce gene mutations in bacterial or mammalian cells and is negative in the dominant lethal assay and for unscheduled DNA synthesis *in vivo* and *in vitro* in rat hepatocytes and human fibroblasts (*18*).

Carcinogenicity

No evidence of carcinogenicity was found in a long-term dietary feeding study in albino mice at dose levels up to and including 3000 mg/kg (*19*). One study in rats showed an increase in the incidence of hepatocellular neoplasia in females receiving 3000 mg/kg in the diet for 2

years. One adenosarcoma and one fibrosarcoma were found in the nasal tissues of males at the highest dose only. No increase in tumour incidence was found in males or in females exposed to levels less than 3000 mg/kg. The increase in neoplasia in females was primarily due to an increased incidence of neoplastic nodules (*14*).

EFFECTS ON HUMANS

Signs of intoxication by metolachlor include abdominal cramps, anaemia, ataxia, dark urine, methaemoglobinaemia, cyanosis, hypothermia, collapse, convulsions, diarrhoea, jaundice, weakness, nausea, shock, sweating, vomiting, central nervous system depression, dizziness, dyspnoea, liver damage, nephritis, cardiovascular failure, dermatitis, sensitization, eye and mucous membrane irritation, corneal opacity, and reproductive effects [Source: HAZARDLINE. Bethesda, MD, National Library of Medicine, National Institutes of Health, 1985].

GUIDELINE VALUE

There is no evidence from available studies that metolachlor is carcinogenic in mice. In rats, an increase in liver tumours in females and a few nasal tumours in males have been observed. Metolachlor is not genotoxic.

Toxicity data are available from long-term studies in rodents and from a 1-year study in dogs. An apparent decrease in kidney weight was observed at the two highest dose levels in the 1-year dog study, giving a NOAEL of 3.5 mg/kg of body weight per day (*12*). An uncertainty factor of 1000 (100 for inter- and intraspecies variation and 10 because of some concern regarding carcinogenicity) was applied to this NOAEL to give a TDI of 3.5 µg/kg of body weight. A 10% allocation of the TDI to drinking-water results in a guideline value of 10µg/litre (rounded figure).

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