

Alachlor 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.: 15972-60-8

Molecular formula: $C_{14}H_{20}ClNO_2$

Alachlor is the common name for 2-chloro-*N*-(2,6-diethylphenyl)-*N*-methoxymethylacetamide.

Physicochemical properties (1,2)

<i>Property</i>	<i>Value</i>
Physical state	White crystalline solid at 23 °C
Water solubility	242 mg/litre at 25 °C
Vapour pressure	2.9×10^{-3} Pa at 25 °C
Log octanol–water partition coefficient	2.6–3.1

Organoleptic properties

Taste and odour thresholds in water of 33 and 110 mg/litre, respectively, have been reported (1).

Major uses

Alachlor is used pre- or early post-emergence to control annual grasses and many broad-leaved weeds mainly in maize, but also in cotton, brassicas, oilseed rape, peanuts, radish, soy beans, and sugar-cane (2).

Environmental fate

Alachlor dissipates from soil mainly through volatilization, photodegradation, and biodegradation (3–5). Many metabolites have been identified; diethylaniline, detected in some soil studies, interacts rapidly with humic substances in the soil (3). A half-life in soil of 7–38 days has been reported (6). Under certain conditions, alachlor can leach beyond the root zone and migrate to groundwater (1,3).

ANALYTICAL METHODS

Water samples are extracted with chloroform, and alachlor determined in the extracts by gas–liquid chromatography with electrolytic conductivity detection in the nitrogen mode or by capillary column gas chromatography with a nitrogen–phosphorus detector (7). The detection limit is about 0.1 µg/litre.

ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

Water

Alachlor was detected in the surface water and groundwater of 10 states of the USA between 1979 and 1987 (3). In two recent surveys in the USA, alachlor was detected in one of 750 and in 38 of 1430 private wells sampled (A.J. Klein, Monsanto Agricultural Company, personal communication). A review of monitoring data showed that alachlor was present in groundwaters in the USA at levels ranging from less than 0.1 to 16.6 µg/litre (8). In Italy, in a

survey carried out in 1987–88, alachlor was detected in three out of 322 drinking-water supplies at a maximum level of 1.6 µg/litre (9).

Food

Food does not appear to be a major route of exposure for the general population since residues of alachlor in food are usually below the detection limit. It is rapidly metabolized by crops after application and does not bioaccumulate (1). In tolerant plants, it is detoxified by rapid conjugation with glutathione (10).

KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS

Alachlor is absorbed through the gastrointestinal tract of rats and distributed to the blood, spleen, liver, kidney, heart, and, to a lesser extent, eyes, brain, stomach, and ovaries (11). Rats, mice, and monkeys differ in the ways in which they metabolize, distribute, and excrete it (12–14). 4-Amino-3,5-diethylphenol, which is suspected to be a key metabolite from the point of view of the carcinogenicity of alachlor, has been found in much larger quantities in the urine of rats than in that of mice and monkeys. Alachlor and its metabolites in urine and faeces are excreted much slowly in rats than in mice and monkeys. Mice excrete alachlor metabolites mainly via the faeces, rats in equal proportions in the urine and faeces, and monkeys mainly via urine (15,16).

EFFECTS ON LABORATORY ANIMALS AND *IN VITRO* TEST SYSTEMS

Acute exposure

Acute oral LD₅₀s of 930–1350 and 1100 mg/kg of body weight for rats and mice, respectively, have been reported (2).

Short-term exposure

In a 6-month feeding study, dogs were given alachlor at 0, 5, 25, 50, or 75 mg/kg of body weight per day; dose-related hepatotoxicity was seen at all dose levels (17). In a subsequent 1-year feeding study in which dogs were given alachlor at 1, 3, or 10 mg/kg of body weight per day, the NOAEL was 1 mg/kg of body weight per day (18).

Long-term exposure

A 2-year feeding study in Long-Evans rats showed alachlor to be toxic at all doses tested (14, 42, or 126 mg/kg of body weight per day). Effects observed included dose-related hepatotoxicity at all dose levels and highly significant levels of ocular lesions, identified as the uveal degeneration syndrome, in the mid- and high-dose groups (19). In another 2-year feeding study in which the same strain of rats was given alachlor at 0, 0.5, 2.5, or 15 mg/kg of body weight per day, 2.5 mg/kg of body weight per day dose was considered to be the NOAEL for uveal degeneration syndrome (20).

Reproductive toxicity, embryotoxicity, and teratogenicity

In a three-generation study, 10 male and 20 female CD rats were fed a diet containing 0, 3, 10, or 30 mg of alachlor per kg. No effects were observed on the reproductive cycle or on postnatal development (21). After female CD rats were treated by gastric intubation with 0, 50, 150, or 400 mg of technical alachlor per kg of body weight per day from days 6 to 19 of gestation, no signs of embryotoxicity were observed at any of the doses tested (22).

Female Dutch Belted rabbits were exposed to alachlor by gavage on days 7–19 of gestation at 0, 10, 30, or 60 mg/kg of body weight per day. No signs of maternal toxicity or embryotoxicity were observed at these doses (23).

Mutagenicity and related end-points

Alachlor does not induce gene mutations in bacteria and in mammalian cells *in vitro* (24), but does induce chromosomal aberrations in mammalian cells *in vitro* (25) and is weakly active in a gene conversion test in yeast (26) and in an *in vitro/in vivo* test of DNA repair in rat hepatocytes (27). Samples of varying purity gave contrasting results for chromosomal aberrations in *in vivo* tests in the rat (26,28). A broad spectrum of genetic damage was observed in plant systems (29,30). There are positive mutagenicity data for 2,6-diethylaniline, which is a known metabolite of alachlor in animals.

Carcinogenicity

Doses of 0, 14, 42, or 126 mg/kg were administered in the diet to Long-Evans rats (50 of each sex) for 2 years. This study provided clear evidence of carcinogenicity based on a statistically significant increase in the incidence of adenomas of the nasal turbinate, malignant stomach tumours, and thyroid follicular tumours in high-dose males. This conclusion is also based on the incidence of adenocarcinomas of the nasal turbinate in mid-dose males and females and the observation of submucosal hyperplasia in nasal tissues, and was supported by a repeated study of the highest dose only (126 mg/kg), in which adenomas and adenocarcinomas of the nasal cavity and malignant stomach tumours were found (31).

A second study on the same rat strain using doses of 0, 0.5, 2.5, and 15 mg/kg for 2 years also provided clear evidence of carcinogenicity. A statistically significant increase in the incidence of adenomas of the nasal turbinate was observed at the highest dose. Submucosal gland hyperplasia of the nasal turbinate was also noted. The presence of stabilizers in the technical material is unlikely to have influenced the carcinogenic response observed in the rat (20).

CD-1 mice were fed technical-grade alachlor in the diet for 18 months at doses of 0, 26, 78, or 260 mg/kg of body weight per day. Statistically significant increases in lung bronchiolar tumours at the highest dose tested were seen in female mice (32). The increase of lung tumours in male mice was not significant at any dose. In the United States, the Environmental Protection Agency has concluded that this study provides inadequate evidence of carcinogenicity (A.J. Klein, Monsanto Agricultural Company, personal communication).

EFFECTS ON HUMANS

The probable oral lethal dose in humans is 0.5–5 g/kg of body weight [Source: Toxicology Data Bank, Bethesda, MD, National Library of Medicine].

GUIDELINE VALUE

IARC has not evaluated alachlor. On the basis of available experimental data, evidence for the genotoxicity of alachlor is considered to be equivocal. However, a metabolite of alachlor has been shown to be mutagenic. Available data from two studies in rats clearly indicate that this compound is carcinogenic, causing benign and malignant tumours of the nasal turbinate, malignant stomach tumours, and benign thyroid tumours.

In view of the data on carcinogenicity, guideline values were calculated by applying the linearized multistage model to data on the incidence of nasal tumours in rats (20). Concentrations of 200, 20, and 2 µg/litre in drinking-water are associated with excess lifetime cancer risks of 10^{-4} , 10^{-5} , and 10^{-6} , respectively.

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