

2,4-D 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

The first draft of 2,4-D 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:

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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 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
BEH	butoxyethylhexyl
CAS	Chemical Abstracts Service
CCME	Canadian Council of Ministers of the Environment
2,4-D	2,4-dichlorophenoxyacetic acid
DEA	diethanolamine
DMA	dimethylamine
EH	2-ethylhexyl
EPA	Environmental Protection Agency (USA)
FAO	Food and Agriculture Organization of the United Nations
IPA	isopropylamine
JMPR	Joint FAO/WHO Meeting on Pesticide Residues
LD ₅₀	median lethal dose
NOAEL	no-observed-adverse-effect level
TIPA	triisopropanolamine
USA	United States of America
WHO	World Health Organization

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1. GENERAL DESCRIPTION

The term 2,4-D is used here to refer to the free acid, 2,4-dichlorophenoxyacetic acid. 2,4-D is a strong acid and forms water-soluble salts with alkali metals and amines. Commercial 2,4-D products are marketed as the free acid, alkali and amine salts and ester formulations. 2,4-D itself is chemically stable, but its esters are rapidly hydrolysed to the free acid (CCME, 1995).

1.1 Identity

CAS No.:	94-75-7
Molecular formula:	C ₈ H ₆ Cl ₂ O ₃

1.2 Physicochemical properties (Tomlin, 1994)

<i>Property</i>	<i>Value</i>
Water solubility	311 mg/litre (pH 1, 25 °C)
Vapour pressure	1.1 × 10 ⁻² Pa (20 °C)
Log octanol–water partition coefficient	2.58–2.83 (pH 1)

1.3 Organoleptic properties

The taste and odour threshold of 2,4-D is 3.13 mg/litre (US EPA, 1987). However, the taste threshold in water of 2,4-dichlorophenol, 2,4-D's main degradation product, is 0.3 µg/litre; as a result, public water supplies containing "traces" of 2,4-D are often shut down because of objectionable odours or tastes (IPCS, 1984).

1.4 Major uses

2,4-D is a systemic herbicide used for post-emergence control of annual and perennial broad-leaved weeds in cereal cropland, on lawns, turf and pastures, in forests and in non-cropland (including areas adjacent to water). It is also used to control broad-leaved aquatic weeds. Impurities may be present in the technical product as a result of the manufacturing process (Health Canada, 1993).

1.5 Environmental fate

2,4-D can enter the environment through effluents and spills arising from its manufacture and transport and through direct application as a weed control agent. It is removed from the environment principally by biodegradation through several possible pathways, with the formation of 2,4-dichlorophenol as an intermediate. 2,4-D is removed from the atmosphere by photo-oxidation and rainfall, with a half-life of less than 1 day. The half-life of 2,4-D in soil is reported to range from 4–7 days in most soil types to up to 6 weeks in acidic soils. 2,4-D is rapidly biodegraded in water, although some may be degraded by photolysis near the surface. Half-lives in water range from 1 to several weeks under aerobic conditions and can exceed 120 days under anaerobic conditions. 2,4-D is not expected to accumulate in bottom sediments

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and mud. Except for some algae, it does not bioaccumulate in aquatic or terrestrial organisms because of its rapid degradation (Health Canada, 1993).

2. ANALYTICAL METHODS

Residues of 2,4-D and its salts and esters in water are commonly measured by extraction, chemical derivatization, separation by gas-liquid chromatography and electron capture detection. This method is suitable for the detection of picogram levels. Electrolytic conductivity detection is also used; its detection limit is 0.1 µg/litre (Health Canada, 1993).

3. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

3.1 Air

Atmospheric contamination by 2,4-D may occur as a result of volatilization and drift from application by spraying. Residues in the atmosphere are predominantly in the form of isopropyl and butyl esters. In large-scale studies in areas of intense 2,4-D use in Canada, about 40% of all air samples were found to contain between 0.01 and 0.1 µg of 2,4-D per m³. In a general programme of air quality monitoring undertaken in citrus-growing regions in the USA, only 1 out of 880 samples analysed was found to contain 2,4-D, at a level of 4 µg/m³ (IPCS, 1984).

3.2 Water

2,4-D was detected, at a maximum concentration of 29 µg/litre, in 52 of 805 samples of raw and treated drinking-water from municipal and private water supplies in surveys conducted in six Canadian provinces from 1971 to 1986 (Health Canada, 1993). Surface water samples taken between 1983 and 1984 in Manitoba, Canada, indicated the presence of 2,4-D at concentrations ranging from 0.01 to 0.13 µg/litre (CCME, 1995). In the USA, reported levels of 2,4-D in drinking-water supplies have been below 0.5 µg/litre, with most levels below 0.1 µg/litre (US EPA, 1987). Generally, 2,4-D residues in surface waters are <0.1 µg/litre. This is not unexpected, in view of the relatively rapid biodegradation of 2,4-D in the environment (IPCS, 1984).

3.3 Food

2,4-D and its esters and degradation products do not tend to accumulate in food. Available evidence indicates that residues of 2,4-D rarely exceed a few tens of µg/kg in food. Exceptions may occur in liver and kidney from range animals; in berries and mushrooms grown in treated right-of-way areas; or when the herbicide is used in quantities far in excess of the rates applied in normal agricultural practice. High residues of 2,4-D can produce disagreeable odours or flavours in fruits and vegetables, and this may reduce the likelihood that highly contaminated foods are ingested (IPCS, 1984).

3.4 Estimated total exposure and relative contribution of drinking-water

The available data are insufficient to determine whether food or water is the greater source of exposure to 2,4-D.

4. KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS¹

2,4-D was rapidly absorbed, distributed and excreted after oral administration to mice, rats and goats. At least 86–94% of an oral dose was absorbed from the gastrointestinal tract in rats. Once absorbed, 2,4-D was widely distributed throughout the body but did not accumulate because of its rapid clearance from the plasma and rapid urinary excretion. 2,4-D was excreted rapidly and almost exclusively (85–94%) in urine by 48 h after treatment, primarily as unchanged 2,4-D. No metabolites have been reported other than conjugates. Pharmacokinetic studies with salts and esters of 2,4-D have shown that the salts dissociate and esters are rapidly hydrolysed to 2,4-D, after which their fate was indistinguishable from that of the acid. The similarity in the fate of 2,4-D and its salts and esters explains their similar toxicity.

In humans who ingested 2,4-D, it was quickly absorbed and excreted rapidly in the urine; about 73% of the administered dose was found in the urine after 48 h. No metabolites were detected.

After dermal applications of 2,4-D to volunteers, ≤5.8% of the dose was absorbed within 120 h. When the acid and its dimethylamine (DMA) salt were applied, about 4.5% of the acid and 1.8% of the salt were absorbed; of this, about 85% of the acid and 77% of the salt were recovered in the urine 96 h after application.

5. EFFECTS ON EXPERIMENTAL ANIMALS AND IN VITRO TEST SYSTEMS²

2,4-D, its amine salts and its esters are slightly toxic when administered orally or dermally, the oral LD₅₀ values being 400–2000 mg/kg of body weight and the dermal LD₅₀ value generally exceeding 2000 mg/kg of body weight. In rats exposed to 2,4-D at the maximum attainable concentration (up to 5.39 mg/litre) by inhalation for 4 h, no deaths were seen. While 2,4-D and its amine salts and esters do not induce dermal irritation in rabbits or dermal sensitization in guinea-pigs, they cause severe eye irritation in rabbits. WHO (1996) has classified 2,4-D as “moderately hazardous.”

In mice fed diets that provided 2,4-D at doses of 0, 5, 15, 45 or 90 mg/kg of body weight per day for 3 months, renal lesions were observed in animals of both sexes at all doses. A NOAEL was not identified.

¹ This section has been taken from FAO/WHO (1997).

² This section has been taken from FAO/WHO (1997).

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In mice fed diets providing 2,4-D at doses of 0, 1, 15, 100 or 300 mg/kg of body weight per day for 90 days, treatment-related changes were observed in animals of both sexes at doses of ≥ 100 mg/kg of body weight per day. These effects included decreases in glucose level in females, decreases in thyroxine activity in males and increases in absolute and/or relative kidney weights in males. The NOAEL was 15 mg/kg of body weight per day.

In rats fed diets providing 2,4-D at doses of 0, 1, 5, 15 or 45 mg/kg of body weight per day for 90 days, renal lesions were observed at doses of ≥ 5 mg/kg of body weight per day. The NOAEL was 1 mg/kg of body weight per day.

In rats fed diets providing 2,4-D at doses of 0, 1, 15, 100 or 300 mg/kg of body weight per day for 90 days, treatment-related changes were observed in animals of both sexes at doses of ≥ 100 mg/kg of body weight per day. These effects included decreases in body weight gain, haematological and clinical chemical alterations, changes in organ weights and histopathological lesions in the adrenals, liver and kidneys. The NOAEL was 15 mg/kg of body weight per day.

In six studies of toxicity, in which rats were fed diets containing the diethanolamine (DEA), DMA, isopropylamine (IPA) or triisopropanolamine (TIPA) salts or the butoxyethylhexyl (BEH) or 2-ethylhexyl (EH) esters at acid-equivalent doses of 0, 1, 15, 100 or 300 mg/kg of body weight per day for 13 weeks, the results demonstrated the comparable toxicity of the acid, salts and esters. The NOAEL was 15 mg of acid-equivalent per kg of body weight per day for all six compounds.

Dogs were given gelatin capsules containing 2,4-D at 0, 0.03, 1, 3 or 10 mg/kg of body weight per day or diets containing 2,4-D, the DMA salt or the EH ester at acid-equivalent doses of 0, 0.5, 1, 3.75 or 7.5 mg/kg of body weight per day for 13 weeks. Treatment-related findings were observed in the three studies at doses of ≥ 3.0 mg/kg of body weight per day. The NOAEL was 1.0 mg of acid-equivalent per kg of body weight per day in all three studies.

In a 2-year study of toxicity and carcinogenicity, mice were fed diets providing 2,4-D at doses of 1, 15 or 45 mg/kg of body weight per day. Increases in absolute and/or relative kidney weights and renal lesions were observed at 15 and 45 mg/kg of body weight per day. There was no evidence of carcinogenicity. The NOAEL was 1 mg/kg of body weight per day.

In another 2-year study of toxicity and carcinogenicity, mice were fed diets providing 2,4-D at doses of 0, 5, 62.5 or 125 mg/kg of body weight per day (males) or 0, 5, 150 or 300 mg/kg of body weight per day (females). Dose-related increases in absolute and/or relative kidney weights and renal lesions were seen in animals of both sexes at doses of ≥ 62.5 mg/kg of body weight per day. There was no evidence of carcinogenicity. The NOAEL was 5 mg/kg of body weight per day.

In another 2-year study, rats received diets providing 2,4-D at doses of 0, 1, 5, 15 or 45 mg/kg of body weight per day. Renal lesions were seen in animals of both sexes at

doses of ≥ 5 mg/kg of body weight per day. There was no evidence of carcinogenicity. The NOAEL was 1 mg/kg of body weight per day.

In a further 2-year study, rats were fed diets providing 2,4-D at doses of 0, 5, 75 or 150 mg/kg of body weight per day. Treatment-related effects were observed in animals of both sexes at doses of ≥ 75 mg/kg of body weight per day. The effects included decreases in body weight gains and food consumption, increases in serum alanine and aspartate aminotransferase activities, decreased thyroxine concentrations, increases in absolute and relative thyroid weights and histopathological lesions in the eyes, kidneys, liver, lungs and mesenteric fat. There was no evidence of carcinogenicity. The NOAEL was 75 mg/kg of body weight per day in males and 5 mg/kg of body weight per day in females.

Dogs were fed diets providing 2,4-D at doses of 0, 1, 5 or 7.5 mg/kg of body weight per day for 52 weeks. At 5 and 7.5 mg/kg of body weight per day, body weight gains were decreased, increases were seen in blood urea nitrogen, creatinine, alanine aminotransferase activity and cholesterol, and histopathological lesions were seen in the kidneys and liver. The NOAEL was 1 mg/kg of body weight per day.

In a two-generation study of reproductive toxicity, rats received dietary doses of 2,4-D of 0, 5, 20 or 80 mg/kg of body weight per day. Reduced body weights of F₁ dams and renal lesions in F₀ and F₁ adults were observed at 20 and 80 mg/kg of body weight per day. The NOAEL for parental and reproductive toxicity was 5 mg/kg of body weight per day.

In order to evaluate the dermal toxicity of 2,4-D and its salts and esters, rabbits received 15 dermal applications of the acid, the DEA, DMA, IPA or TIPA salt, or the BEH or EH ester at acid-equivalent doses of 0, 10, 100 or 1000 mg/kg of body weight per day for 6 h per day on 5 days per week for 21 days. No systemic toxicity was seen at any dose, and no dermal toxicity was seen with the acid, the TIPA salt or the BEH ester. Dermal lesions were observed in rabbits treated with the DEA, DMA or IPA salt or the EH ester at doses of ≥ 100 mg/kg of body weight per day. The lesions were characterized as acanthosis, hyperkeratosis, oedema, inflammation and epidermal hyperplasia. The NOAEL was 10 mg of acid-equivalent per kg of body weight per day for dermal toxicity and 1000 mg of acid-equivalent per kg of body weight per day (the highest dose tested) for systemic toxicity.

In a study of developmental toxicity, pregnant Sprague-Dawley rats were given 2,4-D in corn oil by gavage at doses of 12.5, 25, 50, 75 or 88 mg/kg of body weight per day during days 6–15 of gestation. There was no maternal toxicity. Fetotoxicity was manifested as decreased fetal body weights at doses of ≥ 50 mg/kg of body weight per day. The NOAELs were 88 mg/kg of body weight per day for maternal toxicity and 25 mg/kg of body weight per day for developmental toxicity.

In a further study, pregnant Fischer-344 rats received 2,4-D in corn oil by gavage at doses of 8, 25 or 75 mg/kg of body weight per day during days 6–15 of gestation. Decreased body weight gain of dams at the high dose during the treatment period and

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increased incidences of skeletal variations (7th cervical and 14th rudimentary ribs and missing sternbrae) were observed at 75 mg/kg of body weight per day. The NOAEL was 25 mg/kg of body weight per day for both maternal and developmental toxicity.

The developmental toxicity of the DEA, DMA, IPA and TIPA salts and the BEH and EH esters was evaluated in pregnant rats after oral administration during days 6–15 of gestation. The acid-equivalent doses tested were 11, 55 or 110 mg/kg of body weight per day for DEA; 12.5, 50 or 100 mg/kg of body weight per day for the DMA salt; 9, 25 or 74 mg/kg of body weight per day for the IPA salt; 12, 37 or 120 mg/kg of body weight per day for the TIPA salt; 17, 50 or 120 mg/kg of body weight per day for the BEH ester; and 10, 30 or 90 mg/kg of body weight per day for the EH ester. The maternal and developmental toxicities of the salts and esters of 2,4-D were comparable to those of the acid. Maternal toxicity, as evidenced by reduced body weight gain during treatment, was seen in all dams at the high dose of each compound; in addition, mortality, clinical signs and reduced food consumption were seen in dams given 120 mg of TIPA salt per kg of body weight per day. Although embryo- and fetotoxicity and teratogenicity were observed with the high dose of the TIPA salt, this may be attributed to maternal toxicity; none of the other compounds had such effects. No external gross or visceral anomalies (malformations or variations) were observed in any of the fetuses, but skeletal variations were seen at the high dose of each compound except the IPA salt; these skeletal variations were similar to those seen in the fetuses of dams given the acid. The overall NOAELs were approximately 10 mg of acid-equivalent per kg of body weight per day for maternal toxicity and 50 mg of acid-equivalent per kg of body weight per day for developmental toxicity.

In a study of developmental toxicity, pregnant rabbits were given 2,4-D orally at 0, 10, 30 or 90 mg/kg of body weight per day during days 6–18 of gestation. Maternal toxicity, which included clinical signs, abortions and reduced body weight gain during and after the treatment period, was seen only at the high dose. No gross, visceral or skeletal malformations or variations were seen in fetuses at any dose. The NOAELs were 30 mg/kg of body weight per day for maternal toxicity and 90 mg/kg of body weight per day (the highest dose tested) for developmental toxicity.

The developmental toxicity of the DEA, DMA, IPA and TIPA salts and the BEH and EH esters was evaluated in rabbits after oral administration during days 6–18 of gestation. The acid-equivalent doses tested were 10, 30 or 60 mg/kg of body weight per day for the DEA salt; 10, 30 or 90 mg/kg of body weight per day for the DMA salt; 10, 30 or 75 mg/kg of body weight per day for the IPA salt; and 10, 30 or 75 mg/kg of body weight per day for the TIPA salt and for the BEH and EH esters. Unlike 2,4-D, which produced maternal toxicity only at the high dose, most of the amine salts and esters were maternally toxic at the middle and high doses, as evidenced by mortality, clinical signs of neurotoxicity, abortions and decreases in body weight gain. No gross, visceral or skeletal malformations or variations were seen in fetuses at any dose. The overall NOAELs were approximately 10 mg of acid-equivalent per kg of body weight per day for maternal toxicity and 90 mg of acid-

equivalent per kg of body weight per day (the highest dose tested) for developmental toxicity.

In summary, of the four salts tested for developmental toxicity, only the TIPA salt had developmental toxicity in rats and only at a maternally toxic dose; no developmental toxicity was seen in rabbits with this or the other salts. Consequently, the Meeting concluded that the developmental toxicity of the TIPA salt is of little concern.

The genotoxic potential of 2,4-D has been adequately evaluated in a range of assays *in vivo* and *in vitro*. Overall, the responses observed indicate that 2,4-D is not genotoxic, although conflicting results were obtained for mutation in *Drosophila*. In a more limited range of assays, the DEA, DMA, IPA and TIPA salts and the BEH and EH esters were also not genotoxic *in vivo* or *in vitro*. The Meeting concluded that 2,4-D and its salts and esters are not genotoxic.

In rats given single doses of 2,4-D at 0, 15, 75 or 250 mg/kg of body weight by gavage, there were no treatment-related gross or neuropathological changes at any dose. Animals of both sexes at the highest dose exhibited incoordination and gait abnormalities on day 1, but the signs had disappeared by day 5. The NOAEL was 75 mg/kg of body weight. When rats were fed diets containing 2,4-D at doses of 0, 5, 75 or 150 mg/kg of body weight per day for 12 months, neurotoxicity, manifested as increased relative forelimb grip strength, was seen in animals of both sexes at 150 mg/kg of body weight per day. The NOAEL was 75 mg/kg of body weight per day.

6. EFFECTS ON HUMANS³

Epidemiological studies have suggested an association between the development of soft-tissue sarcoma and non-Hodgkin lymphoma and exposure to chlorophenoxy herbicides, including 2,4-D. The results of these studies are not, however, consistent; the associations found are weak, and conflicting conclusions have been reached by the investigators. Most of the studies did not provide information on exposure specifically to 2,4-D, and the risk was related to the general category of phenoxyacetic acid herbicides, a group that includes 2,4,5-T, which can be contaminated with dioxins. Case-control studies provide little evidence of an association between the use of 2,4-D and soft-tissue sarcoma. Although some case-control studies have shown a relationship with non-Hodgkin lymphoma, others (even the positive studies) have produced inconsistent results, raising doubt about the causality of the relationship. Cohort studies of exposed workers have not confirmed the hypothesis that 2,4-D causes either neoplasm.

The JMPR Meeting was informed of the ongoing “Agricultural Health Study” initiated in North Carolina and Iowa, USA, and of a study of pesticide applicators in Finland. The Agricultural Health Study addresses both cancer and non-cancer risks in men and women directly exposed to pesticides and other agricultural agents, including

³ This section has been taken from FAO/WHO (1997).

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neurotoxicity, reproductive effects, immunological effects, kidney disease, non-malignant respiratory disease and the growth and development of their children.

7. GUIDELINE VALUE

JMPR concluded that it was not possible to evaluate the carcinogenic potential of 2,4-D on the basis of the available epidemiological studies (FAO/WHO, 1997). The JMPR Meeting concluded that the toxicity of the salts and esters of 2,4-D was comparable to that of the acid. An ADI was therefore established for the sum of 2,4-D and its salts and esters, expressed as 2,4-D. An ADI of 0.01 mg/kg of body weight was established on the basis of the NOAEL of 1 mg/kg of body weight per day in the 1-year study of toxicity in dogs and the 2-year study in rats, using an uncertainty factor of 100.

The resulting guideline value of 30 µg/litre (using the ADI of 0.01 mg/kg of body weight and assuming a 60-kg body weight, drinking-water consumption of 2 litres/day and a 10% allocation to drinking-water) remains the same as in the second edition, but is based on the most recent toxicological evaluation conducted by JMPR. This guideline value applies to 2,4-D, as salts and esters of 2,4-D are rapidly hydrolysed to the free acid in water.

8. REFERENCES

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