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Chlorophenoxy herbicides (excluding 2,4-D and MCPA) 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

Although many chlorophenoxy compounds are used in weed control, only dichlorprop, 2,4-DB, 2,4,5-T, fenoprop, mecoprop, and MCPB will be considered here

Compound	*CAS no.*	*Molecular formula*	*Other names*
Dichlorprop	120-36-5	$C_9H_8Cl_2O_3$	2,4-dichlorophenoxypropionic acid; 2,4-DP
2,4-DB	94-82-6	$C_{10}H_{10}Cl_2O_3$	4-(2,4-dichlorophenoxy) butyric acid
2,4,5-T	93-76-5	$C_8H_5Cl_3O_3$	2,4,5-trichlorophenoxyacetic acid
Fenoprop	93-72-1	$C_9H_7Cl_3O_3$	2,4,5-trichlorophenoxypropionic acid; 2,4,5-TP; silvex
Mecoprop	93-65-2; 7085-19-0 (racemic mixture)	$C_{10}H_{11}ClO_3$	2(2-methyl-4-chlorophenoxy)propionic acid; MCPP
MCPB	94-81-5	$C_{11}H_{13}ClO_3$	4(2-methyl-4-chlorophenoxy)butyric acid

Physicochemical properties (1)

Compound	*Melting-point (°C)*	*Water solubility (mg/litre)*	*Vapour pressure*
Dichlorprop	116–118	350 at 20 °C	Negligible
2,4-DB	117–119	46 at 25 °C	Negligible
2,4,5-T	153	150 at 25 °C	1×10^{-5} Pa at 25 °C
Fenoprop	179–181.6	140 at 25 °C	Practically nonvolatile
Mecoprop	94–95	620 at 20 °C	$<1 \times 10^{-5}$ Pa at 20 °C
MCPB	100	44 at 20 °C	$<1 \times 10^{-5}$ Pa at 20°C

Major uses

Chlorophenoxy herbicides are used extensively throughout the world for the control of broad-leaved annual and perennial weeds in a variety of agricultural crops. They are also used in brush control in non-agricultural areas, to control broad-leaved aquatic weeds, and as a pre-harvest treatment to reduce early drop in apple orchards. Chlorophenoxy herbicides are usually applied post-emergence, often in combination with other herbicides.

Chlorophenoxy compounds are derived from chlorophenols, which may be contaminated by dioxins; the herbicide preparations, especially those containing the trichlorophenoxy acids, may therefore also be contaminated by dioxins.

Environmental fate

Residues of chlorophenoxy herbicides in the environment are the consequence of the direct application of these compounds to agricultural and non-agricultural areas. Biodegradation is the primary route of elimination from the environment; photolysis and hydrolysis also contribute to their removal.

The half-life for the degradation of dichlorprop to 2,4-dichlorophenol in soil is estimated to be 8–12 days (2–4); disappearance is essentially complete in 14 days (5). The degradation half-life of 2,4,5-T in soil is 12–59 days (2,4); residues do not usually persist beyond one growing season (3). Reported half-lives of fenoprop are in the range 8–17 days (2,3,6) to 3–4 months (7). The primary degradation product of 2,4,5-T and fenoprop is 2,4,5-trichlorophenol (1,8). Mecoprop is broken down in soil to 4-chloro-4-methylphenol (1), with a half-life of 7–9 days (9); residues of mecoprop have been reported to persist in soil for up to 2 months following application (10). The half-life of MCPB in soil is 4–6 days (3,9), unless the soil microorganisms have been acclimatized to the herbicide, in which case its

half-life is less than 1 day (3). MCPB degrades in soil to MCPA (9) and 4-chloro-2-methylphenol (1). The half-life of 2,4-DB in soil is less than 7 days (1).

The chlorophenoxy herbicides are considered to have only marginal potential for leaching to groundwater (11). In basic waters, phenoxy herbicide esters are hydrolysed to the anionic forms; in acidic waters, photodegradation or vaporization predominates, depending on the ester. The photolytic half-life of 2,4,5-T in near-surface waters has been calculated to be 15 days (12). Fenoprop was essentially cleared from three Louisiana ponds within 5 weeks of treatment (13).

ANALYTICAL METHODS

Common methods for the determination of chlorophenoxy herbicides in water include solvent extraction, separation by gas chromatography, gas–liquid chromatography, thin-layer chromatography, or high-performance liquid chromatography, with electron capture or ultraviolet detection. Detection limits range from 1 µg/litre to 1 mg/litre (8,14). Specific ion monitoring mass spectroscopy can be used for confirmation (8). Chemical derivatization of chlorophenoxy acids and salts is often necessary, as they are practically nonvolatile and too polar to chromatograph directly (15).

ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

Air

Chlorophenoxy herbicides may be transported in the atmosphere in the form of droplets, vapour, or powder following application by spraying. Concentrations of particulate 2,4,5-T of up to approximately 0.045 µg/m^3 in air have been found in Pullman, Washington, whereas up to 0.04 mg of 2,4,5-T per kg was present in a dust sample collected in Cincinnati, OH (16).

Water

Mecoprop was not detected in a survey of 91 farm wells in Ontario (Canada) during 1984 (detection limit 0.1 µg/litre) (17). 2,4,5-T was not detected in 602 samples of private and municipal drinking-water supplies in 90 communities in three Canadian provinces surveyed from 1978 to 1986 (detection limits 0.005–0.05 µg/litre) (18). Fenoprop was detected in only a small number of drinking-water supplies in several national and regional surveys in the USA (detection limits not specified) (7).

In 1984, 2,4,5-T was detected in groundwater near a dump in New Brunswick (Canada) at a concentration of 3.7 µg/litre (18). In other studies, 2,4,5-T concentrations as high as 17 µg/litre have been reported in groundwater (19). Groundwater in the Netherlands was found to contain a maximum concentration of 2 µg of mecoprop per litre (20). Most groundwaters surveyed in the USA contained less than 0.1 µg of fenoprop per litre (7).

In a survey of three Canadian agricultural river basins, dichlorprop, mecoprop, 2,4-DB, and MCPB were found in 4%, 3%, 0.5%, and 0%, respectively, of 447 surface water samples at mean concentrations of 0.1–3.1 µg/litre (detection limits 0.1–0.5 µg/litre) (21). Concentrations of 2,4,5-T in 1548 samples of Canadian surface waters surveyed from 1980 to 1985 ranged from not detectable to 0.04 µg/litre (detection limit 0.01 µg/litre); concentrations of fenoprop in 1339 surface water samples from western Canada were less than 4 ng/litre (22). Surface water in the Netherlands has been found to contain maximum mecoprop and MCPB concentrations of 1–10 µg/litre; a maximum concentration of 0.1 µg of mecoprop/litre was found in infiltrated river bank water (20).

Food

Chlorophenoxy herbicides may be present in food as a result of their direct application to crops; however, concentrations are normally low (16). In a Canadian total diet study conducted from 1976 to 1978, MCPB, 2,4,5-T, and fenoprop were not detected (detection limits 300, 100, and 50 µg/kg,

respectively) (23). Neither 2,4,5-T nor 2,4-DB was detected in a survey of 14 492 domestic and imported foods in the USA in 1987 (24). Dichlorprop was present at levels of up to 0.1 mg/kg in cereal grains at harvest time (25).

Estimated total exposure and relative contribution of drinking-water

Based on maximum residue limits for 2,4,5-T established by the Codex Alimentarius Commission (26), the theoretical maximum daily intake of 2,4,5-T from food ranges from 10.8 to 68.8 µg/day, with a global mean of 24.6 µg/day for a 60-kg adult. The average daily intake of 2,4,5-T in food is estimated to be 0.2 ng/kg of body weight per day for a male or female aged 25□30, based on the concentrations found in foods in the USA (27).

KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS

In general, chlorophenoxy herbicides are rapidly absorbed from the gastrointestinal tract (28) and evenly distributed throughout the body; accumulation in human tissues is not expected (6). A steady-state level in the human body will be achieved within 3–5 days of exposure (6). The herbicides are eliminated mainly in the urine, mostly unchanged, although fenoprop may be conjugated to a significant extent (29). Biological half-lives of chlorophenoxy herbicides in mammals range from 10 to 33 h; between 75% and 95% of the ingested amount is excreted within 96 h (28). Dogs appear to retain chlorophenoxy acids longer than other species as a result of relatively poor urinary clearance and thus may be more susceptible to their toxic effects (29). Metabolic conversions occur only at high doses. The salt and ester forms are rapidly hydrolysed and follow the same pharmacokinetic pathways as the free acids (28).

EFFECTS ON LABORATORY ANIMALS AND IN VITRO TEST SYSTEMS

Dichlorprop

Dichlorprop

Acute exposure

The oral LD_{50}s of dichlorprop in rats and mice are 800 and 309 mg/kg of body weight, respectively (30).

Short-term exposure

Slight liver hypertrophy was seen in rats receiving a dietary dose of 50 mg dichlorprop per kg of body weight per day for 3 months; no adverse effects were noted in rats consuming 12.4 mg/kg of body weight per day (1).

Long-term exposure

In a 2-year study in Fischer 344 rats (80 per sex per dose), animals were fed diets containing 0, 100, 300, 1000, or 3000 mg of dichlorprop per kg. At 3000 mg/kg, survival was slightly reduced in females; body weight was depressed by 10% in both males and females; there was diffuse hepatocellular swelling and deposition of brown pigment in liver cells; and rats exhibited mild anaemia, as indicated by decreased haematocrit, erythrocyte count, and haemoglobin. The incidence of brown pigment in the kidneys was increased in both sexes in the 1000 and 3000 mg/kg groups, possibly indicative of slight degeneration of the tubular epithelium. Urinary specific gravity and protein were decreased in males exposed to 300 mg/kg and in females exposed to 1000 mg/kg. The authors considered the NOAEL for renal toxicity to be 100 mg/kg (3.64 mg/kg of body weight per day) in males and 300 mg/kg (13.1 mg/kg of body weight per day) in females (31).

Reproductive toxicity, embryotoxicity, and teratogenicity

No adverse effects on reproduction or fertility were reported in a three-generation reproduction study in which groups of rats were fed diets containing 125, 500, or 2000 mg of dichlorprop per kg (32). In a

study in which doses of 0, 100, 200, 300, 400, or 500 mg of dichlorprop per kg of body weight were orally administered to pregnant mice on days 6–15 of pregnancy, embryotoxic effects were observed at 300 mg/kg of body weight, and skeletal malformations occurred at 400 mg/kg of body weight (33). No toxic effects were reported in a summary of a study in which pregnant rats were given doses of 0, 5, 30, 100, or 200 mg of dichlorprop per kg of body weight by gavage on days 4, 10, 13, and 18, although it was shown to cross the placental barrier (34).

Mutagenicity and related end-points

Dichlorprop was not mutagenic in eight strains of Salmonella typhimurium in the absence of mammalian metabolic activation (35). However, it induced respiration-defective mutant cells of Saccharomyces cerevisiae (36) and caused mitotic gene conversion and gene mutation in S. cerevisiae (37,38) and DNA damage in Escherichia coli (39) at concentrations of 4.0 mg/ml or greater. Dichlorprop did not significantly influence testicular DNA synthesis in male mice following a single intraperitoneal dose of 200 mg/kg of body weight (40).

Carcinogenicity

In an 18-month oncogenicity study, Charles River CD-1 mice were fed diets containing 0, 25, 100, or 300 mg of dichlorprop per kg. The incidence of benign hepatomas was increased in males in the highest dose group, but the authors speculated that this was due to an increased metabolic burden on the liver, which impaired the metabolic process necessary for the suppression of neoplastic development; they concluded that dichlorprop was not carcinogenic at the doses administered (41).

2,4-DB

Acute exposure

The oral LD_{50} of 2,4-DB in rats is 700 mg/kg of body weight (30).

Short-term exposure

Beagle dogs (4 per sex per dose) were fed diets containing 0, 316, 1000, or 3160 mg of 2,4-DB per kg for 2 weeks, then given the compound in capsules daily for 7 weeks at doses equivalent to 0, 8, 25, or 80 mg/kg of body weight per day. An additional group of 4 males and 4 females were given capsules containing the equivalent of 2.5 mg/kg of body weight per day for 13 weeks. At 25 and 80 mg/kg of body weight per day, effects on animals included diarrhoea, inactivity, depression, weakness, cysts, increased mortality, reduced body weight and food consumption, haematological effects, abnormal blood chemistry and urinalysis, jaundice, increased relative thyroid, liver, spleen, and kidney weights, and decreased relative testes weight. At 8 mg/kg of body weight per day, serum alanine aminotransferase was elevated and nodular lymphoid hyperplasia of the gastric mucosa occurred in one of four males and one of four females (both with gross lesions). The NOAEL was considered to be 2.5 mg/kg of body weight per day (Department of National Health and Welfare, Canada, unpublished data, 1973).

In a study in which groups of Charles River rats were fed diets containing 0, 100, 316, 1000, or 3160 mg of 2,4-DB per kg for 3 months, relative liver and kidney weights were significantly elevated in males in the 3160 mg/kg group and in females in the 1000 and 3160 mg/kg groups; a significant decrease in the relative adrenal weight in females at 3160 mg/kg was also noted. All animals consuming 1000 mg of 2,4-DB per kg and above had hepatocytic hypertrophy, as did one male and one female exposed to 316 mg/kg. The NOAEL for hepatocytic hypertrophy was considered to be 100 mg/kg, equivalent to 5 mg/kg of body weight per day (Department of National Health and Welfare, Canada, unpublished data, 1973).

Long-term exposure

Groups of Charles River Crl:CD (SD)BR rats were fed diets containing 0, 60, 600, or 1800 mg of 2,4-DB per kg (equivalent to doses of 0, 3, 30, or 90 mg/kg of body weight per day) for 2 years. Rats in the highest dose group exhibited adverse effects such as decreased body weight gain, lower spleen and liver weights, higher relative kidney weights, and altered blood chemistry and haematological parameters. Rats consuming 30 mg of 2,4-DB per kg of body weight per day had decreased mean body weight gain, lower mean body weights (females only), altered blood chemistry and haematological parameters (although to a lesser extent than in the highest dose group), and slightly but not significantly lower mean heart weight (males only). The NOAEL was considered to be 3 mg/kg of body weight per day (42).

Reproductive toxicity, embryotoxicity, and teratogenicity

In a two-generation reproduction study in which rats were fed diets containing 0, 60, 300, or 1500 mg of 2,4-DB per kg (equivalent to doses of 0, 3, 15, or 75 mg/kg of body weight per day), effects noted in the highest dose group included reduced ovarian weight, lower mean birth weights, slightly longer gestation periods, fewer total pups per litter at birth, greater numbers of dead pups at birth, and extremely high mortality during the lactation period. No effects on reproduction were reported in the 300 mg/kg group, although offspring had increased mean liver, spleen, and kidney weights and decreased mean thymus, heart, lung, and adrenal weights (43).

In a teratological study in New Zealand white rabbits, groups of pregnant does were given doses of 2.5, 12, or 60 mg of 2,4-DB per kg of body weight per day in capsules on days 5–15 or 5–20 of gestation. In the highest dose group, many rabbits lost weight, three rabbits aborted their litters before day 29, and three others resorbed their litters. No adverse effects were noted in the does in the low or intermediate dose groups. The mean body weight of live fetuses was significantly reduced in the group receiving 12 mg/kg of body weight per day. The researchers concluded that 2,4-DB was not teratogenic in rabbits but had an indirect embryotoxic effect at 12 mg/kg of body weight per day (May and Baker, Ltd., unpublished data, 1974).

In a study in which groups of pregnant Charles River mice were fed diets containing 0, 400, or 2000 mg of 2,4-DB per kg on days 6□15 of gestation, the number of resorption sites per dam was increased in the mice consuming 2000 mg/kg, as were the mean number of dead fetuses per female and the number of females with dead fetuses; the mean number of live fetuses per female was reduced in this group. The NOAEL for fetotoxic effects in this study has been considered to be 400 mg/kg (Department of National Health and Welfare, Canada, unpublished data, 1973), equivalent to 60 mg/kg of body weight per day (44).

Mutagenicity and related end-points

2,4-DB did not induce point mutations in Salmonella typhimurium (35) but was weakly mutagenic in the CHO/HGPRT forward mutation assay (45). It caused a significant increase in chromosomal aberrations in Chinese hamster ovary cells, but only in the absence of metabolic activation (46). No unscheduled DNA synthesis was induced in rat hepatocytes (47).

Carcinogenicity

Tumour incidence was not increased in a 2-year study in which groups of rats were fed 0, 3, 30, or 90 mg of 2,4-DB per kg of body weight per day in the diet (42). Except in the highest dose group, in which survival was significantly reduced, a possible dose–response relationship in the incidence of hepatocellular carcinomas was reported in male mice fed 0, 25, 250, or 750 mg of 2,4-DB per kg of diet (equivalent to doses of 0, 3.75, 37.5, and 112.5 mg/kg of body weight per day) for 78 weeks. Tumour incidence was not increased in females (48).

2,4,5-T

Acute exposure

The oral LD_{50}s for 2,4,5-T range from 100 mg/kg of body weight in the dog to 300 mg/kg of body weight in the rat and 425 mg/kg of body weight in the hamster (30).

Long-term exposure

Sprague-Dawley rats (50 per sex per dose in treated groups, 86 per sex in the control group) were fed 2,4,5-T (practically free from dioxin contamination) at doses equivalent to 0, 3, 10, or 30 mg/kg of body weight per day in the diet for 2 years. Rats of both sexes in the highest dose group had reduced body weight gain, elevated urinary excretion of porphyrins, and hepatocellular swelling and paleness. Animals in the groups receiving 10 and 30 mg/kg of body weight per day had increased relative kidney and liver weights. Dose-related increases in mineralization in the renal pelvis were noted in the kidneys of female rats fed diets containing 10 and 30 mg/kg of body weight per day. The NOAEL for reduced body weight gain, increased liver and kidney weights, and renal toxicity was considered to be 3 mg/kg of body weight per day (49).

Reproductive toxicity, embryotoxicity, and teratogenicity

In a three-generation reproduction study, Sprague-Dawley rats were fed dietary doses of dioxin-free (<0.03 μg/kg) 2,4,5-T equivalent to 0, 3, 10, or 30 mg/kg of body weight per day. Reductions were seen in neonatal survival in the F_2 generation and decreases in fertility in the F_{3b} litter in the group consuming 10 mg/kg of body weight per day; postnatal survival, relative liver weights, and thymus weights were reduced in several litters in the highest dose group. The NOAEL for reproductive effects was 3 mg/kg of body weight per day (50).

Results of various reproductive studies indicate that 2,4,5-T not appreciably contaminated with dioxin caused teratogenic effects (cleft palate and kidney malformations) only in mice at doses above 20 mg/kg of body weight (51,52). Some skeletal anomalies (delayed ossification) were observed in rats exposed to fetotoxic doses in excess of 50 or 100 mg/kg of body weight (53,54). There was no teratogenic response in other studies in rats, rabbits, or monkeys (55).
Mutagenicity and related end-points
The results of several short-term genotoxicity tests on 2,4,5-T have been reviewed by IARC (55,56). Negative results were obtained for several species of bacteria and yeast, but mutagenicity was observed in the yeast Saccharomyces cerevisiae. 2,4,5-T was not mutagenic in several in vivo tests in mammalian cells, including a mouse micronucleus test and dominant lethal tests in mice and rats. Chromosomal aberrations were induced in in vitro tests in bone marrow cells of gerbils but not in spermatogonia of Chinese hamsters. Aneuploidy was not induced in Drosophila or in oocytes of rats treated in vivo.

Carcinogenicity

No compound-related increase in the incidence of tumours was reported in a study in which Sprague-Dawley rats were fed doses equivalent to 0, 3, 10, or 30 mg of 2,4,5-T per kg of body weight per day in the diet for 2 years (51). 2,4,5-T was not carcinogenic when administered orally or subcutaneously in mice (55,57). Although a significant increase in the incidence of total tumours was reported in female C3Hf mice given approximately 12 mg/kg of body weight per day for life (58), the small number of animals employed in the tests and the high incidence of spontaneous tumours in the controls suggest that the evidence for carcinogenicity in animals is inadequate (56).

Fenoprop

Acute exposure

The oral LD_{50} of fenoprop in rats is 650 mg/kg of body weight (30).

Short-term exposure

In a 90-day study in which rats were fed concentrations of 100, 300, 1000, 3000, or 10 000 mg of the sodium salt of fenoprop per kg in the diet, body weight gain was depressed at 300 mg/kg and above and liver weight was increased at 100 mg/kg; animals in all treatment groups, except females in the lowest dose group, had liver and kidney damage (59). In a study in which beagle dogs were fed doses equivalent to 53, 160, or 530 mg of fenoprop per kg of body weight for 89 days, no adverse effects were reported except for a decrease in body weight gain in females in the highest dose group (59).

Long-term exposure

In an 18-month study, rats were fed diets containing a potassium salt of fenoprop at concentrations equivalent to doses of 0, 0.26, 0.8, 2.6, or 7.9 mg/kg of body weight per day. Males in the highest dose group had reduced body weight and increased relative kidney weight. The NOAEL was considered to be 2.6 mg/kg of body weight per day (29). In a similar study in which male and female rats were fed the potassium salt of fenoprop in the diet at concentrations equivalent to 5.3, 16, 53, or 160 mg of fenoprop per kg of diet for 2 years, increased kidney weight was observed in males in the 160 mg/kg group. The authors concluded that the NOAEL was 53 mg/kg, equal to 3.18 mg/kg of body weight per day (59).

In a study in which beagle dogs were fed concentrations of 30, 101, or 300 mg of fenoprop per kg of diet as the potassium salt for 2 years, severe liver pathology was reported in both sexes in the highest dose group after 1 year and in males consuming 101 mg of fenoprop per kg of diet after 2 years. The NOAELs were considered to be 30 mg/kg in male dogs and 101 mg/kg in females, equivalent to 0.75 and 2.5 mg/kg of body weight per day, respectively (59).

In a 2-year study in beagle dogs, animals (4 per sex per dose) were fed diets containing the potassium salt of fenoprop at concentrations equivalent to doses of 0.9, 2.6, and 8.2 (males) or 9.9 (females) mg of fenoprop per kg of body weight per day. Adverse effects on the liver (mild degeneration and necrosis of the hepatocytes and fibroblastic proliferation) were reported in both males and females receiving the highest dose and in males receiving the intermediate dose. Females in the highest dose group had altered serum enzyme levels. The NOAEL was considered to be 0.9 mg/kg of body weight per day for males and 2.6 mg/kg of body weight per day for females (29).

Reproductive toxicity, embryotoxicity, and teratogenicity

A decrease in fetal body weight and an increase in maternal weight (probably due to increased liver weight) were observed when pregnant CD-1 mice were given 400 mg of fenoprop per kg of body weight per day by gavage or subcutaneously on days 12–15 of gestation; toxic effects appeared to be dependent on the vehicle and route of administration (60).

No teratogenic effects were reported in a study in which pregnant rats were given 100, 150, 200, or 300 mg of fenoprop per kg of body weight per day by gavage on days 6–15 of gestation, based on gross examination of the fetuses (Dow Chemical Company, unpublished data, 1970; cited in reference 16). Fenoprop increased the incidence of cleft palate by 7% and 3%, respectively, for oral and subcutaneous administration (60). It was reported to be nonteratogenic in both the CD rat and the CD-1 mouse (dose not specified) (61). Significant effects on fetal mortality and birth weight were observed in litters of pregnant Sprague-Dawley rats given fenoprop (containing <0.05 mg of dioxin

per kg) at doses of 25–100 mg/kg of body weight per day on days 6–15 of gestation (62). It caused teratogenic effects on the fetuses (dose levels not specified), including skeletal anomalies such as cleft palate, retarded ossification and extra cervical ribs, microphthalmia, and cardiovascular abnormalities. Similar effects were observed in animals treated with the propylene glycol butyl ether ester of fenoprop (62).

Mutagenicity and related end-points

Fenoprop was not mutagenic in the Salmonella typhimurium assay (35).

Carcinogenicity

No increase in the incidence of tumours was reported in a 2-year study in which beagle dogs were fed doses of fenoprop ranging from 0.9 to 9.9 mg/kg of body weight per day in the diet (29). No significant increase in the incidence of tumours was noted in mice administered 46.4 mg of fenoprop per kg of body weight per day initially by gavage (28 days) and subsequently in the diet for 76–77 weeks (57).

Mecoprop

Acute exposure

The oral LD_{50}s for rats and mice are 650 and 369 mg/kg of body weight, respectively (30).

Short-term exposure

Weanling SPF-Wistar rats were fed diets containing 0, 50, 400, or 3200 mg of mecoprop per kg for 90 days; effects experienced at the highest dose included significantly decreased blood haemoglobin content and erythrocyte counts, a decrease in neutrophils (females only), a significant increase in alkaline phosphatase activity, and decreased relative kidney weights. Effects at 400 mg/kg included decreased relative kidney weights and significantly decreased numbers of erythrocytes. The NOAEL for effects on the kidney and blood parameters was considered to be 50 mg/kg, equivalent to 3 mg/kg of body weight per day (63).

Beagle dogs were fed diets containing mecoprop at concentrations equivalent to doses of 0, 4, 16, or 64 mg/kg of body weight per day for 13 weeks; effects experienced at the highest dose included depressed body weight gain, increased relative weights of heart, liver, kidney, brain, and lungs, increased blood urea levels, decreased blood haemoglobin levels (weeks 6 and 13), decreased packed cell volume and red blood cells (week 13), and decreased lymphocyte and increased neutrophil counts (week 6). Effects at 16 mg/kg of body weight per day included depressed body weight gain and a decrease in packed cell volume and red blood cell values (week 6). The NOAEL for blood parameters and body weight gain is considered to be 4 mg/kg of body weight per day (Department of National Health and Welfare, Canada, unpublished data, 1980).

In a study in which rats were fed diets containing 0, 100, 400, 1000, or 2500 mg of the diethanolamine salt of mecoprop per kg of feed for 7 months, animals consuming 400 mg/kg and above showed reduced erythrocyte counts, haemoglobin, and packed cell volume. Relative liver weight was increased in females in the 400 mg/kg group and in males in the 2500 mg/kg group. Relative kidney weights were increased in rats in all treatment groups. The NOAEL for effects on blood parameters and organ weights was 100 mg/kg of diet for the diethanolamine salt, equal to a dose of 67 mg of mecoprop per kg of diet, and equivalent to 4 mg/kg of body weight per day (64).

Long-term exposure

Male Wistar rats fed mecoprop over a period of 52 weeks at doses of 20, 100, or 400 mg/kg in the diet experienced an increase in relative kidney weights at the two highest doses. When the rats were fed the same doses for 24 months, there was a statistically significant increase in the absolute kidney weights of the males dosed at 100 and 400 mg/kg and in the relative kidney weights of those dosed at 400 mg/kg. No treatment-related effects were reported in female rats. The NOAEL of 20 mg/kg is equivalent to 1 mg/kg of body weight per day (65).

Reproductive toxicity, embryotoxicity, and teratogenicity

Groups of pregnant rats were given doses of 20, 50, or 125 mg of mecoprop per kg of body weight per day on days 6–15 of gestation. Increased intrauterine deaths, decreased crown–rump lengths, and an increased incidence of delayed or absent ossification of the sternebrae were reported in the highest dose group, although no toxic effects were noted in the dams (66). There were no teratogenic or fetotoxic effects in offspring of groups of 15 pregnant rabbits receiving doses of 12, 30, or 75 mg of mecoprop per kg of body weight per day on days 6–18 of gestation (66). In a study in which mice were given doses of 0, 100, 200, 300, 400, 500, or 700 mg of mecoprop per kg of body weight per day by the oral route on days 6–15 of pregnancy, doses of 300 mg/kg of body weight per day and above were embryotoxic, and skeletal malformations were observed at doses of 400 mg/kg of body weight per day and above (33). In a summary of a study in which pregnant rats and mice were given the potassium salt of mecoprop (0–330 mg/kg of body weight per day for rats and 0–150 mg/kg of body weight per day for mice) by gavage on days 4, 10, 13, and 18, a significant increase in the number of fetuses with hydroureter was induced by the highest dose. Mecoprop was found to readily cross the placental barrier (34).

Mutagenicity and related end-points

Mecoprop was not mutagenic in reverse-mutation assays with Salmonella typhimurium (35,67) and Escherichia coli (67). It was not mutagenic in Streptomyces coelicolor in the forward-mutation test (68), nor did it induce point mutation, nondisjunction, or mitotic crossing-over in Aspergillus nidulans (69,70). It did induce mitotic gene conversion in yeast cultures heteroallelic at two loci (71).

Carcinogenicity

No significant increase in the incidence of tumours was reported in Wistar rats fed mecoprop in the diet at concentrations of 0, 20, 100, or 400 mg/kg for 2 years (65).

MCPB

Acute exposure

The oral LD_{50}s of MCPB in rats and mice are 680 and 800 mg/kg of body weight, respectively (30).

Short-term exposure

In a 13-week study, rats were fed diets containing 0, 4, 12, or 40 mg of MCPB per kg of body weight per day. No effects on mortality, food intake, body weight gain, haematology, clinical chemistry, urinalysis, organ weights, gross pathology, or histopathology were reported. The NOAEL was considered to be 40 mg/kg of body weight per day (Department of National Health and Welfare, Canada, unpublished data, 1988). It should be noted, however, that the doses administered did not approach the maximum tolerated dose; thus, the potential short-term effects of MCPB were not fully assessed.

In a study in which beagle dogs were fed dietary concentrations of MCPB of 0, 160, 480, or 1600 mg/kg of diet for 13 weeks, no compound-related effects were reported on mortality, appearance, behaviour, food intake, body weight, haematology, clinical chemistry, urinalysis, or gross pathology. Weights of testes were depressed in males in the highest dose group; spermatogenesis was absent; the seminiferous tubules, which appeared atrophic, and the epididymis contained spermatozoal precursors and/or giant cells; and the prostate was not fully developed and appeared atrophic. The NOAEL for testicular effects is 480 mg/kg of diet, equivalent to 12 mg/kg of body weight per day (Department of National Health and Welfare, Canada, unpublished data, 1988).

Mutagenicity and related end-points

MCPB was not mutagenic in bacterial reverse-mutation assay systems in five strains of Salmonella typhimurium and one strain of Escherichia coli (35,67). MCPB administered subcutaneously at doses of 200 mg/kg enhanced the mutation frequency of S. typhimurium in NMRI mice (72). It did not produce any deviation from normality when tested for chromosome loss, nondisjunction, or induced X–Y recombination in male Drosophila (73).

EFFECTS ON HUMANS

Acute exposure

Dichlorprop is rated as moderately to highly acutely toxic to humans (74). 2,4,5-T is considered to be moderately acutely toxic; the symptoms produced by high oral doses include nausea, vomiting, drowsiness, fever, increases in pulse and respiration, shock, coma, and death (75). No adverse effects were reported following the ingestion of a single dose of 1 mg of fenoprop per kg of body weight by eight human volunteers (76). The symptoms described in case histories of acute poisoning by weedkiller solutions containing mecoprop include coma, fever, respiratory problems, myotonia, muscle cramps, skeletal muscle damage, electrocardiographic changes, decreased blood pressure, distended abdomen, and rhabdomyolysis with renal failure (77–79).

Carcinogenicity

Until recently, most epidemiological studies of the effects of chlorophenoxy herbicides dealt with populations exposed in the 1950s and 1960s, when the trichlorophenol-based herbicides 2,4,5-T and fenoprop were contaminated with polychlorinated dioxins and furans, including 2,3,7,8-tetrachlorodibenzodioxin (TCDD); the effects observed may therefore have been a consequence of the presence of the dioxin contaminants. In addition, most epidemiological studies on chlorophenoxy herbicides conducted to date have involved multiple exposures to chemical agents, including other pesticides and synthetic organic compounds.

In a series of case–referent studies conducted in Sweden in the late 1970s and early 1980s, strong associations were noted between soft tissue sarcomas (STS) and multiple lymphomas (including Hodgkin disease (HD) and non-Hodgkin lymphoma (NHL)) and the use of chlorophenoxy herbicides by agricultural or forestry workers (80–82). Although the methodology employed has been extensively criticized, these studies served to focus attention on STS, NHL, and HD as the outcomes of interest in succeeding case–referent and cohort studies.

The association between STS and chlorophenoxy herbicide use observed in the Swedish studies has not been confirmed in other case–referent studies (83–87). Although a number of cohort studies of occupationally exposed workers have been conducted, the small size of many of them limits their usefulness in assessing the relationship between STS and the herbicides.

The risk for malignant lymphoma (HD + NHL) was almost five times greater for agricultural and forestry workers exposed to a mixture of chlorophenoxy herbicides than for controls in the case–referent study in Sweden (81,88) but was not significantly elevated in a Danish cohort study of 3390

workers in a chemical plant manufacturing MCPA, dichlorprop, mecoprop, and 2,4-D, as well as other industrial chemicals and dyes (89).

Several case–referent studies suggest a weak link between chlorophenoxy herbicide use and NHL; however, concurrent exposure to other chemicals used in agriculture may contribute to this risk. In a study in Washington (576 cases of NHL), the relative risk increased from 1.1 for subjects with any past occupational exposure to chlorophenoxy herbicides, primarily 2,4-D and 2,4,5-T, to 1.7 for people occupationally exposed to such herbicides for at least 15 years (the minimum latency period) (87). In a case–referent study in Kansas (200 cases), farm herbicide use was marginally associated with NHL, with a relative risk of 1.4, which rose to 2.2 for farmers who had used chlorophenoxy herbicides at any time (almost all 2,4-D) and to 6.0 for those who had used unspecified herbicides for more than 20 days per year. The trend towards increasing risk with increasing number of days of use per year was highly significant (86). The risk for NHL (27 cases) was not elevated in a cohort of more than 20 000 Swedish pesticide applicators who applied MCPA, mecoprop, dichlorprop, and smaller amounts of 2,4-D (90). There was a slight nonsignificant trend towards a small increase in risk with increased number of years of exposure.

A nonsignificant excess in the relative risk for HD was seen in a cohort of 20 245 licensed pesticide applicators in Sweden who were exposed to MCPA, dichlorprop, mecoprop, and 2,4-D. There was a nonsignificant trend towards an increase in risk with the number of years since first licensing, with the risk increasing from 0.93 for those with 4 or fewer years to onset of disease to 2.2 for those with 10 or more years. The average follow-up time in this study was 13.9 years, a little less than the 15–20-year latency period reported for malignant lymphoma (90). In a study in Kansas, the relative risk for HD in people using herbicides (including chlorophenoxy compounds) was not elevated, nor was there evidence of a trend towards elevation of risk with increasing years of use of herbicides or frequency of use in days per year (86).
For the three end-points examined, the studies reviewed provide limited evidence that exposure to chlorophenoxy herbicides is associated with NHL rather than with HD or STS. With the exception of the early studies in Sweden (81,88), the associations seen in most studies were weak; there was usually a less than two-fold increase in relative risk for all three outcomes.

Reproductive effects

In cross-sectional epidemiological studies (91,92), long-term maternal exposure to low doses of 2,4,5-T were suspected of causing miscarriages and birth defects, particularly cleft palate and neural tube defects. In similar cross-sectional studies (93–95) and a cohort study on chemical workers (96), there was no correlation between exposure of either parent to 2,4,5-T and these effects (97,98).

GUIDELINE VALUES

Chlorophenoxy herbicides as a group, including 2,4-D and MCPA, have been classified by IARC in Group 2B (possibly carcinogenic to humans). However, the available data from studies on exposed populations and animals do not permit assessment of the carcinogenic potential to humans of any specific chlorophenoxy herbicide. Therefore, drinking-water guidelines for these compounds are based on a threshold approach for other toxic effects.

Dichlorprop

Based on the 2-year study in rats (31), the NOAEL for renal toxicity is 100 mg/kg of diet, equal to 3.64 mg/kg of body weight per day. The TDI for dichlorprop was calculated to be 36.4 µg/kg of body weight by applying an uncertainty factor of 100 (for intra- and interspecies variation) to this NOAEL. With the allocation of 10% of the TDI to drinking-water, the guideline is 100 µg/litre (rounded figure).

2,4-DB

In a 2-year study in rats, the NOAEL for effects on body and organ weights, blood chemistry, and haematological parameters was determined to be 3 mg/kg of body weight per day (42). This value is similar to the NOAEL of 2.5 mg/kg of body weight per day obtained in the short-term study in beagle dogs and the NOAEL for hepatocytic hypertrophy of 5 mg/kg of body weight per day obtained in a 3-month study in rats (Department of National Health and Welfare, Canada, unpublished data, 1973). A TDI of 30 µg/kg of body weight was derived using an uncertainty factor of 100 (for intra- and interspecies variation). With the allocation of 10% of the TDI to drinking-water, the guideline value is 90 µg/litre.

2,4,5-T

The NOAEL for reduced body weight gain, increased liver and kidney weights, and renal toxicity in a 2-year study in rats was 3 mg/kg of body weight per day (49). A NOAEL of 3 mg/kg of body weight per day for reproductive effects was also obtained in a three-generation study in rats (50). A TDI of 3 µg/kg of body weight was derived using the NOAEL from the 2-year rat study and an uncertainty factor of 1000 (100 for intra- and interspecies variation and 10 for the suggested association between 2,4,5-T and soft-tissue sarcoma and non-Hodgkin lymphoma in epidemiological studies). With the allocation of 10% of the TDI to drinking-water, the guideline for 2,4,5-T is 9 µg/litre.

Fenoprop

A NOAEL of 0.9 mg/kg of body weight per day for adverse effects on the liver was reported in a study in which beagle dogs were administered fenoprop in the diet for 2 years (29). A TDI of 3 µg/kg of body weight was derived using an uncertainty factor of 300 (100 for intra- and interspecies variation and 3 for limitations of the database). With an allocation of 10% of the TDI to drinking-water, the guideline value for fenoprop is 9 µg/litre.

Mecoprop

A NOAEL of 1 mg/kg of body weight per day for effects on kidney weight in 1- and 2-year studies in rats (65) was used with an uncertainty factor of 300 (100 for intra- and interspecies variation and 3 for limitations of the database) to derive a TDI of 3.33 µg/kg of body weight. With the allocation of 10% of the TDI to drinking-water, the guideline for mecoprop is 10 µg/litre (rounded figure).

MCPB

Currently available toxicological data are insufficient to be used as the basis for a guideline value for MCPB in drinking-water.

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