



2-Methyl-4-chlorophenoxyacetic Acid (MCPA) in Drinking Water

Document for public comment

Prepared by the Federal-Provincial-Territorial
Committee on Drinking Water

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MCPA in Drinking Water
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2-Methyl-4-chlorophenoxyacetic acid (MCPA) in drinking water

Purpose of consultation

The Federal-Provincial-Territorial Committee on Drinking Water (CDW) has been assessing the available information on 2-methyl-4-chlorophenoxyacetic acid (MCPA) with the intent of developing a drinking water guideline. The purpose of this consultation is to solicit comments on the proposed guideline, on the approach used for its development and on the potential economic costs of implementing it, as well as to determine the availability of additional exposure data.

The CDW has requested that this document be made available to the public and open for comment. Comments are appreciated, with accompanying rationale, where required. Comments can be sent to the CDW Secretariat via email at water_eau@hc-sc.gc.ca. If this is not feasible, comments may be sent by mail to the CDW Secretariat, Water, Air and Climate Change Bureau, Health Canada, 3rd Floor, 269 Laurier Avenue West, A.L. 4903D, Ottawa, Ontario K1A 0K9.

It should be noted that this Guideline Technical Document on MCPA in drinking water will be revised following evaluation of comments received, and a drinking water guideline will be established, if required. This document should be considered as a draft for comment only.

October 2006

2-Methyl-4-chlorophenoxyacetic acid (MCPA)

1.0 Proposed guideline

The proposed maximum acceptable concentration (MAC) for 2-methyl-4-chlorophenoxyacetic acid (MCPA) in drinking water is 0.002 mg/L (2 µg/L).

2.0 Executive summary

2-Methyl-4-chlorophenoxyacetic acid (MCPA) is a phenoxyacetic acid herbicide, registered in Canada for use on agricultural sites, fine turf and lawns, in forestry and at industrial sites. It is among the top 10 pesticides sold in Canada and is used across the country, most extensively in the Prairie provinces. Herbicide formulations can use various forms of MCPA, including the free acid, salts and esters, but all release the acid as the active ingredient.

This Guideline Technical Document reviews the health risks associated with MCPA in drinking water. It assesses all identified health risks, taking into account available studies and approaches, as well as the limitations of available treatment technology. It considers exposure to MCPA through drinking water only from ingestion, as exposure through inhalation and skin contact is not considered to be significant. From this review, the guideline for MCPA in drinking water is proposed at a maximum acceptable concentration of 0.002 mg/L (2 µg/L), based on health effects.

2.1 Health effects

Some studies have been conducted on the impacts of chlorophenoxy herbicides, including MCPA, on human health. However, because of exposures to several pesticides, as well as to other organic compounds, these studies cannot be used to assess the toxicity of MCPA to humans. A health-based value of 0.002 mg/L can be established for MCPA in drinking water, based on nephrotoxicity (kidney) endpoints in the dog.

Health Canada classifies MCPA as unclassifiable with respect to carcinogenicity in humans, based on inadequate data from human studies and a lack of adequate animal studies. This is consistent with the classification of the International Agency for Research on Cancer (IARC).

2.2 Exposure

There are limited data available on human exposure to MCPA. Based on these data, drinking water is not expected to be a significant route of exposure. Low levels of MCPA in sources of drinking water have been found in many Canadian provinces. In specific situations, MCPA can be found in water as a result of spills, deliberate dumping of tank residues or equipment washing operations.

2.3 Analysis and treatment

The establishment of a drinking water guideline must take into consideration the ability to both measure the contaminant and remove it from drinking water supplies. MCPA can be detected at levels well below the proposed guideline of 0.002 mg/L.

MCPA can be effectively treated in municipal-scale treatment facilities through a number of well-documented methods and reduced to levels below the proposed guideline level.

At the residential scale, no drinking water treatment devices available on the market are currently certified for the removal of MCPA; however, certified devices capable of reducing the concentration of organic compounds may be suitable for MCPA removal.

3.0 Application of the guideline

Note: Specific guidance related to the implementation of drinking water guidelines should be obtained from the appropriate drinking water authority in the affected jurisdiction.

The guideline for MCPA is based on a lifetime exposure to MCPA from drinking water. Drinking water guidelines are protective against health effects from lifelong exposure. Short-term exceedances above the guideline value, are unlikely to have an impact on health. However, in the event that monitoring results show elevated levels on a yearly basis, it is suggested that a plan be developed and implemented to address these situations.

MCPA, a phenoxyacetic acid herbicide registered for use in Canada, is not a concern for the majority of Canadians. Although MCPA is used everywhere in Canada, it is used most extensively in the prairie provinces for agriculture where it is used in the production of cereals, canary seeds, legumes and grasses, asparagus, field and sweet corn. Therefore its application is limited to the growing season. As a result in these high use areas, MCPA can be introduced into surface water and possibly groundwater through runoff, or as the result of spills, deliberate dumping of tank residues or equipment washing operations. MCPA is not persistent in water or soil as a result of biological degradation, (under aerobic conditions), an important degradation pathway. However, under oxygen deprived environments such as groundwater or during periods of cold weather and low light, the degradation of MCPA via biological degradation or photodecomposition is rather limited.

3.1 Monitoring

MCPA is registered in Canada for various uses, with the major one being on agricultural sites, where it is used most extensively in the prairie provinces during the growing season.

Weekly monitoring of surface treated water from the water treatment plant is recommended in areas of high use such as the prairies and other agricultural areas during periods of peak use which occurs from May to early fall. This frequency will provide a complete picture of runoff contamination and especially after rainfall has occurred. Monitoring of ground water from areas of high use is also recommended for MCPA, but at a reduced frequency.

4.0 Identity, use and sources in the environment

MCPA is a phenoxyacetic acid herbicide, with various formulations: as the free acid, as a dimethylamine salt (MCPA-DMAS), as a sodium salt (MCPA sodium salt) and as an ester (MCPA 2-ethylhexyl ester, or MCPA-EHE) (U.S. EPA, 2004b,d). Although MCPA may be applied in various forms, a single common functional group (the parent acid) is the active portion of the herbicide formulation (U.S. EPA, 2004c,e; PMRA, 2006). Diethanolamine MCPA, another amine salt formulation, is not discussed in this document, because there is no information available on its toxicology and because Health Canada's Pest Management Regulatory Agency (PMRA) is proposing that it be phased out (PMRA, 2006).

MCPA acts as a plant growth regulator and is used to control broadleaf weeds in post-emergence in agriculture, in urban, forestry and aquatic environments (IARC, 1983; Weed Science Society of America, 1989; HSDB, 2005). MCPA is absorbed through both leaves and roots and is translocated throughout the plant. By stimulating nucleic acid and protein synthesis, MCPA affects enzyme activities, respiration and cell division. As a result, treated plants exhibit malformed leaves, stems and roots (U.S. EPA, 1990).

Those physicochemical properties of MCPA acid and its related forms that are relevant to their behaviour in the environment are summarized in Table 1.

Table 1: Physicochemical properties^a

Properties/values	MCPA	MCPA-EHE	MCPA-DMAS	MCPA sodium salt
Form	Solid, flakes or crystalline powder	Liquid	Liquid	N/A
Melting point	120°C	260–265°C	111°C	N/A
Henry's law constant	4.7×10^{-8} kPa·m ³ /mol at 25°C	N/A	N/A	N/A
Density at 20°C	1.18–1.21 g/mL	1.06 g/mL	1.181 g/mL	N/A
Vapour pressure at 20°C	7.7×10^{-6} mbar (2.0×10^{-4} Pa at 25°C)	1.77×10^{-5} mbar	N/A	N/A
Water solubility	Practically insoluble in water	Slightly soluble (0.1%, w:w) in water	Water soluble; dissociates quickly to form the free phenoxy acid moiety and dimethyl ammonium	Water soluble; reverts to the acid form under acidic conditions
Octanol/water partition coefficient (log K _{ow})	2.69	5.37	1.415 at 25°C	N/A
Organic carbon partition coefficient (log K _{oc})	2.07	N/A	N/A	N/A

Properties/values	MCPA	MCPA-EHE	MCPA-DMAS	MCPA sodium salt
Dissociation constant (pK _a)	3.07	N/A	N/A	N/A

N/A = not available

^a From Kenaga (1980); Gerstl and Helling (1987); Weed Science Society of America (1989); Woodrow et al. (1990); Worthing and Hance (1991); USDA (2000); Struger et al. (2004); U.S. EPA (2004d).

The physical properties of these other forms of MCPA vary widely according to the formulation. In general, the salts are water soluble, while the esters are lipophilic and less water soluble (U.S. EPA, 2004d,e). Based on its Henry's law constant, MCPA is not expected to volatilize from water or moist surfaces. Its vapour pressure also indicates a low potential to volatilize, and its dissociation constant indicates that it will dissociate rapidly at environmental pH (PMRA, 2006). As available environmental fate data show that all forms of MCPA will revert to MCPA acid, the physicochemical characteristics of MCPA in the environment will be those associated with MCPA acid (U.S. EPA, 2004a).

It should be noted that MCPA is usually applied along with other phenoxy herbicides, such as 2,4-dichlorophenoxyacetic acid (2,4-D), 4-(2,4-dichlorophenoxy)butyric acid (2,4-DB), (R)(+)-2-(4-chloro-2-methylphenoxy)propanoic acid (MCP-p) and 4-(2-methyl-4-chlorophenoxy)butyric acid (MCPB) (U.S. EPA, 2004b).

MCPA is registered for use in Canada for agricultural sites, for fine turf (parks, playgrounds, golf courses, zoos, botanical gardens and athletic playing fields), for lawns (residences, public and commercial buildings) and sod (grown in sod farms harvested for transplanting), in forestry (spruce seedlings for reforestation) and at industrial sites (vegetation control) (PMRA, 2005a). In Canada, the major applications of MCPA are in agriculture, where it is used in the production of cereals (barley, oats, rye, wheat and flax) and in the production of canary seeds, legumes and grasses, asparagus, field corn and sweet corn. MCPA is also applied to stubble/summerfallow fields and pastures/rangeland (PMRA, 2005a). MCPA is used everywhere in Canada, particularly in the Prairies (PMRA, 2005a).

MCPA is among the top 10 pesticides sold in Canada. Table 2 presents the limited data available on the sales/use of MCPA from recent years. Brimble et al. (2005) report that Saskatchewan is responsible for approximately 36% of all pesticide sales in Canada, making it the largest pesticide user in Canada. Although sales data for Saskatchewan are not currently available, a database to collect this information is under development. In Quebec, legislation bans the application of MCPA (and other specific pesticides) around all daycare facilities, schools, some public lands and private green spaces (Ministère du Développement durable, de l'Environnement et des Parcs du Québec, 2005).

Table 2. Sales/use of MCPA (active ingredient) in Canada^a

Province	Year	Sales/used (active ingredient in kg)	% of use based on top 20 active ingredients
British Columbia	2003	23 598	0.51
Alberta	1998	885 239	9.52
Manitoba ^b	2003	450 091	12.48
Ontario ^b	2003	129 337	3.07
Quebec	2001	114 188 (estimated)	N/A
New Brunswick	2003	17 053	2.18
Nova Scotia ^b	2003	6 109	1.38
Prince Edward	2001	28 999	N/A

N/A = not available

^a Adapted from Brimble et al. (2005).

^b MCPA values include MCPB.

^c PMRA, 2005e

4.1 Environmental fate

4.1.1 Soil

MCPA is not persistent in soil (U.S. EPA, 2004a), with a half-life varying between 15 and 50 days (Soderquist and Crosby, 1975; Sattar and Paasivirta, 1980). The rate of degradation depends upon several factors, such as soil type, soil pH, soil moisture, concentration of MCPA, climatic conditions and organic matter content (Sattar and Paasivirta, 1980). Degradation of MCPA occurred within 5–9 weeks in acidic soil versus 1 week in neutral soil (pH 6.3 and above) (Sattar and Paasivirta, 1980).

Microbial degradation is the most important transformation process for MCPA in soil (Caux et al., 1995); the presence of both oxygen and proper moisture is important for its biodegradation (Sattar and Paasivirta, 1980). In the absence of oxygen, the biotransformation of MCPA in anaerobic soil is negligible (PMRA, 2006). Photodecomposition and hydrolysis in soil are not important degradation processes for MCPA (U.S. EPA, 2004a,b; PMRA, 2006). When MCPA was applied to the soil surface and irradiated with natural sunlight, its calculated half-life was 67 days (U.S. EPA, 2004a,b).

MCPA's potential for leaching is low, since MCPA was not detected below soil depths of 15 cm (PMRA, 2006). MCPA's mobility has been shown to be related to the soil's organic matter content, increasing as the organic matter content decreases (WHO, 2003). However, there is potential for MCPA to enter surface water and possibly groundwater, since it is subject to surface runoff. The mobility and leaching for the forms of MCPA other than the acid (i.e. amine and sodium salts, esters) have not been determined.

Field studies with MCPA-EHE have shown that, under normal conditions, a large proportion converts to MCPA acid on the day of application, and the MCPA-EHE is nearly completely converted by day 3 (U.S. EPA, 2004a). However, under dry conditions, MCPA-EHE has been found to persist for days, with greater than 90% present after 48 hours (Smith and Hayden, 1980). In a non-sterile soil:calcium chloride system at pH 5.6 and pH 6.8, MCPA-EHE adsorbed to the soil particles but was available for degradation to MCPA, with a half-life ≤ 12 hours (U.S. EPA, 2004a).

4.1.2 Water

Agricultural herbicides such as MCPA have been detected in lakes, rivers and reservoirs (dugouts), which may serve as sources for drinking water. Their migration from soil to water is the result of direct or indirect transport mechanisms, including non-target drift from aerial or ground boom spraying (vaporization in air), deposition in rain, erosion of soil particles by wind or water, surface runoff and leaching. In specific situations, MCPA can be found in water as a result of spills, deliberate dumping of tank residues or equipment washing operations (Caux et al., 1995; Murray et al., 2004).

In water, biological degradation (under aerobic conditions) is an important process affecting MCPA's environmental fate (Soderquist and Crosby, 1975; Sattar and Paasivirta, 1980; Smith and Hayden, 1981; PMRA, 2006). MCPA in rice paddy water under dark conditions is totally degraded by aquatic microorganisms in 13 days (Soderquist and Crosby, 1975). However, in anaerobic aquatic systems (sediment/water), the biodegradation of MCPA was negligible (PMRA, 2006). Hydrolysis and photodegradation are not important routes in the degradation of MCPA in water (PMRA, 2006). In an aqueous solution (pH 8.3), MCPA had a photolytic half-life of 20–24 days in sunlight. Photolysis of dilute aqueous MCPA solutions yielded 4-chloro-2-methylphenol as the major by-product; *o*-cresol and 4-chloro-2-formylphenol were also identified (Soderquist and Crosby, 1975). During periods of cold weather and low light, the degradation of MCPA via biological degradation or photolysis is rather limited (Byrtus et al., 2004). MCPA acid does not readily hydrolyse in sterile buffer solution at pH 5–9 (U.S. EPA, 2004a). MCPA has not been shown to bind significantly to sediments (Caux et al., 1995).

The derivatives of MCPA have been shown to dissociate in water to MCPA acid. In deionized water, MCPA-DMAS completely dissociated to MCPA acid and dimethylammonium ion within 1.5 minutes (U.S. EPA, 2004a). In sterile buffers, the hydrolysis of MCPA-EHE to MCPA acid was pH dependent (half-life < 117 hours at pH 9, but no hydrolysis at pH 5 and pH 7).

4.1.3 Atmosphere

Pesticides can enter the atmosphere via application drift, evaporation, sublimation or erosion of treated soil. Once in the air, pesticides can be transported and redistributed, degraded or returned to the earth's surface via wet deposition (dissolved in rain) and dry deposition (as gases or aerosols or sorbed to macro solid particles) (Hill et al., 2002; Waite et al., 2005). However, little information on the fate of MCPA is available. Waite et al. (2005) demonstrated, by high-volume air sampling at various heights above ground level in the Canadian Prairies, that

atmospheric concentrations of MCPA are strongly influenced by regional atmospheric transport and that its primary transport mechanism is via adsorption to solid particles in the atmosphere. The volatilization of MCPA in the acid form or salt form is low (Weed Science Society of America, 1989; Caux et al., 1995). The half-life of MCPA due to photooxidation was estimated at 2.2 days (Caux et al., 1995).

5.0 Exposure

Canadians can be exposed to MCPA through its presence in drinking water, air and food. In addition, certain segments of the population can be exposed through the use of specific consumer products or in occupational settings related to pesticide use and application. Although some exposure data are available, they are considered insufficient to justify modifying the default allocation factor for drinking water (i.e. the proportion of the total daily intake of MCPA allocated to drinking water) of 20%.

5.1 Air

During 1989 and 1990, MCPA was detected in only 4% of atmospheric samples at two dugout sites near Regina (Saskatchewan) where it was being applied locally, with a maximum concentration of 0.39 ng/m³ (Waite et al., 2004). It was detected in 24% of bulk (dry plus wet) atmospheric deposits at these same sites, with a mean deposition rate of 129 ng/m³ per day.

In a small southern Manitoba watershed, MCPA was detected at concentrations up to 13 ng/m³ in atmospheric samples between 1993 and 1996 and at concentrations ranging from 0.0044 to 0.95 µg/L (yearly maximum levels) in rainfall, which correlated mostly with periods of local use (Rawn et al., 1999).

In a province-wide survey of herbicide concentrations in rainfall conducted in Alberta between April and September (1999–2000), MCPA was detected in less than 50% of samples taken (Hill et al., 2002). Among the major pesticides, MCPA was detected in the second highest total amount, with maximum concentrations ranging from 38 to 84 µg/m². The total amount of MCPA deposited in rainfall varied over the season, with levels highest during June and July (spraying season), and varied with the region sampled: the highest levels were observed in central rural Alberta, the second highest in southern rural Alberta and the lowest in remote regions and city locations.

5.2 Water

5.2.1 Drinking water

In Alberta, MCPA was seldom detected (11%) in a Treated Water Survey Program during the period 1995–2003 (Byrtus et al., 2004). MCPA was detected in 190 water samples out of a total of 1788 samples collected for analysis throughout this period. MCPA was detected more at treatment facilities with surface water sources (13.7%) than at facilities with groundwater sources (2%), where the maximum concentrations detected were 571 ng/L and 5 ng/L, respectively. The data showed no overall or seasonal trend over the nine years in detection frequency or concentration, suggesting that MCPA could be detected in treated water supplies all year round.

MCPA was detected in 2 of 403 samples of municipal drinking water in surveys conducted in Manitoba from 1981 to 1999 (Manitoba Conservation, 2000). The maximum concentration found was 0.049 ng/L.

In various towns in Ontario, MCPA was detected in 4 of 29 raw water samples for 2004, at concentrations ranging from 27 to 49 ng/L, and in 2 of 132 treated water samples for the year 2004 and January 2005, at concentrations ranging from 27 to 66 ng/L (Ontario Ministry of the Environment, 2005). The detection limit was 20 ng/L.

In Nova Scotia, MCPA was not detected in raw or treated water from Dartmouth (detection limit 2 µg/L) or Stellarton (effective quantitation limit 50 µg/L) during sampling done in June 2003 (Nova Scotia Department of Environment and Labour, 2005).

In Newfoundland and Labrador, MCPA was not detected in two wells sampled in 1982 (detection limit 2 µg/L) (Newfoundland and Labrador Department of Environment and Conservation, 2005).

MCPA was not detected in any of the 10 groundwater samples taken in Prince Edward Island in 1998 (Blundell and Harman, 2000).

5.2.2 *Potential sources of drinking water*

In British Columbia, MCPA was detected in 1 of 13 samples of runoff in the Lower Fraser Valley in 2003. The maximum concentration was 110 ng/L (Tuominen et al., 2005).

In Saskatchewan, runoff water from flood-irrigated fields enters a system of drainage ditches, which then drain into the South Saskatchewan River, potentially affecting downstream water quality. The concentrations of MCPA and other herbicides in the drainage water from two drainage ditches in an irrigation district that emptied into the South Saskatchewan River were sampled during the 1994–1996 growing seasons (Cessna et al., 2001). The maximum concentration of MCPA in the drainage water was 2.8 µg/L. Input of MCPA into the river was approximately 0.06% of the amounts applied; in all three years, MCPA was applied to flood-irrigated land irrigated by both drainage ditches. No significant increase in herbicide concentration was seen in the river as a result of herbicide input, because of the large flows seen in the river.

In a preliminary 2003 spring/summer pesticide surveillance study, MCPA was detected in all of 15 small reservoirs (dugouts) sampled in the three Prairie provinces (Murray et al., 2004). Mean MCPA concentrations in most of the dugouts ranged from 13 to 108 ng/L. The detection limit was 0.58 ng/L. Two reservoirs had higher levels, ranging from 200 to 320 ng/L, possibly a result of commercial formulations (which include MCPA) being applied in the watershed or catchment (Murray et al., 2004).

MCPA was detected in 10 of 49 samples of surface water taken from three of the Great Lakes — Lake Ontario (1998–1999), Lake Erie (1994, 1998, 2000) and Lake Huron (1999–2000) — with a maximum concentration of 5.4 ng/L, whereas it was not detected in nine samples from Lake Superior (1996–1997) (Struger et al., 2004). The detection limit was between 0.27 and 0.30 ng/L. Spatial and seasonal variations observed were related to MCPA's use patterns.

In sampling around the Great Lakes Areas of Concern in 2004, MCPA was detected in 127 out of 217 samples, with a maximum concentration of 350 ng/L (Struger et al., 2005). The detection limit was 5.8 ng/L. MCPA was detected in 120 out of 171 samples of surface water around the Great Lakes Areas of Concern and small streams in the Niagara and Burlington areas in 2003; the maximum concentration was 1.23 µg/L, with a mean of 0.0139 µg/L. MCPA was detected in 27 out of 59 samples of surface water in Great Lakes Areas of Concern and connecting channels in 2002, with a maximum concentration of 40 ng/L (mean 2.9 ng/L). In Lake Huron tributaries sampled in 2002, MCPA was detected in 11 out of 47 samples, with a maximum concentration of 80 ng/L (Struger et al., 2005). MCPA was not detected in all 133 samples taken in 1998–2000 in the area of the Don and Humber river watersheds (detection limit 100 ng/L) (Struger et al., 2002).

In Quebec, MCPA was seldom detected (11%) during the summer of 2003 in the tributaries of the St. Lawrence River; the maximum concentration seen was 120 ng/L (Murray et al., 2004). These tributaries drain from agricultural areas where MCPA is used in the cultivation of cereals, vegetables and grassland.

MCPA was detected in 531 of 1447 samples of surface water taken from five rivers in the corn and soy growing areas of Quebec from 1994 to 2001; the maximum concentration found was 7.0 µg/L, and the detection limit varied from 0.02 to 0.05 µg/L (Giroux et al., 1997; Giroux, 1999, 2002). MCPA was also detected in 69 out of 122 samples from six other surface waters in agricultural areas in Quebec surveyed in 1996 and 1997, with a maximum concentration of 2.6 µg/L (Giroux 1998).

In the Maritime provinces, MCPA was not detected in any of the 60 surface water samples taken in New Brunswick (2003 and 2004), Nova Scotia (2004) and Prince Edward Island (2003 and 2004); the detection limit was 1 µg/L (Murphy and Mutch, 2005). MCPA was also not detected in the rivers of eight different municipalities with agricultural or urban activities in New Brunswick in 2004 (Office of Chief Medical Officer of Health, 2005).

5.3 Food

There are limited Canadian data available on the concentration of MCPA in food. Between 1980 and 1985, 354 composite vegetable samples representing nine vegetable commodities were collected from Ontario farm deliveries. MCPA was detected in one of six samples of asparagus, at a concentration of 0.06 mg/kg, below the maximum residue limit (MRL) of 0.1 mg/kg (Frank et al., 1987a). Monitoring studies in 1980–1982 in Ontario found MCPA levels of 0.01 mg/kg in peaches and 0.02 mg/kg in strawberries, both below the MRL (Frank et al., 1987b).

No current U.S. data were identified. Historically, during monitoring of pesticides in foods in the Total Diet Study program, in which ready-to-eat foods were sampled (June 1964 – April 1969), MCPA was found very infrequently at low levels (maximum concentration 0.4 mg/kg) in products such as dairy products, grains and cereals and sugars (Bovey, 1980a). MCPA was not detected in any food composites collected from June 1969 to 1976 (IARC, 1983; HSDB, 2005).

MCPA-DMAS was not detected in grain 56 days after application to wheat treated in the tillering stage (Chow et al., 1971).

6.0 Analytical methods

The only U.S. Environmental Protection Agency (EPA) approved method for measuring MCPA in drinking water is EPA Method 555 (Rev. 1.0). This method employs high-performance liquid chromatography (HPLC) with a photodiode array ultraviolet detector (PDA-UV). Samples are hydrolysed, acidified, filtered and extracted prior to separation and analysis using HPLC with a PDA-UV. The method detection limit is 0.8 µg/L (U.S. EPA, 1992).

The World Health Organization (WHO) recognizes liquid-liquid extraction with dichloromethane and derivatization with diazomethane using gas chromatography (GC) with either mass spectrometry (MS) or an electron capture detector. The method detection limit is approximately 0.1 µg/L (WHO, 2003). It is considered a very common method of analysis for MCPA (Hernandez et al., 1993; Tekel and Kavacicova, 1993).

Several experimental methods can be used for the analysis of MCPA in drinking water. Solid-phase extraction (SPE) followed by reversed-phase HPLC with UV detection has a method detection limit of 0.015 µg/L (Frébortová, 1995). Extraction using porous polymeric sorbent material followed by HPLC and UV detection has a method detection limit of less than 0.1 µg/L (Geerdink et al., 1991). An alternative approach involves the fluorescent derivatization of MCPA using 9-anthryldiazomethane followed by reversed-phase HPLC with fluorescence detection. The detection limit for this method is 0.2 µg/L (Suzuki and Watanabe, 1991).

Butz et al. (1994) reported a method detection limit of less than 0.001 µg/L for MCPA using SPE and GC with mass selective detection employing selected-ion monitoring. A more recent experimental method for the analysis of MCPA uses liquid chromatography and electrospray ionization with tandem MS. This method eliminates the requirement for sample derivatization using GC-MS and permits the direct injection of water samples for MCPA analysis. The method detection limit is 0.04 µg/L (Pozo et al., 2001). These methods are considered to be experimental and are not commonly used for routine analyses.

7.0 Treatment technology

7.1 Municipal scale

Treatment technologies reported to be effective for the reduction of MCPA in drinking water include activated carbon adsorption and/or ozonation, membrane filtration, UV irradiation and advanced oxidation processes (AOPs). Full-scale and pilot-scale studies have demonstrated that effluent concentrations of MCPA below 0.1 µg/L are achievable using the methods described below. The selection of an appropriate treatment process for a specific water supply will depend on many factors, including the characteristics of the raw water supply and the operational conditions of the specific treatment method. It is important to note that studies have indicated that the UV dosage required for the degradation of MCPA is much higher than the dosage required for disinfection and that combined disinfection and degradation may not be achievable (Kruithof et al., 2002a,b).

7.1.1 Conventional treatment

Limited scientific literature has been published on the effectiveness of conventional surface water treatment techniques for the reduction of MCPA in drinking water. Conventional treatment techniques are reported to be ineffective in reducing the concentration of a variety of classes of pesticides in drinking water, in particular hydrophilic or lipophobic compounds (Robeck et al., 1965; Miltner et al., 1989; Foster et al., 1991, 1992; Haiste-Gulde et al., 1993). The concentrations of organic compounds, such as pesticides, may be reduced through coagulation/flocculation if they are hydrophobic or have low molecular weight acidic functional groups (Randtke, 1988). The chemical properties of MCPA (moderately lipophilic; substituted acetic acid) may result in limited removal by conventional water treatment.

Operational data collected from a conventional water treatment process demonstrated a 50% reduction of MCPA to levels below 0.033 µg/L (Byrtus et al., 2004). Foster et al. (1992) observed some reduction of low levels of chlorophenoxy acid in a conventional surface water treatment plant. Similarly, the reduction of influent MCPA levels below 1 µg/L using slow sand filtration was reported by Lambert and Graham (1995).

7.1.2 Adsorption

Activated carbon adsorption has been widely used to reduce the concentration of pesticides in drinking water and is recognized by WHO as a suitable treatment technology for the removal of MCPA to levels below 0.1 µg/L (Robeck et al., 1965; Miltner et al., 1989; Foster et al., 1992; Duguet et al., 1994; WHO, 2004). The capacity of activated carbon to remove pesticides by adsorption is affected by a variety of factors, such as concentration, pH, competition from other contaminants or natural organic matter, contact time and the physicochemical properties of the pesticide. The effectiveness of granular activated carbon (GAC) filtration is also a function of the empty bed contact time (EBCT), flow rate and the filter run time. The effectiveness of powdered activated carbon is also a function of the carbon dosage.

Operational data from a municipal-scale treatment plant using conventional treatment with a GAC filter-adsorber demonstrated that this type of treatment system can reduce low influent levels of MCPA from 0.47 µg/L to below 0.02 µg/L (Frick and Dalton, 2005). No information was provided on the operational conditions of the GAC adsorber used in this study. Pilot-scale study results indicated that post-filtration GAC adsorbers can reduce influent levels of 2 µg/L of MCPA to below 0.1 µg/L. No breakthrough of MCPA was observed over a period greater than 400 days using an EBCT of 20 minutes (Schippers et al., 2004). Other pilot-scale studies also found that GAC filtration was capable of reducing influent MCPA concentrations of 1 µg/L to below 0.1 µg/L; however, the bed life was not determined, as MCPA was only periodically present in the water supply (Hart, 1989; Hart and Chambers, 1991).

Laboratory studies conducted to determine the equilibrium capacities of several activated carbons for MCPA indicated that MCPA is readily adsorbed by certain activated carbons and that adsorption may be a feasible treatment method (Petrie et al., 1993; Gerard and Barthelemy, 2003; Gimeno et al., 2003).

7.1.3 Ozonation and ozonation/adsorption

WHO (2004) also recognizes ozonation as a suitable treatment technology for the reduction of MCPA to levels below 0.1 µg/L. Bonne et al. (2000) observed a 65% reduction of MCPA from influent levels of 20 µg/L to below 7 µg/L using ozonation alone and a reduction to effluent levels below 0.1 µg/L using combined ozonation and biological activated carbon filtration treatment. Additional pilot-scale studies using ozonation followed by GAC found 100% removal at ozone doses of 2–4 mg/L and contact times of less than 15 minutes (Foster et al., 1992). The potential presence of aliphatic acids, aldehydes, ketones and other ozonation by-products such as bromate and assimilable organic carbon (AOC) may require additional treatment following ozonation and/or process optimization to minimize by-product formation. Camel and Bermond (1998) reported that mineralization of pesticides using ozonation or other oxidation techniques is generally incomplete; as a result, water treatment process design using this method should include sand or GAC filtration following oxidation. It has also been suggested that the use of ozonation prior to GAC adsorption increases the biological activity of the filter bed and may extend the bed life for pesticide removal (Lambert and Graham, 1995).

The relatively rapid and complete degradation of MCPA using ozonation has been reported in numerous laboratory studies (Doré et al., 1980; Legube et al., 1981; Reynolds et al., 1989). Several degradation studies identified aliphatic acids of short chain length, such as glycolic and pyruvic acids, as the primary by-products of the ozonation of MCPA (Doré et al., 1980; Legube et al., 1981; Benoit-Guyod et al., 1986). Results from bench-scale experiments indicated that ozonation is an effective method for the reduction of MCPA to levels below 0.1 µg/L. Doses of 1.0 g/g of ozone (O₃) to dissolved organic carbon (DOC) were required to achieve effective removal rates. At doses suitable for disinfection alone (O₃/DOC = 0.5 g/g), ozonation achieved only between 61% and 89% removal of MCPA. Results from this study suggest that ozone doses intended for disinfection alone may not be sufficient to adequately degrade MCPA (Meijers et al., 1995). Similar bench-scale experiments demonstrated the degradation of MCPA to concentrations below 0.1 µg/L using an ozone dose of 2.2 mg/L (Meijers et al., 1993).

7.1.4 Ultraviolet

Pilot-scale studies evaluating the effectiveness of UV treatment for the reduction of pesticides from groundwater achieved a removal efficiency of 94% to effluent levels below 0.1 µg/L for MCPA with UV energy inputs of 300 Wh/m³. Removal efficiency was found to be dependent on the energy dose and was not affected by the initial pesticide concentration. In addition, it was reported that the formation of by-products from the UV irradiation of MCPA may include organics as well as nitrite (Bourguine et al., 1997). Bench-scale experiments examining the effectiveness of UV irradiation observed complete degradation of MCPA using a low-pressure lamp and a wavelength of 254 nm. Removal of 90% and 100% of the initial reaction concentrations (50 mg/L) of MCPA following 20 and 40 minutes of reaction time, respectively, was observed (Benitez et al., 2004).

7.1.5 Ultraviolet and hydrogen peroxide oxidation

Full-scale AOPs such as UV and hydrogen peroxide oxidation (UV/H₂O₂) treatment have been assessed for the reduction of different classes of pesticides (Kruithof et al., 2002a,b). Although MCPA was not studied specifically, other chlorophenoxy herbicides were studied. Results indicated that a variety of UV doses (<1200 mJ/cm²) and hydrogen peroxide doses (<15 g/m³) resulted in an 80% or greater degradation of several chlorophenoxy herbicides (e.g. 2,4-D and trichloroacetic acid) to effluent levels below 0.1 µg/L. Formation of bromate and metabolites was reported to be insignificant; however, GAC filtration was required following UV/H₂O₂ oxidation to remove AOC and residual hydrogen peroxide. This study also noted that the UV doses required for oxidation of pesticides were much higher than those needed for disinfection (Kruithof et al., 2002a,b).

Ijpelaar et al. (2002) observed greater than 95% reduction of MCPA in bench-scale experiments using UV/H₂O₂. UV doses of 1000 mJ/cm² and a hydrogen peroxide concentration of 13 mg/L were effective in removing MCPA to levels below 0.1 µg/L. The formation of nitrite from the UV irradiation of nitrate found in the source water was found to be significant, but could be limited by increasing the hydrogen peroxide concentrations. Laboratory-scale studies found that the degradation of MCPA is accelerated using UV/H₂O₂ when compared with UV treatment alone. Within 12 minutes, 90% degradation was observed; however, initial concentrations were high, and the results did not include information on the final effluent levels (Benitez et al., 2004).

7.1.6 Membrane filtration

Various membrane filtration techniques, including ultrafiltration, nanofiltration and reverse osmosis, have been shown to be effective methods for the reduction of MCPA in drinking water (Taylor et al., 1995; Hofman et al., 1997; Taylor et al., 2000; Schippers et al., 2004). Pilot-scale studies of ultrafiltration membranes have reported average MCPA removals of ≥99% to effluent levels below 0.1 µg/L (Schippers et al., 2004). Similarly, pilot-scale studies of reverse osmosis membranes demonstrated average MCPA removals ranging from 97% to 99%, resulting in effluent concentrations below 0.2 µg/L. Results of this study also indicated that pesticide removal did not decrease with increasing membrane age (Bonne et al., 2000). Taylor et al. (2000) conducted reverse osmosis pilot-scale studies to evaluate various factors affecting pesticide removal. An average MCPA removal of 97.5 % was observed under varying flux, recovery and source water quality conditions, to produce effluent concentrations below 0.3 µg/L. Pesticide rejection was found to be dependent on a variety of system components, including type of membrane system, flux, recovery, pesticide solubility, charge and molecular weight. Results from this study also indicated that representative influent water quality and bench- or pilot-scale membrane units should be used for the selection of membranes for full-scale application.

Laboratory-scale studies examining the effectiveness of various membrane characteristics in the removal of pesticides found that several types of polyamide membranes were the most effective for the removal of MCPA. Selected membranes were capable of reducing greater than 99% of influent MCPA concentrations to produce effluent water with concentrations less than

0.1 µg/L (Taylor et al., 2000). Similarly, a 97% reduction of influent MCPA concentrations to below 0.1 µg/L was observed by Hofman et al. (1997) using polyamide and ultra-low-pressure reverse osmosis membranes in spiral wound configurations.

7.1.7 Emerging treatment technologies

Several drinking water treatment technologies for MCPA are being developed but are still primarily in the experimental stage or do not have published information on the effectiveness of pilot- or large-scale application. Some of the emerging technologies include the following:

- *Other AOPs* — Experiments examining the degradation pathways of MCPA using ozone and UV indicate that the addition of UV results in a more rapid degradation of MCPA than with ozone alone (Benoit-Guyod et al., 1986). Other AOPs, such as ozone combined with hydrogen peroxide, have been effective for the removal of several classes of pesticides, including other chlorophenoxy herbicides; however, no information was found on the removal of MCPA specifically (Ijpelaar et al., 2002; Kruithof et al., 2002b; Benitez et al., 2004). Laboratory studies have shown that the Fenton process is also an effective AOP for the degradation of MCPA (Fdil et al., 2003).
- *Electrochemical degradation* — A variety of electrochemical degradation techniques have been examined. Laboratory studies found electrochemical degradation by peroxi-coagulation and photoperoxi-coagulation was effective for the removal of MCPA (Boye et al., 2003). Electrochemical degradation by anodic oxidation and electro-Fenton using a boron-doped diamond electrode was also found to be effective for MCPA removal (Brillas et al., 2004).
- *Alternative adsorbents* — Adsorption of MCPA from aqueous solutions has also been demonstrated using acid-activated spent bleaching earth, organo-clays and an adsorbent produced from elutrilithe (Ackay and Yurdakoc, 2003; Mahramanlioglu and Kubilay, 2003; Mahramanlioglu et al., 2003).

7.2 Residential scale

Generally, it is not necessary that drinking water treatment devices be used with municipally treated water. In cases where an individual household obtains its drinking water from a private well, a private residential drinking water treatment device (treatment device) may be an option for reducing MCPA concentrations in drinking water. Although no certified treatment devices are currently available for the reduction of MCPA, treatment devices using activated carbon filters or reverse osmosis may be effective. Treatment devices certified under NSF International/American National Standards Institute (NSF/ANSI) Standard 53 (Drinking Water Treatment Units Health Effects) for the reduction of the concentration of volatile organic compounds or NSF/ANSI Standard 58 (Reverse Osmosis Drinking Water Treatment Systems) for the reduction of the concentration of organic compounds may be suitable alternatives for the

reduction of MCPA. Before a treatment device is installed, the well water should be tested to determine general water chemistry and to select the type of device that is appropriate.

Periodic testing by an accredited laboratory should be conducted on both the water entering the treatment device and the finished water to verify that the treatment device is effective. Devices can lose removal capacity through usage and time and need to be maintained or replaced. Consumers should verify the expected longevity of the components in their treatment device as per the manufacturer's recommendations and service it when required.

No federal regulations currently exist in Canada regarding drinking water materials, which include drinking water treatment additives, components of distribution systems and drinking water treatment devices. Health Canada does not recommend specific brands of drinking water treatment devices, but it strongly recommends that consumers look for a mark or label indicating that the device or its components have been certified by an accredited certification body as meeting the appropriate NSF/ANSI drinking water materials standards. These standards have been designed to safeguard drinking water by helping to ensure the material safety and performance of products that come into contact with drinking water. Certification organizations provide assurance that a product conforms to applicable standards and must be accredited by the Standards Council of Canada (SCC). In Canada, the following organizations have been accredited by the SCC to certify drinking water devices and materials as meeting NSF/ANSI standards:

- Canadian Standards Association International (www.csa-international.org);
- NSF International (www.nsf.org);
- Water Quality Association (www.wqa.org);
- Underwriters Laboratories Inc. (www.ul.com);
- Quality Auditing Institute (www.qai.org);
- International Association of Plumbing & Mechanical Officials (www.iapmo.org).

An up-to-date list of accredited certification organizations can be obtained from the SCC (www.scc.ca).

8.0 Metabolism

MCPA is rapidly absorbed following ingestion, is not extensively metabolized and is eliminated primarily in the urine, mostly as unchanged MCPA, in rats, dogs and humans. However, dogs have a longer plasma half-life and slower elimination than other species, including humans. MCPA-DMAS and MCPA-EHE were rapidly converted to MCPA in rat studies, and the metabolism and toxicokinetics were similar to those of MCPA.

8.1 Absorption

MCPA is readily absorbed from the gastrointestinal tract (via gavage and following direct gastric intubation) in rats, dogs and humans (Elo, 1976; Fjeldstad and Wannag, 1977; Kolmodin-Hedman et al., 1983; Jahanshahi and Stow, 1995; Hardwick, 1999, 2000; Lappin et al., 2002).

Oral administration of single MCPA doses of 5 or 100 mg/kg bw resulted in peak plasma concentrations being attained within 2–4 hours of dosing in rats and within 4.5–7 hours in beagle dogs (Lappin et al., 2002). Similar peak plasma concentrations were attained (within 2–3 hours

of dosing) in rats with a single dose of 5 mg/kg bw of either MCPA-DMAS or MCPA-EHE (van Ravenzwaay et al., 2004). Human volunteers given an MCPA dose of 0.015 mg/kg bw per day exhibited a peak plasma concentration after 1 hour (Kolmodin-Hedman et al., 1983). Timchalk (2004), in a comparison review of these metabolism studies in rats, dogs and humans, showed that dogs had a longer plasma half-life than rats and humans. At a dosage of 5 mg/kg bw, the plasma half-life was 63 hours in dogs, which was considerably higher than that in rats (6 hours) or humans (11 hours), but humans received a lower dose of MCPA (0.015 mg/kg bw).

8.2 Distribution

Once absorbed, MCPA diffuses readily across biological membranes and is widely distributed to various tissues and organs via the circulatory system. Concentrations decline rapidly; in rats, MCPA is rapidly excreted, mainly unchanged, in the urine (Elo, 1976; Jahanshahi and Stow, 1995; van Ravenzwaay et al., 2004). No significant accumulation of MCPA is observed in the tissues.

In rats administered [¹⁴C]MCPA by direct gastric intubation at a single dose of 11.5 mg/kg bw, the peak concentration in tissues was reached between 2 and 8 hours after dosing, after which the concentrations declined rapidly (Elo, 1976). The tissues/organs with the highest concentrations were the blood, kidney, suprarenal gland, lung, heart, liver, thyroid gland and bone marrow. In contrast, the brain, adipose tissue, testis and muscle contained the lowest concentrations.

In rats administered [¹⁴C]MCPA at single oral dose of 5 or 100 mg/kg bw, the radioactivity in the tissues and carcasses accounted for $\leq 2.3\%$ of the dose at sacrifice (Jahanshahi and Stow, 1995; van Ravenzwaay et al., 2004). In sacrificed rats receiving the low-dose regimens (sacrificed on day 4), MCPA was non-detectable in most tissues, except in fat, skin and kidneys. In sacrificed rats receiving the higher dose (sacrificed on day 7), the level of radioactivity was also highest in fat, skin and kidneys, but MCPA was detected at higher concentrations and in more organs than at the lower dose. In addition, females had higher levels of radioactivity than males. The authors observed that small amounts of residual activity found in kidneys were consistent with continued excretion of the compound (van Ravenzwaay et al., 2004).

8.3 Metabolism

The metabolism and toxicokinetics of MCPA-DMAS and MCPA-EHE were investigated in rats administered single doses of 5 mg/kg bw each and compared with MCPA (van Ravenzwaay et al., 2004). Toxicokinetics and metabolism were indistinguishable from those of MCPA. MCPA, MCPA-DMAS and MCPA-EHE were not extensively metabolized in rats after oral administration.

8.4 Excretion

Renal excretion is reported as the major route of MCPA elimination in rats and dogs when dosed orally with MCPA (Elo, 1976; Jahanshahi and Stow, 1995; Lappin et al., 2002; van

Ravenzwaay et al., 2004). Dogs have a different recovery pattern than rats. Studies showed that renal clearance in dogs was slower and less extensive than in rats (Lappin et al., 2002) or humans (Fjeldstad and Wannag, 1977; Kolmodin-Hedman et al., 1983).

In rats, 75–80% of the administered dose was excreted in the urine over 24 hours, irrespective of the dose. In dogs, after oral administration of MCPA in single doses of 5 or 100 mg/kg bw, elimination was not complete at the end of 120 hours (Lappin et al., 2002).

In rats, the parent compound (MCPA) was the major compound excreted in the urine, along with lower levels of an oxidation product (4-chloro-2-hydroxymethyl-phenoxyacetic acid [HMCPA]) and trace amounts of the glycine conjugate (Lappin et al., 2002). In dogs, the parent compound was also present in the urine, but at lower levels than in the rat. In addition, three metabolites were recovered in the urine: the glycine conjugate, at higher levels than in the rat, and, to a lesser extent, HMCPA and a taurine conjugate (Lappin et al., 2002).

Faecal elimination was a minor route for both species; however, dogs had a higher proportion of MCPA in the faeces compared with rats. Radioactivity was not detected in expired air of rats orally dosed with [¹⁴C]MCPA at 5 mg/kg bw (van Ravenzwaay et al., 2004).

In human volunteers given MCPA at 0.015 mg/kg bw, an average of 40% of the given dose was excreted in the urine during the first 24 hours (Kolmodin-Hedman et al., 1983). In another study, volunteers given 5 mg of MCPA excreted 50% in the urine within 48 hours and 55% within 96 hours; by the fifth day, the concentration in the urine was below the detection limit (Fjeldstad and Wannag, 1977). No attempt to analyse metabolites were seen in either human study, nor were the doses radiolabelled using [¹⁴C]MCPA.

In a comparison review of metabolism studies in rats, dogs and humans, Timchalk (2004) showed that dogs had a longer plasma half-life and slower elimination than rats and humans, which resulted in a substantially higher body burden of MCPA, at comparable doses, than in other species. In previous studies with organic acids, the dog had a more limited capacity than other species to excrete organic acids via the kidney. The authors suggested that the following two mechanisms may be responsible for this decrease in renal clearance: saturation of renal secretion and increased renal tubule reabsorption. These differences in the pharmacokinetics of MCPA and other related organic acids between dogs and other species suggest that the use of dog toxicity data for determining human health risk may not be appropriate.

9.0 Health effects

9.1 Effects in humans

The lowest published lethal oral dose for MCPA in humans is 814 mg/kg bw (RTECS, 2005). Symptoms of acute exposure to large doses of MCPA have been reported as a result of poisoning from accidental ingestion and accidental exposure during manufacturing or application in the field. The symptoms include fatigue, weakness, anoxia, nausea, vomiting and diarrhoea, lowering of the blood pressure, body temperature disturbance, progressive hypotension, ataxia, neuromuscular irritability and convulsion (Popham and Davis, 1964; Johnson and Koumides, 1965; Jones et al., 1967; Palva et al., 1975; Bovey, 1980b; Timonen and Palva, 1980; U.S. EPA, 1984).

Various epidemiological studies have been conducted with phenoxy herbicides in Canada, the United States, Australia, New Zealand and several European countries. Most epidemiological studies conducted to date have dealt with multiple exposures to various chlorophenoxy herbicides, including principally 2,4-D and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), and to other pesticides, raw materials, intermediates and processing chemicals. It has been reported that some phenoxy herbicides, such as 2,4,5-T, were contaminated by dioxins and furans during production, but MCPA was not shown to be contaminated with dioxin (Wiklund et al., 1988; Eriksson et al., 1990; Mannetje et al., 2005). Controversy exists as to whether the presence of dioxin increased the risk of certain cancers. Cases of soft tissue sarcoma (STS), non-Hodgkin's lymphoma (NHL) and Hodgkin's disease have been associated with phenoxy herbicides, including those contaminated with dioxin; however, results were not consistent (Mannetje et al., 2005).

Some of these epidemiological studies have included MCPA as part of the repertoire of herbicides examined (Hardell and Sandstrom, 1979; Eriksson et al., 1981; Hardell et al., 1981; Becher et al., 1996; Vineis et al., 1986, 1991; Wiklund et al., 1987, 1988, 1989; Eriksson et al., 1990; Sarraci et al., 1991; Bueno de Mesquito et al., 1993; Lynge, 1998); however, very few studies report outcomes specific to MCPA (and related compounds).

A population-based case-control study in northern and central Sweden investigated the potential association between exposure to a group of several classes of pesticides including MCPA and the risk of NHL. Male cases (404) with NHL were selected during 1987-1990, along with twice as many controls. The authors found that among the pesticides, herbicide use was marginally associated with NHL, with an odds ratio (OR) of 1.6 and a 95% confidence interval (CI) of 1.0-2.5; however, the sample size was small (61 cases and 81 controls). Further analysis, looking at subjects exposed to specific classes of herbicides, showed that the phenoxyacetic acids group predominated, with an OR of 1.5 (CI = 0.9-2.4), which was not significant. However, among the phenoxyacetic acid group, MCPA showed an OR of 2.7 (CI = 1.0-6.9). Because of the small number of exposed cases and controls for MCPA (12 cases and 11 controls), not much reliance can be placed on the results (Hardell and Eriksson, 1999).

Two nested case-control studies looking at STS and NHL were conducted within an international cohort of workers exposed to phenoxy herbicides, chlorophenols and dioxin, as well as other pesticides in the workplace (Kogevinas et al., 1995). Results showed an excess risk of STS for exposure to any phenoxy herbicide (OR = 10.3; CI = 1.2-90.6; 10 exposed cases of STS were observed vs. 30 controls) and to each of the three major classes of phenoxy herbicides, including the class of MCPA (MCPA/MCPP/MCPB; OR = 11.3; CI = 1.3-98; 10 exposed cases vs. 29 controls). The association for NHL was weaker than those observed for STS; no excess risk was strongly associated with any of the exposures. According to the authors, it is complicated to evaluate the independent effect of each herbicide or contaminant on cancer risk, since workers are rarely exposed to a single herbicide. The authors found no specific association between risk and those herbicides contaminated with dioxin.

A cohort study was conducted in Denmark on the health effects related to potential herbicide exposure in 4461 workers (3390 males and 1071 females) working between 1947 and 1993 in two phenoxy herbicide production facilities. MCPA, 2-(2,4-dichlorophenoxy)propanoic

acid (2,4-DP or dichlorprop) and MCPP were the main herbicides produced in these facilities, but other compounds, such as dyes and pigments, were also manufactured (Lyngge, 1993, 1998). A non-significant twofold risk of STS was observed in persons potentially exposed to phenoxy herbicides compared with the Danish population; four cases were observed compared with 1.68 expected cases (standardized incidence ratio = 2.38; CI = 0.7–6.1). No excess of NHL was observed among workers potentially exposed to phenoxy herbicides compared with the Danish population. The overall cancer risk was found to be similar for both the Danish population and workers. However, the contribution of MCPA could not be determined due to multiple exposure. The authors suggested that their findings continue to suggest a possible association between exposure to MCPA and exposure to other related phenoxy herbicides, such as MCPP and 2,4-DP. Previous Swedish case-control studies with phenoxy herbicides by Eriksson et al. (1981) and Hardell et al. (1981) suggested a possible association (i.e. an increased risk) between STS and exposure to phenoxy herbicides as well as chlorophenols and their contaminants.

In another cohort study (1947–1975), mortality and cancer incidences were examined in 5754 workers from a British factory that manufactured, formulated and sprayed principally MCPA, but also other agricultural chemicals during that same period (Coggon et al., 1986). The overall mortality as well as mortality from cancer was less than expected from national rates; however, when the rural correction factor was applied, the deficit of deaths from cancer became a slight excess but was not statistically significant. Only one death from STS was observed in this study, compared with the expected number of 0.9 in the complete cohort and 0.6 in workers potentially exposed to phenoxy acids. Mortalities from Hodgkin's disease and NHL were less than expected from the national rates. The authors concluded that "if there is a hazard of STS due to MCPA, then the risk is less than suggested by earlier studies of 2,4,5-T and 2,4,5-trichlorophenol, and it is small in absolute terms."

Because of the small size of most of the cohorts, not much reliance could be placed on the results, whether positive or negative.

Although several epidemiological studies were conducted on the reproductive and developmental outcomes of pesticides, only a few included MCPA and are reported below.

A study was conducted to analyse the effect of pesticide exposure on the risk of spontaneous abortion in an Ontario farm population (Arbuckle et al., 1999). A questionnaire was used to obtain information from 2110 women on 3936 pregnancies, including 395 spontaneous abortions. Preconception (four-month period from three months before conception to the calendar month of conception) and post-conception (four-month period from calendar month of conception to the end of the first trimester) exposure windows were examined separately, in addition to differentiating between early (<12 weeks) and late (12–19 weeks) spontaneous abortions for these same windows of exposure. Results showed a slight increase in risk of early abortions for preconception exposure to any phenoxyacetic acid herbicides (adjusted OR = 1.1; CI = 0.6–1.9). However, when restricted to early abortions, the adjusted OR increased to 2.5 (CI = 1.0–6.4); in contrast, the adjusted OR for late abortions decreased to 0.4 (CI = 0.2–1.0). When the analysis accounted for the use of protective equipment or clothing in male applicators exposed to a phenoxy herbicide, the OR (for all spontaneous abortions or for early abortions subgroup) was less than 1 in males reporting the use of such equipment/clothing. In contrast, it

was considerably higher in the early spontaneous abortion subgroup when males failed to use the protective equipment/clothing while being exposed. When the analysis was restricted to exposure to MCPA, the results showed no elevated risk of preconception exposure for all gestational ages; the adjusted OR was 0.8 (CI = 0.4–1.7). In contrast, the adjusted OR for MCPA for early abortions increased to 2.3 (CI = 0.8–6.5), whereas the adjusted OR for late abortions decreased to 0.4 (CI = 0.1–1.2). Further analysis suggested that if preconception exposure to MCPA occurred for one month or more, the adjusted OR increased to 5.4 (CI = 1.7–17.3) for early abortions; the OR was less than 1 for late abortions for MCPA, as well as for all the other phenoxy herbicides analysed.

Limitations of the study (Arbuckle et al., 1999) include small sample size (e.g. the unexposed group, MCPA subgroup), memory recall (quality of information limited by the memory of the respondents and the length of recall for pesticide usage generally greater than 10 years) and no detailed information on dose used and amount of time spent applying pesticides. According to the authors, the findings of the study suggest that there may be a preconceptual effect with MCPA and phenoxy herbicides in adverse pregnancy outcomes, particularly early spontaneous abortions (which may suggest a male-mediated effect due to the higher risk seen as a result of not using protective equipment or clothing). However, given the limitations of the study, additional studies are needed to confirm these findings.

In order to evaluate the possibility that offspring of agricultural pesticide applicators might have increased risks of birth anomalies, Garry et al. (1996) compared the births (n = 4935) of state-licensed, private pesticide applicators (n = 34 772) in Minnesota between 1989 and 1992 with those of the state's birth registry (containing 210 723 live births within the same time period). The birth defect rate for all birth anomalies was significantly increased in children born to private applicators. The pattern of excess frequency of birth anomalies was analysed by region, pesticide use, season and male/female sex ratio. Analyses of the various regions showed western Minnesota, a major growing region for wheat, sugar beet and potato, as having the highest rate of birth anomalies per 1000 live births. Data for MCPA and 2,4-D were pooled because of their similarities of chemical structure, spectrum of biocidal activity and crop use, although 2,4-D was used more than MCPA. In the case of 2,4-D and MCPA, the frequency of anomalies in high-use areas was significantly increased (OR = 1.86; CI = 0.69–2.05) for combined births with central nervous system, circulatory/respiratory, urogenital and muscular anomalies and for all anomalies (OR = 0.51; CI = 1.40–1.62). No individual data were available for MCPA in this cohort study (Garry et al., 1996).

Very few epidemiological studies have been conducted with regards to reproductive and developmental outcomes with MCPA, and those that have been conducted are limited by small sample sizes. Because workers may be exposed to multiple phenoxy herbicides and other compounds, and as well possibly to contaminants such as dioxin, it is difficult to isolate exposure to MCPA alone.

Another key limitation of the studies above was that there was only potential for exposure to have occurred, and none of the studies had any direct measurements of exposure for the individuals in the study.

9.2 Effects on laboratory animals and *in vitro* test systems

9.2.1 Acute toxicity

Details on the available acute oral toxicity studies are provided in Table 3.

Table 3. Summary of acute oral toxicity studies

Forms of MCPA	Oral LD ₅₀ (mg/kg bw) ^a		
	Rats	Mice	Guinea pigs
MCPA acid	700–1383 ^{1,2,3,4}	439–800 ^{5,6}	700 ⁵
MCPA-EHE	2235 ³		
MCPA-DMAS	1200–1867 ^{2,3}	550 ⁷	
MCPA sodium salt	3500 ³	560 ⁷	

^a References: 1. Ben-Dyke et al. (1979); 2. Rowe and Hymas (1954); 3. U.S. EPA (2003); 4. U.S. EPA (1990); 5 RTECS (2005); 6. Weed Science Society of America (1989); 7. Gurd et al. (1965).

9.2.2 Short-term exposure studies

Short-term studies were conducted on the effects of MCPA, MCPA-DMAS and MCPA-EHE in mice, rats and dogs. Adverse health effects were noted in the liver and kidney. In general, dogs appear to be more sensitive than rats to the adverse effects of MCPA after repeated exposure. According to the U.S. EPA (2003, 2004e), this increased sensitivity appears to be a consequence of reduced capacity in the elimination of MCPA in dogs relative to rats.

In a 28-day oral range-finding toxicity study, MCPA (94.8%) was administered to mice (4–6 per sex per dose) in the diet at dose levels of 0, 100, 300, 900 or 2700 ppm (equivalent to 0, 19.1–22.0, 56.3–67.7, 173.4–184.8 and 453.7–820.1 mg/kg bw per day for males and 0, 20.7–26.2, 69.2–73.9, 193.4–223.9 and 442.3–956.3 mg/kg bw per day for females). Observed effects at the highest dose in both sexes included motor disturbances, significant cumulative body weight loss, hepatotoxicity (increased serum alanine aminotransferase [ALT] and alkaline phosphatase [ALP] activities, increased liver weight and related histopathological findings), spleen effects (decreased mean spleen weights, gross observation of involution, increased neutrophil counts and decreased lymphocyte counts) and decreased kidney weights. High-dose males had decreased mean testicular weight with histopathological findings of testicular atrophy, whereas females had atrophy of the ovaries and uterine glands. At necropsy, high-dose animals were shown to be cachectic (state of general ill health characterized by malnutrition, weakness and emaciation). Liver effects (cloudy swelling) were observed in one mid-dose female. The lowest-observed-adverse-effect level (LOAEL) for female mice is 900 ppm (193.4–223.9 mg/kg bw per day) based on cloudy swelling in the liver, and the no-observed-adverse-effect level (NOAEL) is 300 ppm (69.2–73.9 mg/kg bw per day). In male mice, the LOAEL is 2700 ppm (453.7–820.1 mg/kg bw per day), and the NOAEL is 900 ppm (173.4–184.8 mg/kg bw per day) (Kirsch, 1985a). The highest dose used in this study was within range of the LD₅₀ for mice, which may explain the significant effects at this dose.

Effects on the kidney were also noted in 90-day studies in rats. Technical-grade MCPA (94.8%) was administered orally to rats (15 per sex per dose) at dose levels of 0, 50, 150 or

450 ppm (equivalent to 0, 3.6, 10.9 and 32.6 mg/kg bw per day for males and 0, 4.0, 12.1 and 35.8 mg/kg bw per day for females). At 450 ppm, an increase in creatinine values in the plasma of females was observed. At the same dose, decreases in cholesterol and calcium values in the males were observed. The authors mentioned that these effects are difficult to evaluate since they occur only in males. Also, an increase in absolute and relative kidney weights in males was observed. At 150 ppm, increased absolute kidney weights (108% of controls) were noted ($p < 0.05$). No changes were observed at the lowest dose (50 ppm). Based on the authors, the NOAEL lies between 50 and 150 ppm and is based on renal impairment related to calcium and kidney weight changes, but no histopathological alterations were detected to correlate this increase in kidney weight (Kirsch, 1985b).

In a combined subchronic toxicity and neurotoxicity study, MCPA (94.2%) was administered to groups of 15 male and 15 female Wistar rats for three months at dietary concentrations of 0, 50, 500 or 2500 ppm (equivalent to 0, 3, 34 or 177 mg/kg bw per day for males and 0, 4, 42 or 188 mg/kg bw per day for females) (Mellert et al., 1994). At the highest dose, a significant decrease in body weight was observed in both sexes beginning on day 7 of the administration period and continuing until the end of the study. At the highest dose, in both sexes, a significant decrease in haematological parameters (red blood cells, haemoglobin and haematocrit), a significant increase in liver enzymes (ALT, ALP and aspartate aminotransferase [AST]) and alteration of hepatocytes, characterized by cytoplasmic eosinophilia and granular cytoplasm in the liver, were observed. In addition, a higher incidence/grading of foam cell accumulations in the lung and myeloid atrophy of the haematopoietic marrow were seen in both sexes. In high-dose males, a decrease in testes weights, testicular atrophy and atrophy of the seminal vesicles and prostate, aspermia or oligospermia in the epididymides were observed. For the neurotoxicity evaluation, functional observatory battery and motor activity assessments were performed on 10 animals per group per sex prior to the treatment and on treatment days 22, 50 and 85. Effects observed at 2500 ppm were a decreased value of hindlimb grip strength in females on day 85; decreased foot splay test values ($p < 0.02$) in males on day 22; and reduced values ($p < 0.02$) of forelimb grip strength in males on day 50. No significant treatment-related changes were seen at the two lowest doses. The U.S. EPA set the NOAEL at 500 ppm (34 and 42 mg/kg bw per day for males and females, respectively) and the LOAEL at 2500 ppm (177 and 188 mg/kg bw per day for males and females, respectively), based on decreased body weight and body weight gains, liver pathology, changes in clinical chemistry and haematological parameters, testicular atrophy and changes in motor activity.

U.S. EPA (2004e) considered MCPA “a neurotoxicant based on clinical signs of neurotoxicity” based on the study by Mellert et al. (1994) and an acute neurotoxicity study conducted with rats (U.S. EPA, 2003). Additional studies (acute and subchronic oral studies) conducted with MCPA-DMAS and MCPA-EHE and rats also showed adverse neurotoxic effects, with MCPA-EHE being the most toxic of the three forms of MCPA (U.S. EPA, 2004e). Neurotoxic effects seen in these studies included impaired coordination and gait, reduced motor activity, ataxia (muscle incoordination), decrease in arousal and reduced hind grip strength.

MCPA was administered in the diet to Charles River rats (10 per sex per dose) at dose levels of 0, 4, 8 or 16 mg/kg bw per day for 90 days. No treatment-related effects were observed

other than a significant increase in both relative and absolute kidney weight for males at the high dose, with moderate increases at the other two treatment levels in males. There were no treatment-related histopathological alterations in either sex at any dose level tested. The no-observed-effect level (NOEL) for increased kidney weights in rats was 8 mg/kg bw per day (Holsing and Kundzin, 1970).

In two separate 90-day studies, technical MCPA (94.8%) was given in the diet to beagle dogs (four per sex per dose) at dose levels of 0, 3, 12 or 48 mg/kg bw per day and at dose levels of 0, 0.3, 1 or 12 mg/kg bw per day, respectively. Severe toxicity and mortality were seen at the highest dose (48 mg/kg bw per day): one female died during week 5, and the remaining three females and three out of four males were sacrificed moribund during weeks 7–8. A decrease in kidney and liver function, characterized by an increase in blood urea, ALT and creatinine levels, was noted at 3 mg/kg bw per day and above. A NOAEL of 1 mg/kg bw per day was reported in this study, and a LOAEL of 3 mg/kg bw per day based on impaired renal function, without histopathological change, was also reported. This lack of histopathological change probably indicates that the effects are reversible (Reuzel and Hendriksen, 1980).

In a one-year study, male and female beagle dogs (six per sex per dose) were administered technical-grade MCPA (94.8%) in the diet at doses of 0, 6, 30 or 150 ppm (equivalent to 0, 0.22, 1.02 or 5.32 mg/kg bw per day in males and 0, 0.21, 1.02 or 5.12 mg/kg bw per day in females) (Hellwig, 1986). No treatment-related clinical signs or deaths were seen during the study. In the high-dose males, mean cumulative body weight gain was 77% of controls for the 1- to 364-day interval. At the high dose (both sexes), statistically significant increases were observed in serum creatinine concentration (at 13, 26 and 52 weeks) and serum ALT and AST activities at most sampling intervals. Gross necropsy showed dark brown discoloration of the kidney in four of six mid-dose females, in four of six high-dose males and in all high-dose females. Histopathological changes were observed in the kidney and included a dose-related increase in severity in kidney pigment deposition in the proximal tubular epithelium in all females and three of the six males at the highest dose and in four females at the middle dose. No treatment-related effects were seen at the low dose (Hellwig, 1986). Based on this study, the U.S. EPA (2003a) established a NOAEL of 6 ppm (0.22 and 0.21 mg/kg bw per day for males and females, respectively) and a LOAEL of 30 ppm (1.02 mg/kg bw per day in both sexes) based on nephrotoxicity (evident as gross necropsy and hispathological changes).

Two subchronic studies were also conducted with the other forms of MCPA. MCPA-DMAS (99.9% active ingredient) was administered in beagle dogs at dietary concentrations of 0, 20, 80 or 360 ppm (equivalent in the males to 0, 0.6, 2.4 and 10.9 mg/kg bw per day and in the females to 0, 0.7, 2.9 and 12.8 mg/kg bw per day) for a period of 110–118 days (Hellwig et al., 1995a). At the highest dose, both sexes had increases in creatinine, urea and ALT levels, whereas males had increases in partial thromboplastin times. At 80 ppm, increases in creatinine and urea levels were observed in both sexes, whereas increases in ALT levels and partial thromboplastin times were observed in females. Increases in ALT levels correlated with a subacute to chronic interstitial inflammation of the liver. No significant changes were observed at the lowest doses in either sex. The U.S. EPA (2003) set the LOAEL at 80 ppm (2.4 mg/kg bw

per day) based on histopathology changes (increases in a subacute to chronic interstitial inflammation of the liver), haematology and clinical chemistry, and the NOAEL is 20 ppm (0.6 mg/kg bw per day) No statistical details were provided in the review.

Beagle dogs were administered MCPA-EHE (93.5% active ingredient) at dietary concentrations of 0, 20, 80 or 360 ppm (equivalent in the males to 0, 0.6, 2.5 and 11.1 mg/kg bw per day and in the females to 0, 0.7, 2.8 and 12.7 mg/kg bw per day) for a period of 110–118 days. The administered doses are equivalent to 0, 0.4, 1.6 and 7.1 mg/kg bw per day in males and 0, 0.4, 1.8 and 8.1 mg/kg bw per day in females as MCPA acid. At 360 ppm, both sexes had increases in clinical chemistry parameters (creatinine, urea and ALT levels), partial thromboplastin times, relative and absolute thyroid weights and relative ovary weights (females). Increases in ALT levels correlated with a subacute to chronic interstitial inflammation of the liver. At 80 ppm, both sexes had increases in creatinine and urea levels, whereas females had increases in ALT levels. No treatment-related changes were observed at the lowest dose in either sex. U.S. EPA set the LOAEL for systemic toxicity in beagles dogs is 80 ppm (1.6 mg/kg bw per day as MCPA acid) based on changes in clinical chemistry parameters (increases in creatinine, urea and ALT levels). The NOAEL is 20 ppm (0.4 mg/kg bw per day as MCPA acid) (Hellwig et al., 1995b). No statistical details were provided in the review.

9.2.3 Long-term exposure (chronic toxicity) and carcinogenicity

Long-term exposure and/or carcinogenicity studies with MCPA were conducted in rats and mice. No evidence of carcinogenicity was seen in either species; however, both rats and mice showed evidence of adverse effects in the liver and kidney similar to those observed in the subchronic studies, and at comparable dose levels. No long-term study in dogs was located.

Wistar rats (50 per sex per dose) received MCPA (94.8%) in their diet for two years at dose levels of 0, 20, 80 or 320 ppm (corresponding to 0, 1.1, 4.4 or 17.6 mg/kg bw per day in males and 0, 1.4, 5.7 or 23 mg/kg bw per day in females) (Kirsch, 1988; Bellet et al., 1999). Two satellite groups (n = 10–15 per sex per dose per group) were also studied. No treatment-related effects were seen at 20 ppm. Changes in clinical chemistry in the absence of histopathology were seen at 80 ppm in both sexes. Effects at the high dose included a minimal decrease in body weight in males (day 14 and beyond; $p < 0.05$) and a small but sporadic increase in body weight in females ($p < 0.05$). Clinical chemistry parameters showed a significant decrease in triglycerides in males at weeks 78 and 104 and an elevation of ALT levels in females at weeks 52, 78 and 104. At the high dose, gross and microscopic pathological changes in male rats indicated a chronic progressive nephropathy, as seen by an increase in the retraction and glandular surface of the kidney. At the doses tested, there was no treatment-related increase in tumour incidence when compared with controls. The systemic NOEL was 20 ppm (1.1 mg/kg bw per day in males and 1.4 mg/kg bw per day in females). U.S. EPA (2003a) set the NOAEL for systemic toxicity at 80 ppm (4.4 mg/kg bw per day in males and 5.7 mg/kg bw per day in females) and the LOAEL at 320 ppm (17.6 mg/kg bw per day in males and 23 mg/kg bw per day in females) based on hepatotoxicity (increased ALT levels in females) and kidney effects in

males. However, PMRA (2005b, 2006) found that this study did not test high enough doses to reach a maximum tolerated dose (MTD) and, as a result, was not adequate to fully assess the oncogenic potential of MCPA.

B6C3F1 mice (50 per sex per dose) received MCPA (94.6%) for two years in the diet at dose levels of 0, 20, 100 or 500 ppm, corresponding to 0, 3.2, 15.7 or 79.5 mg/kg bw per day in males and 0, 3.9, 19.5 or 97.2 mg/kg bw per day in females (Kuhborth et al., 1988; Bellet et al., 1999). One satellite group (n = 10 per sex per dose) was used for haematological examination. Body weight changes were observed in both sexes during the course of the study; however, the final body weights in males and females were not statistically different from those of the control group. The kidney was the only organ with treatment-related lesions. Kidney weights were statistically significantly higher in high-dose females. The kidney lesions included increased incidences of intratubular calcification and tubular hyaline-proteinaceous casts in high-dose males and females. In the mid- and high-dose females, there was a non-dose-related increase in the incidence of slight renal hyperplasia (7/50 and 4/50, respectively) compared with controls and the low dose, at which none was observed. In addition, there was an increased incidence of renal tubular epithelial focal hyperplasia in high-dose males (not specified if statistically significant). The author set the systemic NOEL at 100 ppm (15.7 mg/kg bw per day in males and 19.5 mg/kg bw per day in females). In a 2003 review, the U.S. EPA set the systemic NOAEL in males at 100 ppm (15.7 mg/kg bw per day) and the LOAEL at 500 ppm (79.5 mg/kg bw per day) based on histopathological changes in the kidneys. In female mice, U.S. EPA (2003) set the systemic NOAEL at 20 ppm (3.9 mg/kg bw per day), and the LOAEL at 100 ppm (19.5 mg/kg bw per day), based on renal hyperplasia, which was considered toxicologically significant at that dose (Kuhborth et al., 1988; Bellet et al., 1999).

9.2.4 Mutagenicity/genotoxicity

Based on the weight of evidence, MCPA acid and its other forms are not considered to be of genotoxic concern *in vivo*. As outlined below, MCPA was not mutagenic in the majority of bacterial and mammalian cell gene mutation assays reported and did not induce DNA damage in the SOS chromotest. In addition, no *in vivo* evidence was found to suggest clastogenicity in bone marrow, and sister chromatid exchange tests gave negative or weakly positive results.

With the exception of one positive and two weakly positive results (reviewed in Elliott, 2005), MCPA acid was negative in *in vitro* bacterial assays using *Salmonella typhimurium* (several strains) (Räsänen et al., 1977; Nishimura et al., 1982; Moriya et al., 1983; Kappas, 1988; Jones et al., 1993a), and both MCPA-DMAS and MCPA-EHE were also negative (Jones et al., 1992, 1993b; Elliot, 2005).

Negative results with MCPA acid, MCPA-DMAS and MCPA-EHE were observed in mammalian cell mutation assays (CHO HPRT with and without S9) (Adams et al, 1993a,b,c; Elliot, 2005).

One positive result was obtained with MCPA acid in a mitotic recombination assay with *Aspergillus nidulans* (Kappas, 1988). A weakly positive result was found in the yeast mutagenicity test in *Saccharomyces cerevisiae* with MCPA acid (Zetterberg, 1978, 1979).

Negative results with MCPA acid were observed in an SOS chromotest (*Escherichia coli* PQ37 with and without S9) (Mersch-Sundermann et al., 1989).

Chromosomal aberrations *in vitro* were detected in human peripheral lymphocytes (with and without S9) at high cytotoxic concentrations with MCPA acid and MCPA-DMAS, but not with MCPA-EHE (Akhurst et al., 1993a,b,c; Elliot, 2005).

In vivo chromosomal aberration assays with MCPA acid were negative in the Chinese hamster for doses up to 1200 mg/kg bw administered by oral gavage (Gelbke and Engelhardt, 1985a,c), whereas sister chromatid exchange assays were either negative or weakly positive at the same dose level and for the same route of exposure (Linnainmaa, 1984; Mustonen et al., 1989; Gelbke and Engelhardt, 1985b,c). Negative results were observed in *in vivo* bone marrow micronucleus assays with MCPA acid, MCPA-DMAS and MCPA-EHE in which mice were given a 384 mg/kg bw dose by oral gavage (Proudlock et al., 1993a,b,c).

This overall lack of genotoxicity following MCPA exposure is consistent with the lack of carcinogenicity in animals (Elliott, 2005).

9.2.5 Reproductive and developmental toxicity

Developmental effects in the presence of maternal toxicity were seen with rats when dosed with MCPA, MCPA-DMAS and MCPA-EHE. No developmental effects in the presence of maternal toxicity were seen in the rabbit. No reproductive effects were seen in a two-generation study involving rats.

MCPA (94.22%) was administered daily by gavage to pregnant female Wistar rats on days 6–15 of gestation at dose levels of 0, 15, 60 or 120 mg/kg bw per day (Hellwig and Hildebrand, 1993a). The LOAEL for maternal toxicity was 120 mg/kg bw per day, based on treatment-related decreases in body weight, body weight gain and food consumption during treatment and for the remainder of the gestation period. The LOAEL for development toxicity was 120 mg/kg bw per day, based on decreased placental and fetal body weights and on an increase in the number of fetuses with skeletal retardation. The NOAEL for maternal and developmental toxicity was 60 mg/kg bw per day.

MCPA (94.22%) was administered once daily by gavage to Himalayan rabbits on days 7–19 of gestation at dose levels of 0, 15, 30 or 60 mg/kg bw per day (Hellwig and Hildebrand, 1993b). At 60 mg/kg bw per day, treatment-related decreases were noted in maternal body weight, body weight gain and food consumption. The LOAEL for maternal toxicity was 60 mg/kg bw per day based on significant decreases in body weight, body weight gain and food consumption during the treatment period. The NOAEL for maternal toxicity was 30 mg/kg bw per day. The NOAEL for developmental toxicity was equal to or greater than the highest dose tested, 60 mg/kg bw per day. No developmental LOAEL was determined.

MCPA-DMAS (78.2%) was administered to 17–25 pregnant CD rats per group by gavage in 0.5% methylcellulose at doses of 0, 18.5, 62 or 185 mg/kg bw per day (equivalent to doses of 0, 15, 50 and 150 mg MCPA free acid/kg bw per day) on gestation days 6–19, inclusive (Cappon, 1999b). Maternal toxicity, consisting of clinical signs, and mortality of one rat were observed in high-dose females. When adjusted to account for gravid uterine weights, the body weight in high-dose females was comparable to the controls. Gravid uterine weights were

significantly reduced in the high-dose group compared with the controls. Complete litter resorption occurred in five high-dose dams; this post-implantation loss was significantly higher than controls (41.8% compared with 3.8% for the controls). The mean fetal body weight in the high-dose group was significantly less than the controls (2.1 g compared with 3.5 g for the controls). An increase in the incidence of major external and/or skeletal malformations was seen in the fetuses of the 150 mg/kg bw per day groups (11/17 litters) compared to controls (3/25 litters). In addition, there was an increase in the incidence of skeletal variations at the high dose compared with controls. The LOAEL for maternal toxicity was 150 mg MCPA acid/kg bw per day based on mortality and clinical signs, with a NOAEL of 50 mg/kg bw per day as MCPA acid. The U.S. EPA (2003) set the LOAEL for developmental toxicity was 150 mg/kg bw per day as MCPA acid based on increased resorptions, decreased fetal body weight and external and skeletal malformations/ variations. The NOAEL for developmental toxicity was set at 50 mg/kg bw per day as MCPA acid (U.S. EPA, 2003).

MCPA-EHE (99.9%) was administered to 25 pregnant CD rats per group by gavage in 0.5% methylcellulose at doses of 0, 23.5, 62.7 and 188 mg bw per day (equivalent to 0, 15, 40 or 120 mg/kg bw per day MCPA acid) on gestation days 6–19, inclusive (Cappon, 1999a). Food consumption was significantly reduced in high-dose females during treatment (83–91% of control group values). As a result, mean net body weight and mean net body weight gain (when adjusted to account for gravid uterine weights) were statistically decreased by 5% and 28%, respectively, compared with controls. Complete litter resorption was seen in two high-dose dams, and there were corresponding slight (but not significant) increases in post-implantation loss, total resorptions and early resorption. At the highest dose, mean fetal weight was significantly decreased compared with controls (2.5 vs. 3.7 g for controls). Significant increases in the incidence of several skeletal variations, including unossified sternbrae and bent ribs, were observed at this dose. The incidence of an ossified cervical centrum number 1 was statistically decreased at 62.7 and 188 mg/kg bw per day (13.7, 12.2, 4.6 and 0.6% per litter for the control, low-, mid- and high-dose groups, respectively). The U.S. EPA (2003) set LOAEL for developmental toxicity at 188 mg/kg bw per day as MCPA-EHE (120 mg/kg bw per day for MCPA acid) based on total litter resorptions, decreased fetal weight and altered growth, and the NOAEL for developmental toxicity was 2.7 mg/kg bw per day as MCPA-EHE (40 mg/kg bw per day for MCPA acid). The LOAEL for maternal toxicity was 188 mg/kg bw per day as MCPA-EHE (120 mg/kg bw per day as MCPA acid) based on reduced body weight gains and reduced food consumption (U.S. EPA, 2003). The NOAEL for maternal toxicity was 63.7 mg/kg bw per day as MCPA-EHE (40 mg/kg bw per day as MCPA acid).

No reproductive effects were observed when male and female albino rats (n = 25 per sex per dose per generation) were exposed to MCPA (94.8%) in the diet at dose levels of 0, 50, 150 or 450 ppm (corresponding to 0, 2.5, 7.5 or 22.5 mg/kg bw per day) for two generations (Bellet et al., 2001). There were no treatment-related effects on mean live litter sizes, sex ratios at birth or pup survival of either litter of the treated groups of either generation. At the high dose (450 ppm), statistically significant differences were noted in body weight gain for both male pups

(F_{1a}) and female pups (F_{1a} and F_{1b}) and body weight and body weight gains for both male and female pups from F_{2a} and F_{2b}. No significant effects on the reproductive function for either generation (both sexes) were observed (MacKenzie, 1986; Bellet et al., 2001).

In this study, the NOEL for reproductive function in rats administered MCPA was determined to be 450 ppm (approximately 22.5 mg/kg bw per day). The NOEL for general systemic toxicity based on body weight in adult animals in the F_{1b} generation and for effects on the offspring of the F_{1b} generation (based on reduced pup weight and pup weight gains) was 150 ppm (approximately 7.5 mg/kg bw per day). Based on the results of the study, MCPA is not a reproductive toxicant for rats, which was confirmed by the U.S. EPA (2003a). However, PMRA (2006) has determined that the MTD had not been achieved in this study. According to PMRA (2006), MCPA showed a potential for increased sensitivity of the young in the absence of maternal toxicity due to decreases seen in body weight and body weight gain of the pups from both generations during lactation.

The U.S. EPA (2004e) reported, because of their concerns with neurotoxicity in the acute and subchronic studies with the various forms of MCPA, that the currently available data supported the need to perform a developmental neurotoxicity study, as recommended by the Hazard Identification Assessment Review Committee report.

10.0 Classification and assessment

Based on inadequate data from epidemiological studies and the lack of adequate animal studies, Health Canada classifies MCPA as Group VI.A (unclassifiable with respect to carcinogenicity in humans), as defined in Health Canada (1994). IARC (1983) has evaluated MCPA and concluded that “no adequate data were available to evaluate the carcinogenicity of MCPA to experimental animals. The data on humans were also considered to be inadequate. The available data are insufficient to evaluate the carcinogenicity to humans of MCPA alone.” IARC (1986) also evaluated the family of chlorophenoxy herbicides and concluded that “there is limited evidence that occupational exposures to chlorophenoxy herbicides are carcinogenic to humans.” The U.S. EPA (2003, 2004c,e) has classified MCPA as “not likely to be carcinogenic to humans,” based on the lack of evidence of carcinogenicity in mice and rats.

Although a limited number of epidemiological studies have been conducted on the effects of MCPA and related chlorophenoxy compounds, the evidence for carcinogenicity and reproductive effects remains inconclusive. Available studies have dealt with multiple exposures to mixtures of chlorophenoxy herbicides, other pesticides as well as other organic compounds. The results were difficult to interpret, and the studies were considered limited for several reasons, such as the lack of consideration of confounding factors and small sample size.

There was no evidence of carcinogenicity in the long-term mouse or rat studies using MCPA acid. However, PMRA (2005b, 2006) has indicated that the long-term rat study did not achieve the MTD and that it was not considered adequate for assessing the overall potential for carcinogenicity. Tests for genotoxicity and mutagenicity were largely negative.

Subchronic studies showed that dogs were more sensitive to the effects of MCPA and related compounds than rats or mice; the NOAEL was at least 10 times lower in dogs than in rats or mice based on chronic and subchronic studies. Unfortunately, no long-term studies on dogs

were located in the literature. The one-year dog study conducted by Hellwig (1986) was selected for the risk assessment. Based on this study, the U.S. EPA (2003a) established a NOAEL of 6 ppm (0.21 and 0.22 mg/kg bw per day for males and females, respectively) for treatment-related changes based on nephrotoxicity (evident as gross necropsy and hispathological changes). This was the lowest NOAEL of all the dog studies. Although Timchalk (2004) did suggest that the dog may not be an appropriate model for use in human health risk assessment, it was decided that the dog study would be appropriate, as the health-based value derived would be protective of human health. Other considerations for choosing this study were based on the appropriateness of the route of exposure (in the diet) and the fact that other short-term studies in rodents also showed kidney effects.

PMRA (2006) proposed a tolerable daily intake (TDI) of 0.0002 mg/kg bw per day for MCPA, based on the NOAEL of 0.22 mg/kg bw per day established for the Hellwig (1986) one-year dog study and using a safety factor of 1000. This is consistent with the NOAEL of 6 ppm determined by U.S. EPA (2003a), corresponding to 0.21 and 0.22 mg/kg bw per day for males and females, respectively.

$$\begin{aligned} \text{TDI} &= \frac{0.22 \text{ mg/kg bw per day}}{1000} \\ &= 0.00022 \text{ mg/kg bw per day (0.22 } \mu\text{g/kg bw per day)} \end{aligned}$$

where:

- 0.22 mg/kg bw per day is the NOAEL in the one-year dog study based on nephrotoxicity endpoints (as calculated by PMRA);
- 1000 is the uncertainty factor ($\times 10$ for intraspecies differences; $\times 10$ for interspecies differences; and $\times 10$ for database deficiency — use of subchronic study, lack of acceptable rat carcinogenicity study and potential sensitivity to the young, as noted in the rat reproduction study).

The maximum acceptable concentration (MAC) for MCPA in drinking water is derived from the TDI as follows:

$$\begin{aligned} \text{MAC} &= \frac{0.22 \text{ } \mu\text{g/kg bw per day} \times 70 \text{ kg} \times 0.20}{1.5 \text{ L/d}} \\ &= 0.002 \text{ mg/L (2 } \mu\text{g/L)} \end{aligned}$$

where:

- 0.22 $\mu\text{g/kg bw per day}$ is the TDI, as derived above;
- 70 kg is the average body weight of an adult;

- 0.20 is the allocation factor — the proportion of the total daily intake of MCPA allocated to drinking water, as opposed to other environmental media (i.e. food, air, soil, consumer products). In the absence of other exposure data, this value is defaulted at 20%;
- 1.5 L/d is the average daily consumption of drinking water for an adult.

11.0 Rationale

MCPA is a commonly used herbicide in Canada. Health Canada classifies MCPA as unclassifiable with respect to carcinogenicity in humans, based on inadequate data from epidemiological studies and the lack of adequate animal studies. This is consistent with the IARC classification. A health-based value of 0.002 mg/L can be established for MCPA in drinking water, based on nephrotoxicity endpoints in the dog.

MCPA is registered for use in Canada for agricultural sites, for fine turf, lawns and sod, in forestry and at industrial sites. Its major applications are in agriculture, where it is used in the production of cereals, canary seeds, legumes and grasses, asparagus, field corn and sweet corn. MCPA is also applied to such agricultural sites, as stubble/summerfallow fields and pastures/rangeland. MCPA is used everywhere in Canada, particularly in the Prairies, and is among the top 10 pesticides sold in Canada.

MCPA is readily measurable in drinking water using a variety of analytical methods, with detection limits below 0.001 mg/L. Full-scale and pilot-scale studies have demonstrated that effluent concentrations of MCPA below 0.0001 mg/L are achievable using a variety of methods.

A MAC of 0.002 mg/L (2 µg/L) is proposed for MCPA in drinking water. As part of its ongoing guideline review process, Health Canada will continue to monitor new research in this area and recommend any change(s) to the Guideline Technical Document that it deems necessary.

12.0 References

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Appendix A: List of acronyms

2,4-D	2,4-dichlorophenoxyacetic acid
2,4-DP	2-(2,4-dichlorophenoxy)propanoic acid (dichlorprop)
2,4,5-T	2,4,5-trichlorophenoxyacetic acid
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANSI	American National Standards Institute
AOC	assimilable organic carbon
AOP	advanced oxidation process
AST	aspartate aminotransferase
bw	body weight
CHO	Chinese hamster ovary
CI	confidence interval
DNA	deoxyribonucleic acid
DOC	dissolved organic carbon
EBCT	empty bed contact time
EPA	Environmental Protection Agency (United States)
GAC	granular activated carbon
GC	gas chromatography
HMCPA	4-chloro-2-hydroxymethyl-phenoxyacetic acid
HPLC	high-performance liquid chromatography
IARC	International Agency for Research on Cancer
LD ₅₀	median lethal dose
LOAEL	lowest-observed-adverse-effect level
MAC	maximum acceptable concentration
MCPA	2-methyl-4-chlorophenoxyacetic acid
MCPA-DMAS	MCPA dimethylamine salt
MCPA-EHE	MCPA 2-ethylhexyl ester
MCPB	4-(2-methyl-4-chlorophenoxy) butyric acid
MCPP	(R)(+)-2-(4-chloro-2-methylphenoxy)-propanoic acid
MRL	maximum residue limit
MS	mass spectrometry
MTD	maximum tolerated dose
NHL	non-Hodgkin's lymphoma
NOAEL	no-observed-adverse-effect level
NOEL	no-observed-effect level
NSF	NSF International
OR	odds ratio
PDA	photodiode array
PMRA	Pest Management Regulatory Agency
S9	metabolic activation

SCC	Standards Council of Canada
SPE	solid-phase extraction
STS	soft tissue sarcoma
TDI	tolerable daily intake
U.S. EPA	United States Environmental Protection Agency
UV	ultraviolet
WHO	World Health Organization

Appendix B: Provincial/territorial cost estimates

Prince Edward Island

Based on the limited likelihood of significant exposure through groundwater, and the fact that treatment on the residential scale, if required, is likely to be both achievable and affordable, no adverse impact of the proposed guideline is anticipated in PEI.

Newfoundland and Labrador

MCPA is, or has the potential to be used in this province. It has been used on forages, and sometimes on golf courses. The standard herbicide mix for lawns in Newfoundland and Labrador, is a combination of 2,4-D, mecoprop and dicamba. Usually that takes care of the lawn weeds. However, MCPA can be used on lawns as well. The overall amount used in Newfoundland and Labrador is not great. This, coupled with the distances between fields/areas which might see an application of MCPA, does not seem to be a matter of concern for this province.

Nova Scotia

Limited drinking water quality data is available in Nova Scotia for MCPA as noted in the technical guideline document. Monitoring in the Thomas Brook Watershed, an agricultural area of Nova Scotia, as part of the PSF National Master Project on Water Quality Surveillance detected MCPA on one occasion in 2005 in surface water at a level of 0.0002 mg/L (0.2 µg/L). MCPA was not detected in any of the other 60 samples (47 surface water; 13 groundwater) taken in 2004 and 2005. Based on the Thomas Brook Watershed results and due to the relatively low use of MCPA in Nova Scotia, as noted on page 6 of technical guideline document, it is not expected that MCPA will be detected above the proposed guideline of 0.002 mg/L (2 µg/L). As such, no cost impact estimates have not been prepared at this time.

New Brunswick

No paragraph submitted.

Quebec

Des suivis réalisés entre 1989 et 1995 par le ministère du Développement durable, de l'Environnement et des Parcs indiquent que les concentrations de MCPA dans 50 réseaux de distribution d'eau potable alimentés en eau de surface, dont près de la moitié en zone agricole, étaient toutes inférieures à 0,07 µg/l. D'autre part, des suivis réalisés par le Ministère entre 1992 et 2004 directement dans des tributaires agricoles ont permis de mesurer le MCPA à des concentrations variant généralement de <0,02 à 4,9 µg/l. Ces tributaires agricoles ne sont pas directement utilisés pour l'approvisionnement en eau potable; ils sont dilués dans des cours d'eau plus importants dans lesquels des installations de production d'eau potable s'approvisionnent. Peu d'impacts sont attendus d'une concentration maximale acceptable de 2 µg/l dans l'eau potable à l'endroit du MCPA au Québec.

Ontario

Review of the available data from the Drinking Water Surveillance Program for the years 2002-2005 inclusive suggests that the adoption of the Canadian Drinking Water Guideline of 2.0 µg/L will have minimal economic impact in Ontario. In Ontario, the highest level of MCPA detected in drinking water sampling surveys over the three years (2003-2005) was 0.066 µg/L.

Manitoba

No paragraph submitted.

Saskatchewan

Given that MCPA is among the top 10 pesticides sold in Canada and Saskatchewan the potential for application of the proposed guideline in Saskatchewan is significant.

In terms of potential application of any future guideline for MCPA in Saskatchewan, as a treatment methodology GAC filtration is sufficient to remove more than 90% MCPA. Some waterworks in the province already employ GAC filtration. Ozonation in combination with GAC will remove more than 95% MCPA. Hence treatment technologies known to provide adequate treatment are available in the event MCPA concentrations are found in excess of the proposed MAC in the future. Costs may be minimal if an affected community needs to retrofit a water treatment facility. Cost estimation of the affected communities in Saskatchewan is not possible or not necessary at this time, since the available MCPA data shows that no community exceeded 2 microgram/L (maximum detected concentration of the affected community is 0.5 microgram/L).

Alberta

Alberta has monitored for MCPA in municipal water supplies for many years. MCPA has been detected at levels below the proposed guideline, primarily at facilities utilizing surface water supplies. MCPA continues to be a widely used compound in Alberta for weed control in agricultural operations, suggesting that MCPA will continue to be detected in municipal water supplies for the foreseeable future.

The new guideline will enable the assessment of existing and future detections of MCPA in municipal water supplies by AENV and municipalities. Given that detections reported to date have been below the proposed guideline, there is not expected to be economic impacts related to system upgrades to remove MCPA. However, the societal and health perspectives of ongoing MCPA detections in treated water supplies may result in an increased focus on managing pesticides for general water quality protection.

British Columbia

No paragraph submitted.

Yukon

No paragraph submitted.

Northwest Territories

The Northwest Territories does not anticipate any significant impact due to implementation of the proposed new guideline, MCPA in Drinking Water.

Nunavut

No paragraph submitted.