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Guidelines for Canadian Drinking Water Quality

Malathion

Guideline technical document
for public consultation

Consultation period ends
May 26, 2021

Canada

Purpose of consultation

This guideline technical document outlines the evaluation of the available information on malathion, in order to update the previous guidelines for malathion in drinking water. The purpose of this consultation is to solicit comments on the proposed guidelines, the approach used for its development, and the potential impacts of implementation.

The existing guideline technical document on malathion, developed in 1986, based its maximum acceptable concentration (MAC) of 0.19 mg/L (190 µg/L) on cholinesterase inhibition in humans. This document has been revised to reflect the most recent PMRA re-evaluation of malathion, and applies a higher no-observed-adverse-effect level. This document proposes a MAC of 0.29 mg/L (290 µg/L) for malathion in drinking water based on kidney toxicity in rats.

This document is available for a 60-day public consultation period. Please send comments (with rationale, where required) to Health Canada by email to HC.water-eau.SC@canada.ca.

All comments must be received before May 26, 2021. Comments received as part of this consultation and the name and affiliation of their author will be shared with members of the Federal-Provincial-Territorial Committee on Drinking Water (CDW). Authors who do not want their name and affiliation shared with CDW members should provide a statement to this effect with their comments.

It should be noted that this guideline technical document will be revised following the evaluation of comments received, and drinking water guidelines will be established, if required. This document should be considered as a draft for comment only.

Proposed guideline value

A maximum acceptable concentration (MAC) of 0.29 mg/L (290 μg/L) is proposed for malathion in drinking water.

Executive summary

This guideline technical document was prepared in collaboration with the Federal-Provincial-Territorial Committee on Drinking Water and is based on assessments of malathion completed by Health Canada's Pest Management Regulatory Agency and supporting documents.

Exposure

Malathion is a registered insecticide and acaricide used on a wide variety of sites including agricultural and non-agricultural sites. In 2018 (the most recent year for which data are available), over 25,000 kg of malathion was sold in Canada (Health Canada, 2020a). Malathion may be released into surface water or soils as runoff from the application site.

Malathion is not usually found in drinking water sources in Canada. Low levels of malathion have been found in several Canadian provinces. The maximum reported concentrations are well below the proposed MAC. Malathion is rarely detected in foods.

Health effects

Animal studies indicate that the kidney is the most sensitive target organ for malathion toxicity. There are no human studies on the effects of malathion on the kidney. The proposed MAC of 0.29 mg/L (290 μg/L) is based on an increase in severity of chronic kidney effects seen in a two-year rat study.

Analytical and treatment considerations

The establishment of drinking water guidelines takes into consideration the ability to both measure the contaminant and remove it from drinking water supplies. Several analytical methods are available for measuring malathion in water at concentrations well below the proposed MAC.

At the municipal level, treatment technologies are available to effectively decrease malathion concentrations in drinking water supplies. Activated carbon, membrane filtration, oxidation, and advanced oxidation processes can all be used in the treatment of malathion in drinking water. Advanced oxidation processes achieve the highest removal, with lower removals achieved through oxidation. When using degradation processes like oxidation or advanced oxidation processes, water utilities should be aware of the potential for the formation of degradation by-products (e.g., malaoxon). Pilot- and/or bench-scale testing are recommended prior to full-scale implementation.

In cases where malathion removal is desired at a small-system or household level, for example, when the drinking water supply is from a private well, a residential drinking water treatment unit may be an option. Although there are no treatment units currently certified for the removal of malathion from drinking water, activated carbon adsorption and reverse osmosis technologies are expected to be effective. When using a residential drinking water treatment unit, it is important to take samples of water entering and leaving the treatment unit and send them to an accredited laboratory for analysis to ensure that adequate malathion removal is occurring.

Application of the guidelines

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

The proposed guideline value for malathion is protective against health effects from exposure to malathion in drinking water over a lifetime. Any exceedance of the proposed MAC should be investigated and followed by the appropriate corrective actions if required. For exceedances in source water where there is no treatment in place, additional monitoring to confirm the exceedance should be conducted. If it is confirmed that source water malathion concentrations are above the proposed MAC, then an investigation to determine the most appropriate way to reduce exposure to malathion should be conducted. This may include the use of an alternate water supply or the installation of treatment. Where treatment is already in place and an exceedance occurs, an investigation should be conducted to verify the treatment and determine if adjustments are needed to lower the treated water concentration below the proposed MAC.

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1.0 Exposure Considerations

1.1 Sources and uses

Malathion or diethyl[(dimethoxyphosphinothioyl)thio]butanedioate is a non-systemic, broad-spectrum organophosphate insecticide and acaricide used to control a broad range of insect and arachnid pests. It acts by inhibiting the acetylcholinesterase (AChE) enzyme, thereby disrupting nervous system function. In Canada, malathion is used on a wide variety of sites including agricultural and non-agricultural sites such as human habitat and recreational areas, and outdoor ornamentals (Health Canada, 2012). In 2018 (the most recent year for which data are available), over 25,000 kg of malathion was sold in Canada (Health Canada, 2020a).

Malathion may be released into surface water or soils as runoff from the application site (ATSDR, 2003; US EPA, 2009; Health Canada, 2012). In natural waters, soil and sediment, breakdown of malathion occurs primarily through microbial degradation and hydrolysis (Laveglia and Dahm, 1977; ATSDR, 2003; Health Canada, 2010; Singh et al., 2014). Malathion hydrolyses readily under neutral to alkaline conditions, but is increasingly stable under acidic conditions and at low temperatures. The major transformation products (as identified in biotransformation studies) are monocarboxylic acid (MCA), dicarboxylic acid (DCA), demethyl monocarboxylic acid and demethyl dicarboxylic acid, which are not expected to persist in the environment (Health Canada, 2010). Photolysis is not a significant breakdown pathway for malathion in water or soil, with reported half-lives ranging from 0.67 to 42 days in natural and distilled waters and 173 days in sandy loam soil (ATSDR, 2003; EFSA, 2009; US EPA, 2009; Health Canada, 2010). However, in some natural waters containing photosensitizing agents, photolysis may contribute to the dissipation of malathion from the water layer in the photic zone (i.e., upper layer penetrated by sunlight) (Health Canada, 2010).

In aquatic environments, malathion is non-persistent to slightly persistent under aerobic conditions (half-life of 0.3-19 days) and non-persistent in anaerobic systems (half-life of 2.5 days reported in flooded soil), with dissipation generally being fastest in alkaline systems, conditions that have been shown to favour hydrolysis (Health Canada, 2010).

As malathion is highly soluble in water (see Table 1) and does not adsorb strongly to soils. It is mobile in most soil types and its use may result in the contamination of groundwater, particularly in areas where soils are permeable (e.g., sandy soil) and/or the depth to the water table is shallow (Gervais et al., 2009; Health Canada, 2012). However, malathion is unlikely to leach into groundwater, as it is rapidly degraded in soil by microbially mediated metabolism (half-life of 0.2-2 days) and hydrolysis under neutral to alkaline conditions (half-lives of 6.2, 1.5 and 0.5 days at pH 7, 8 and 9, respectively) (ATSDR, 2003; Health Canada, 2010). The degradation of malathion in soil is enhanced by increased moisture, pH levels, microbial activity, nitrogen content and carbon content (Laveglia and Dahm, 1977; ATSDR, 2003; EFSA, 2009; US EPA, 2009; Health Canada, 2010; Kumar et al., 2018).

Based on its physical properties (vapour pressure and Henry's law constant), malathion is unlikely to volatilize appreciably from moist soils or water surfaces, or undergo long-range atmospheric transport (Health Canada, 2010). If present in air, malathion can be released to surface water or soils by rain or fog water, or be photo-oxidized (ATSDR, 2003; WHO, 2004).

Malaoxon, the oxidation transformation product that is responsible for some of the toxic effects of malathion, may form under certain environmental conditions but is expected to be non-persistent (Gervais et al., 2009; Health Canada, 2010). Two monitoring studies investigating malaoxon formation in water, sand, and soils reported a maximum of 10% malathion to

malaoxon conversion (Health Canada, 2012). As with malathion, malaoxon is rapidly detoxified via hydrolysis under neutral to alkaline conditions and unlikely to leach into groundwater (ATSDR, 2003; Health Canada, 2010).

1.2 Substance identity

Malathion ($C_{10}H_{19}O_6PS_2$) is a colourless to amber liquid belonging to the organophosphate class of chemicals (US EPA, 2009; Health Canada, 2010). Formulations of malathion can contain a number of impurities at very low levels, notably malaoxon and isomalathion. In the past, manufacturing processes and improper product storage led to the presence of isomalathion, a toxic metabolite that potentiates the toxicity of malathion; however, regulatory standards have since been put in place to limit its presence and formation (Buratti and Testai, 2005; US EPA, 2009; Jensen and Whatling, 2010; Health Canada, 2010, 2012).

Table 1. Properties of malathion relevant to its presence in drinking water

Property	Malathion	Interpretation
CAS Registry Number	121-75-5	
Molecular weight (g/mol)	330.4	
Water solubility (mg/L)	145	Highly soluble in water
Vapour pressure (volatility) (mm Hg)	$3.97x10^{-5}$ at 30°C[a] $1.78x10^{-4}$ at 25°C[a] $1.2x10^{-4}$ to $8x10^{-6}$ at 20°C[a]	Can have a wide range of volatility, but generally slight to low volatility and unlikely to contaminate air [a]
Henry's Law constant (atm m^3/mol)	1.2×10^{-7}	Low volatilization potential
octanol:water partition coefficient (Log Kow)	2.75-2.94	Not likely to bioaccumulate

Unless otherwise indicated, information is from Health Canada, 2010.
[a] Gervais et al., 2009; Health Canada, 2019.

1.3 Exposure

The general Canadian population can be exposed to malathion primarily through food and drinking water (Health Canada, 2010, 2012), although exposure to malathion is rare.

Water monitoring data from the provinces and territories (municipal and non-municipal supplies), Health Canada's Pest Management Regulatory Agency (PMRA) and Environment and Climate Change Canada (Environment Canada, 2011) (Appendix C) were available for malathion.

Data provided by the provinces and territories indicate that malathion levels are below the method reporting limit (MRL) or method detection limit (MDL) in most samples collected from a variety of water supplies in Canada, including surface water and groundwater, as well as treated and distributed water (British Columbia Ministry of Health, 2019; Indigenous Services Canada, 2019; Manitoba Sustainable Development, 2019; Ministère de l'Environnement et de la Lutte contre les changements climatiques, 2019; Nova Scotia Environment, 2019; Saskatchewan Water Security Agency, 2019; Ontario Ministry of the Environment, Conservation and Parks, 2020). Table 2 summarizes the monitoring data for all jurisdictions. The maximum concentration reported was 5 µg/L for treated surface water in Ontario, which is well below the proposed maximum acceptable concentration (MAC). There was no monitoring data available in New Brunswick, Newfoundland and Labrador, Prince Edward Island or Yukon (New Brunswick Department of Health, 2019; Newfoundland and Labrador Municipal Affairs and Environment,

2019; PEI Department of Communities, Land and Environment, 2019; Yukon Environmental Health Services, 2019).

Table 2: Summary of monitoring data for malathion

Jurisdiction (MDL µg/L)	**Monitoring Period**	**Municipal/Non-municipal**	**Water Type** (Municipal: ground/surface – raw, treated, distributed)	**# Detects/ samples**	**Maximum Conc. (µg/L)**
British Columbia (2)	2013–2018	Municipal	Surface – raw	0/18	-
FNIHB[a] Ontario Region (0.1-5)	2014–2018	Public Water Systems	Ground – raw	0/13	-
			Ground – treated	0/190	-
			Ground – distribution	0/16	-
			Surface – raw	0/33	-
			Surface – treated	0/308	-
			Surface – distribution	0/23	-
		Semi-Public Water Systems	Ground – raw	0/3	-
			Ground – treated	0/16	-
			Ground – distribution	0/68	-
			Surface – raw	0/1	-
			Surface – treated	0/9	-
			Surface – distribution	0/2	-
		Private Water Systems	Ground – treated	0/3	-
			Ground – distribution	0/50	-
			Surface – treated	0/5	-
FNIHB[a] Atlantic Region (4-5)	2014–2018	Public Water Systems	Ground – treated	0/4	-
			Ground – distribution	0/4	-
			Surface – treated	0/1	-
FNIHB[a] Quebec (0.01)	2014–2018	Drinking water system	Not given	0/4	-
Manitoba (0.1-10)	2012–2018	Ambient	Surface – ambient	0/431	-
Nova Scotia (1-10)	2007–2018	Municipal	Ground – raw	0/72	-
			Ground – treated	0/35	-
			Surface – raw	0/35	-
			Surface – treated	0/40	-
			Distributed	0/1	-
Ontario (0.0001-9)	2011–2020	Municipal	Ground – treated	2/3955	0.1
			Surface – treated	2/3796	5
			Distribution	0/60	-
Quebec (0.1-15)	2013–2018	Municipal	Ground – distribution	0/290	-
			Surface – distribution	0/1032	-
		Municipal (Special Projects) Potatoes project[b] [2017-2018]	Ground – raw	0/46	-
			Ground – treated	0/17	-
			Ground – distribution	0/5	-
		Small systems[c] [2012-2018]	Ground – raw (municipal)	0/82	-
			Ground – raw (non-municipal)	0/132	-

Jurisdiction (MDL µg/L)	Monitoring Period	Municipal/Non-municipal	Water Type (Municipal: ground/surface – raw, treated, distributed)	# Detects/ samples	Maximum Conc. (µg/L)
Saskatchewan (0.1-10)	2014–2017	Municipal	Ground – raw	0/84	-
			Surface/Ground – distribution	0/32	-
			Surface/Ground – treated	0/4	-

[a] FNIHB – First Nations and Inuit Health Branch
[b] Potato Project 2017–2018: During the period covered, analysis results of malathion pesticide found in raw, treated or distributed ground water were obtained by the Ministère de l'Environnement et de la Lutte contre les changements climatiques (2019) from 9 drinking water supplies.
[c] Small Systems Project 2012–2018: During the period covered, analysis results of malathion found in raw ground water were obtained by the Ministère de l'Environnement et de la Lutte contre les changements climatiques (2019) from 25 drinking water supplies.

As part of its assessment, PMRA (2010) summarized Canadian water monitoring data on malathion up to 2005. Malathion was detected in 10 samples (n = 4,274) from Canadian municipal drinking water sources with a maximum concentration of 0.08 µg/L recorded in Quebec (1991-1993), and in >79 samples (n = >6,716) from Canadian ambient water that may serve as a drinking water source with a maximum concentration of 1.54 µg/L recorded in Ontario (2003). The maximum malathion concentration in water sources unlikely to be used for drinking water was 2.1 µg/L (11 samples with detections; n = 150).

Canadian water monitoring data were available from the published literature and indicated that malathion is not frequently detected in drinking water sources. Sampling in corn and soybean crop sectors in Quebec from 2015-2017 indicated an average malathion detection frequency of 2% and a maximum malathion concentration of 5.5 µg/L in the Chibouet, Saint-Régis, des Hurons and Saint-Zéphirin Rivers (Limit of detection (LOD) = 0.02 µg/L) (Giroux, 2019). The maximum detection frequency and maximum malathion concentration for four streams from orchard and vegetable crop zones in Quebec were 33.3% and 2.7 µg/L, respectively, for the 2013-2014 period (LOD = 0.02 µg/L) (Giroux, 2017). No malathion was detected in Quebec from sampling performed in individual wells in proximity to corn, soybean, vine, orchard, vegetable and small fruit crop sectors (LOD = 0.02 µg/L) (Giroux, 2016, 2019).

In British Columbia, malathion was not detected in a study (2003-2005) of surface water and groundwater from the Lower Fraser Valley region (Reporting limit = 2.22 ng/L; n = 40 samples) (Woudneh et al., 2009a, 2009b).

Based on surveillance and field trial data, malathion residues in food are expected to be low and to not pose a dietary risk to Canadians (Health Canada, 2010, 2012). In Canada, the established maximum residue limits for malathion range from 0.5 to 8 ppm for various food commodities (e.g., fruits, vegetables, grains and beans/legumes) (Health Canada, 2020b). The Canadian Food Inspection Agency (CFIA) sampled and tested domestic and imported food products (i.e., fresh fruits and vegetables, meat, nuts and seeds) between April 1, 2015, and March 31, 2016. Malathion residues were detected in 43 samples (n = 998) at a maximum level of 0.64000 ppm (CFIA, 2019b). In infant foods and formulas monitored by the CFIA, 2 samples (n = 221) tested positive for malathion contamination below the maximum residue limit of 2 ppm, with levels of 0.0195 ppm and 0.0322 ppm recorded (CFIA, 2019a).

Based on its physical properties, airborne exposure to malathion is not expected to be a concern for the Canadian population, with air monitoring data indicating that malathion is only present at low levels in areas where it is used (Health Canada, 2010).

2.0 Health Considerations

All pesticides, including malathion, are regulated by PMRA. PMRA conducts extensive evaluations and cyclical reviews of pesticides, including unpublished and proprietary information, as well as foreign reviews by other regulatory agencies such as the United States Environmental Protection Agency (US EPA). As such, this health assessment is primarily based on PMRA evaluations (Health Canada, 2003, 2010) and supporting documentation. Any reviews and relevant literature available since the PMRA evaluations were completed were also considered.

2.1 Kinetics

Absorption: Following oral exposure, malathion is readily and rapidly absorbed from the gastrointestinal tract (mostly in the intestine) in mammals, including humans (based on excretion data), with peak plasma levels being reached 15 minutes post-dosing in rats (Reddy et al., 1989; Aston, 2000; Gillies and Dickson, 2000; Jellinek, Schwartz & Connolly Inc., 2000; ATSDR, 2003; EFSA, 2009; Health Canada, 2010; IARC, 2017; WHO, 2017a). Dermal absorption of malathion occurs readily and is expected to be slower than oral absorption and varied among species, with rabbits demonstrating a substantially greater capacity for dermal absorption of malathion (e.g., 64.6% for rabbits, 15.5% for pigs in vitro, 6% for rats, and 0.2-8.2% for humans) (ATSDR, 2003; Gervais et al., 2009; Health Canada, 2010; WHO, 2017a).

Distribution: Malathion is rapidly distributed in the body, with no evidence of bioaccumulation (Health Canada, 2010). In human volunteers, no malathion nor malaoxon was detected in plasma at 1-12 hours following the administration of a single oral dose (LOD = 100-102 and 99.8-100 ng/ml respectively) (Aston, 2000; Gillies and Dickson, 2000; Jellinek, Schwartz & Connolly Inc., 2000). In rats gavaged with ^{14}C-malathion, less than 1.5% of the administered dose was detected in the tissues at 72 hours, with the highest concentration observed in the liver, followed by skin, fat, bone and gastrointestinal tract (Reddy et al., 1989).

Metabolism: Following oral exposure in rats and humans, malathion is fully metabolized, with no parent compound present in urine (Reddy, 1989; ATSDR, 2003; Health Canada, 2010; WHO, 2017a). The major metabolic pathway for both malathion and malaoxon is hydrolysis by tissue, liver or plasma carboxylesterases, resulting in the production of MCA and DCA metabolites (>80% in rats) (Health Canada, 2010). Unlike rats, humans have no detectable levels of carboxylesterases in serum, plasma or erythrocytes, but may have more active liver carboxylesterases (ATSDR, 2003; IARC, 2017; WHO, 2017a). Malaoxon, the active metabolite of malathion, may be formed to a lesser extent (4-6% in rats) via oxidative desulphuration of malathion (minor pathway) by microsomal enzymes (ATSDR, 2003; Health Canada, 2010). Once formed, malaoxon is either excreted in the urine, rapidly hydrolyzed to malathion MCA and DCA, or further metabolized by phosphatases and carboxylesterase enzymes. In rats, no dose-related or sex-related differences in malathion metabolism were observed (Health Canada, 2010).

Excretion: In mammals, including humans, excretion of ingested malathion is rapid and occurs primarily in urine and to a lesser amount in feces (Reddy et al., 1989; Aston, 2000; Gillies and Dickson, 2000; Jellinek, Schwartz & Connolly Inc., 2000; ATDSR, 2003; Health Canada,

2010; WHO, 2017a). In human volunteers administered a single dose of malathion, approximately 90% of the dose was excreted in urine within 12 hours, with the entire dose excreted after 24-48 hours (Aston, 2000; Gillies and Dickson, 2000; Jellinek, Schwartz & Connolly Inc., 2000; WHO, 2017a). Malathion MCA was the most prevalent metabolite, followed by O,O,-dimethyl phosphorothiolate, malathion DCA, dimethyl phosphate and dimethyl dithiophosphate (US EPA, 2016; WHO, 2017a). In the rat, 76-88% of excretion occurred in urine within 72 hours of dosing (mainly as malathion MCA and DCA), whereas 6-14% occurred in feces. The excretion profile was similar for single or repeat low dose or single high dose administration in rats, with no sex differences reported (Health Canada, 2010).

2.2 Health effects

The toxicology database for malathion is adequate, covering several endpoints and various types of exposures (see ATSDR, 2003; IARC, 2017; WHO, 2017a for more thorough reviews). Signs of acute toxicity due to malathion exposure are consistent with cholinesterase (ChE) inhibition (tremors, convulsions, salivation and dyspnea) and were observed in a variety of species and by all routes of exposure. Young animals showed greater sensitivity to the effects of malathion on erythrocyte cholinesterase (EChE) than adults. From repeated-dose studies with malathion, the increase in severity of chronic progressive nephropathy in rats is considered the most sensitive adverse effect. Malathion was not found to be genotoxic or teratogenic in animal studies and is unlikely to pose a carcinogenic risk in humans (Health Canada, 2010).

2.3 Effects in humans

No human effects were discussed in PMRA assessments or their supporting documents (US EPA, 2009; Health Canada, 2010, 2012). Studies were available from the literature concerning both cancer and non-cancer endpoints.

Agricultural Health Study: The Agricultural Health Study (AHS) is a large, ongoing questionnaire-based prospective cohort study of licensed pesticide applicators and their spouses (over 89,000 participants) who live in Iowa and North Carolina that investigates cancer and non-cancer endpoints. It began in 1993 with the collection of baseline information on farming practices (including pesticide use), lifestyle and health. Follow-up interviews/questionnaires (including dietary information) and DNA collection were done periodically. Cancer registries were used to assess cancer incidence. Overall, strengths of the AHS include its large size; the inclusion of a large number of women; the collection of baseline, health and lifestyle information, and genetic factors; the use of cancer registries and the many different pesticides and diseases assessed. Its limitations include the indirect assessment of exposure (questionnaires), the lack of exposure refinement measurements (no induction time or latency discussion), and selection bias when controlling for multiple confounders due to the exclusion of many subjects with missing data (Sathiakumar et al., 2011).

Cancer: Several investigators have published studies based on their analyses of the AHS cohort data. No associations were observed between exposure to malathion and the incidence of colorectal cancer (Lee et al., 2007), pancreatic cancer (Andreotti et al., 2009), and childhood cancer (Flower et al. 2004). Lerro et al. (2015) reported a significant increase in thyroid cancer incidence among AHS spouses, but also indicated they failed to control for exposure to elevated nitrate levels in food and drinking water, which has been proposed to play a role in thyroid cancer development in agricultural regions. Although Engel et al. (2005) reported no increased risk of breast cancer in spouses enrolled in the AHS who had used malathion themselves, an

association was noted in wives whose husbands had used the pesticide. The inconsistencies in findings may be due to limitations such as self-reported exposure and the potential for exposure to multiple pesticides (WHO, 2017a). In case-control analyses by Mills and Yang (2005, 2019), an elevated risk of breast cancer was observed in Hispanic agricultural workers who had used malathion; however, the pesticide exposure was estimated based on ecological rather than individual exposures and may have been subject to misclassification (IARC, 2017; WHO, 2017b).

In examining AHS data from 1993-2007, Koutros et al. (2013) reported a significant increase in aggressive prostate cancer risk in the highest malathion exposure category, but found no association between total prostate cancer and malathion exposure. In a case-control study, Mills and Yang (2003) also found no evidence of an association between total prostate cancer and malathion exposure among Californian farm workers. However, the data may have been subject to misclassification as the classification of exposure was based on ecological rather than individual exposure (IARC, 2017; WHO, 2017b). In contrast, Band et al. (2011) reported a correlation between malathion usage and total prostate cancer in British Columbian farmers, with significant dose-response effects. However, pesticide exposures were assessed using a job-exposure matrix and were susceptible to misclassification; also, the data were not corrected for multiple pesticide exposure (Band et al., 2011; IARC, 2017; WHO, 2017b).

Based on the AHS cohort data, no increased risk of non-Hodgkin's lymphoma (NHL) was observed in male pesticide applicators using malathion, while a decreased association was observed in spouses of applicators using the pesticide (Alavanja et al., 2014; Lerro et al., 2015). Investigating agricultural cohorts from France and Norway and from AHS in the US, Leon et al. (2019) also reported a lack of association between malathion use and risk of NHL; although there is a possibility of exposure misclassification due to the use of "crop-exposure matrices" to estimate exposures. In contrast, a cross-Canada, population-based, case-control study demonstrated a significant association between NHL and "ever use" of malathion in comparison to "never use," and for annual days of use amongst men in a diversity of occupations (McDuffie et al., 2001). A similar association was reported in pooled data from three United States Midwestern case-control studies; however, the association was attenuated or no longer significant upon removal of proxy respondents from the analyses and more robust adjustments for other pesticides (Waddell et al., 2001; De Roos 2003: WHO, 2017b). Koutros et al. (2019) further evaluated the potential link between malathion exposure and NHL using pooled data from the cross-Canada study and the three United States Midwestern studies. A significantly increased risk of NHL was observed among "ever" users of malathion compared to "never users" after adjustment for use of other pesticides, as well as an association between malathion use and certain NHL subtypes. Analyses of the pooled data also demonstrated a significant exposure-response relationship with years of malathion use (Koutros, et al., 2019). While the larger dataset considered by Koutros et al. (2019) allowed for a more powerful assessment, limitations attributable to the individual case-control studies (e.g., recall bias, use of proxy respondents) create a potential for exposure misclassification.

Overall, the epidemiological database provides only uncertain indications of associations between malathion exposure and cancer, with studies performed within only a few populations. Study limitations (e.g., small number of cases, failure to control for confounders, use of proxy respondents, recall bias and potential for exposure misclassification) may account for some of the inconsistencies between different study findings and preclude definitive conclusions on the relationship between exposure to malathion and cancer risk.

Non-Cancer: In evaluating non-cancer endpoints in the AHS cohort data, investigators have reported respiratory effects, including wheeze, chronic bronchitis symptoms (occurring with and without chronic obstructive pulmonary disease), and adult onset of allergic asthma in females and non-allergic asthma in males related to malathion exposure (Hoppin et al., 2002, 2006, 2008, 2009; Rinsky et al., 2019). Kamel et al. (2006) did not find a strong association between Parkinson's disease and exposure to malathion in the AHS. In studies evaluating the associations between "ever usage" of malathion and incidence of diabetes, no association was observed among farmers or their wives (Montgomery et al., 2008; Starling et al., 2014). Goldner et al. (2010, 2013) observed no significant association between "ever-use" of malathion and hypothyroidism in either male applicators or their female spouses in the AHS based on data collected up to 2010. However, follow-up studies by Shrestha et al. (2018, 2019) using AHS data up to 2016, reported an increased risk of incidence of hypothyroidism and a reduced risk of hyperthyroidism with malathion exposure.

In a controlled ingestion study, groups of five male volunteers were administered malathion-containing capsules (purity not specified) in doses of approximately 0.11 mg/kg bw per day for 32 days and 0.23 mg/kg of body weight (bw) per day for 47 days, or 0.34 mg/kg bw per day for 56 days (Moeller and Rider, 1962; ATSDR, 2003). No significant decrease of plasma or erythrocyte activity or changes in blood counts or urinalyses resulted from the administration of 0.11mg/kg bw per day of malathion for 32 days or 0.23 mg/kg bw per day for 47 days. Volunteers receiving 0.34 mg/kg bw per day for 56 days of malathion were observed to have a maximum 25% decrease in plasma cholinesterase (PChE) and EChE in absence of clinical signs (Moeller and Rider, 1962; ATSDR, 2003).

A randomized double-blind study in human volunteers administered a single dose of malathion ranging from 0.5 to 15.0 mg/kg (bw (27 male and 7 females test subjects, 11 male and 3 female controls), reported the absence of any treatment-related adverse effects on erythrocytes and plasma AChE activities and no alterations in vital signs, electrocardiograms, hematology, clinical chemistry, urinalysis and physical parameters, up to 24 or 48 hours after dosing (Gillies and Dickson, 2000). Similarly, another volunteer study examining the same dose levels reported no treatment-related adverse effects on AChE activity (Jellinek, Schwartz and Connolly Inc., 2000).

2.4 Effects in animals

Repeat exposure studies in rats, mice, rabbits and dogs showed malathion induced primarily kidney and neurological effects although other effects have also been noted (Shellenberger and Billups, 1987; Daly, 1993a, 1993b, 1996; ATSDR, 2003; EFSA, 2009; US EPA, 2009 Health Canada, 2010; Barnett Jr., 2012a, 2012b; WHO, 2017a).

Malathion has been shown to be slightly toxic to experimental animals via the oral, dermal and inhalation routes. The toxicity of malathion depends on its purity level. Oral median lethal dose (LD_{50}) values of 2,382-8,200 mg/kg bw in rats (96.0-99.1% purity level), 6,100 mg/kg bw in female mice (95% purity level) and >4,000 mg/kg bw in dogs (98% purity level) were reported for malathion. Dermal LD_{50} values for malathion were >2,000 mg/kg bw in rats (96-98% purity level) and 8,900 mg/kg bw in rabbits (95.6% purity level). An inhalation medial lethal concentration (LC_{50}) value of >5.2 mg/L in rats (96-98% purity level) was also reported for malathion (FAO/WHO, 1997; Decker et al., 2003; US EPA, 2009; Health Canada, 2010).

Kidney effects: Nephrotoxicity has been observed in rats and beagle dogs following oral administration (all durations of exposure) of malathion.

In a 24-month chronic toxicity/carcinogenicity study, groups of Fischer 344 rats (90/sex/dose) were administered malathion (97.1% pure) in the diet at doses of 0, 100/50 (reduced day 113), 500, 6,000 or 12,000 ppm (equivalent to 0, 2.4, 26, 327 or 677 mg/kg bw per day in males and 0, 3.0, 32, 386 or 817 mg/kg bw per day in females). Interim sacrifices (10-15/dose/sex) were performed at 3, 6 and 12 months (Daly, 1996). At 12 months and at terminal sacrifice, kidney weights (absolute, relative to body brain weights) were statistically significantly increased at 6,000 ppm and 12,000 ppm in both male and female rats. Macroscopic findings at the end of the study included increased incidence of irregular surfaces of the kidneys at 500, 6,000 and 12,000 ppm in males and at 12,000 ppm in females (US EPA, 1997). An increased severity of chronic progressive nephropathy was observed in both sexes, that is, in females administered ≥500 ppm of malathion and males administered ≥6,000 ppm, with the males also demonstrating an earlier onset of the disease at interim sacrifice (Health Canada, 2010).

Similar effects have been observed in subchronic toxicity studies with higher doses of malathion in both beagle dogs and rats. In a 52-week oral study, beagle dogs (6/sex/dose) were administered 62.5-250 mg/kg bw per day of malathion (95% pure) in capsules. At doses of ≥62.5 mg/kg bw per day, decreases in creatinine and blood urea nitrogen levels were observed accompanied by increases in absolute and relative kidney weights (Shellenberger and Billups, 1987). In a 90-day dietary toxicity study, groups of F-344 rats (10/sex/group) were administered 100-20,000 ppm (equivalent to 6.6-1,190 mg/kg bw per day in males and 7.9-1,597 mg/kg bw per day in females) of malathion (96.4% pure). Increased relative kidney weights were observed at ≥340/384 mg/kg bw per day in males/females, and increased absolute kidney weights were observed at 680 mg/kg bw per day in males and ≥1,597 mg/kg bw per day in females. As well, an increased severity of chronic nephropathy was observed in males at ≥340 mg/kg bw per day (Daly, 1993b). In two dietary toxicity studies (28- and 29/30-day) where rats were administered malathion (95.8% and 96.4% pure, respectively), increases in relative kidney weights were observed starting at 457.5 mg/kg bw per day (Daly, 1993a; Barnett Jr., 2012a).

Toxic effects on kidney tissues were also observed in single-dose toxicity studies (≥100 mg/kg bw) in rats (Alp et al., 2011; Selmi et al., 2017; Akbel et al., 2018).

Neurotoxicity: Dose-related inhibition of PChE, EChE and brain cholinesterase (BChE) activity has been observed in experimental animals (rats, mice, rabbits and beagle dogs) administered malathion by all exposure routes and for various durations of exposure (ATSDR, 2003; US EPA, 2009; Health Canada, 2010; WHO, 2017a).

For animals exposed to malathion, EChE is the most sensitive compartment for ChE inhibition and is a suitable surrogate for peripheral neurotoxic effects in acute and some short-term studies. However, in longer studies, depression of EChE is not considered a toxicologically adverse effect due to the limitations related to the low rate of resynthesis of erythrocyte AChE over extended periods. BChE inhibition typically occurred at higher doses than EChE and PChE inhibition in all species. Assessment of the relative sensitivity of ChE activity with oral dosing reveals no appreciable species differences between mice, rats and dogs. Similarly, studies conducted via all exposure routes do not suggest a sex difference in sensitivity to the effects of malathion on ChE inhibition (Health Canada, 2010).

However, the current neurotoxicity database suggests that preweanling rats are more susceptible than adult rats to the neurotoxic effects of malathion following exposure from the oral route. Finally, neuropathological changes were not observed in the majority of mammalian toxicity studies. However, several isolated incidences of neuropathological changes have been

observed in two rat studies at very high doses (1,500 mg/kg bw per day) in only one sex (males) and are considered equivocal (Health Canada, 2010).

In the study by Daly (1996) where Fischer 344 rats (90/sex/dose) were fed diets containing 50-12,000 ppm of malathion (97.1% pure), decreases in PChE activity were observed at ≥500 ppm while EChE and BChE activities were decreased at ≥6,000 ppm. In an 18-month dietary carcinogenicity study where malathion (96.4% pure) was administered to B6C3F1 mice (65/sex/group), decreases in PChE and EChE activities were observed at ≥143/167 mg/kg bw per day (lowest dose tested) in males/females and decreases in BChE were observed at 2,978/3,448 mg/kg bw per day (highest dose tested) in males/females (Health Canada, 2010).

In subchronic oral toxicity studies with malathion (95-96.4% pure), inhibition of EChE, PChE and BChE was observed at dose levels as low as 7.9 mg/kg per day (rats), 62.5 mg/kg bw per day (dogs) and 250 mg/kg bw per day (dogs), respectively (Shellenberger and Billups, 1987; Daly, 1993a; Daly, 1993b; Barnett Jr., 2012a; Barnett Jr., 2012b). In a 21-day dermal toxicity study in rabbits (10/sex/group), inhibition of EChE occurred at ≥75 mg/kg bw per day of malathion (96% pure) (lowest dose tested) and inhibition of PChE and BChE occurred at 500 mg/kg per day (highest dose tested) (Health Canada, 2010).

In an acute delayed neurotoxicity study (gavage) using 12 hens, there was no evidence of delayed type neuropathology caused by the administration of malathion (EFSA, 2009; Health Canada, 2010; WHO, 2017a).

In a developmental neurotoxicity study, dose levels of 0, 5, 50 or 150 mg/kg bw per day of malathion (96.0% pure) in corn oil were administered (gavage) to 24 dams from gestational day (GD) 6 to postnatal day (PND) 10 and from PND 11-21 to the pups. At the highest dose, clinical signs were observed in the dams (post-dosing salivation) and the pups (e.g., tremors, hypoactivity, prostrate posture, partially closed eyelids). Also in the pups, increased incidence of flattened gait (PND 60; males) and decreased motor activity (PND 17/22; females) were observed at ≥50 mg/kg bw per day. In a comparative ChE rat study, adults and PND 11 pups (8 /sex/group) were treated (gavage) with 0, 5, 50, 150 or 450 mg/kg bw of malathion (96.0%) for 1 day. Repeated exposure by gavage (11 days) was also assessed in this study using similar doses in adults and PND 11-21 pups (8/sex/group), in 19 adult females (9 females treated GD 6-20, 10 females treated GD 1-10) and in pups (2/sex/litter/group) sacrificed 4 hours after dosing of the dam at PND 4. The results of the study showed that, at similar dose levels, PND 11 and PND 21 pups are more sensitive than are adult animals to the ChE-inhibiting effects of malathion. Benchmark dose calculations (using a benchmark dose response of 20%) suggest that the young animals are approximately 6.4 times and 1.8 times more sensitive to the ChE inhibiting effects of malathion compared to adults following acute and repeat dose oral exposure, respectively (Health Canada, 2010).

Reproductive/developmental toxicity: Malathion did not induce reproductive toxicity in rats at the highest dose tested, while fetotoxic effects occurred only at maternally toxic doses in rats and rabbits (Health Canada, 2010).

In a two-generation (2 litters/gen) dietary reproductive toxicity study, Sprague-Dawley rats (25/sex/group) were administered 550-7,500 ppm (equivalent to 43-612 mg/kg bw per day in males and 51-703 mg/kg bw per day in females) of malathion (94% pure). No effect on the reproductive parameters or reproductive tissues was observed. However, decreases in weight gain in the parental rats (F0) (during gestation and lactation [females]) and in the first generation – first litter (F1) (during pre-mating) were observed at the highest dose. Decreased weights were observed in some second-generation pups (2 of 4 litters) at PND 21 at 394/451 mg/kg bw per day

in males/females and in all second generation pups (4 litters) at the highest dose tested (Health Canada, 2010). In 80-week and 103-week feeding studies, no treatment-related gross or microscopic alterations in the prostate or testis of male rats or histopathological alteration in the mammary gland, uterus or ovaries of female rats were observed following the administration of up to 622 mg/kg per day and 332 mg/kg per day of malathion (95% pure), respectively (NCI 1978, 1979). Similar results were noted in male mice administered in the diet up to 2,980 mg/kg per day of malathion (95% pure) for 80 weeks; however, in the females, an increased incidence of cystic endometrial hyperplasia was observed following administration of 1 490 mg/kg bw per day of malathion (95% pure) for 80 weeks (NCI, 1978).

Malathion was evaluated for developmental toxicity in rats and rabbits. Following administration (gavage) to pregnant rabbits (20/group) of 25-100 mg/kg bw per day of malathion (95% pure) on GD 6-18, a slightly increased incidence of dams with resorptions (embryo-fetal loss) was observed at ≥50 mg/kg per day in the presence of maternal toxicity (decreases in weight gain during dosing). When malathion (94% pure) was administered by gavage to pregnant Sprague-Dawley rats (24-25/group; 200-800 mg/kg per day; GD: 6-15), a slightly increased incidence of dams with resorption sites was also observed at the highest dose in the presence of maternal toxicity. Maternal toxicity included red lacrimal secretion, discharge of a pigmented secretion from the nose, urine staining of abdominal fur and decreases in weight gain and food consumption during dosing. Neither developmental study showed evidence of treatment-induced malformations (Health Canada, 2010).

Other effects: Reported treatment-related effects including increases in liver and thyroid/parathyroid weights have been observed at 62.5 mg/kg bw per day and greater in rats and dogs following long-term oral exposure, with non-cholinergic hematological effects being observed at higher dose levels (Daly, 1996; Health Canada, 2010).

Non-neoplastic liver changes were observed in experimental animals but may represent adaptive responses. However, more serious histopathological damage may be observed in the liver with high single doses of malathion (ATSDR, 2003).

There is insufficient evidence to indicate that malathion affects the endocrine system; however, there is some indication that malathion may elicit an immune response in experimental animals by affecting both humoral and cellular immunity (Health Canada, 2010).

2.5 Genotoxicity and carcinogenicity

Based on available scientific evidence, malathion is not considered genotoxic (US EPA, 2009; Health Canada, 2010, 2012).

In in vitro studies, malathion was not mutagenic in bacteria (Ames tests using several bacterial strains, with and without metabolic activation) or in yeast (Saccharomyces cerevisiae gene mutation assay) and did not cause unscheduled DNA synthesis (UDS) in cultured rat hepatocytes (US EPA, 1977; Traul, 1987; Pluth et al., 1996; US EPA, 2009; Health Canada, 2010; IARC, 2017; WHO, 2017a). Some in vitro genotoxicity assays (Comet, DNA-protein-crosslinking, sister-chromatid exchange) reported positive results, although only at high malathion doses (i.e., cytotoxic doses) or while using a test material of unspecified purity (Chen et al., 1981; Nishio and Uyeki, 1981; Health Canada, 2010; Ojha and Srivastava, 2014; Ojha and Gupta, 2015; IARC, 2017; WHO, 2017a).

In animals in vivo, malathion did not cause mutations in spermatogonia of mice (dominant lethal assay), or chromosomal aberrations in bone marrow of rats (Health Canada, 2010; IARC, 2017, WHO, 2017a). In contrast, other rodent studies detected chromosomal

aberrations and DNA damage (as assessed by the Comet assay) following oral administration of malathion at either cytotoxic doses or while using a test material of unspecified identity and/or purity (Dulout et al., 1983; Giri et al., 2002; Health Canada, 2010; Ojha et al., 2013; IARC, 2017).

In human cells, malathion did not cause UDS in lung fibroblasts, but induced mutations in T lymphocytes in the HRPT assay and 8-OH-dG adduct formation in human peripheral blood mononuclear cells (US EPA, 1977; Pluth et al., 1996; Ahmed et al., 2011). Mixed results were reported for sister chromatid exchange (SCE) and DNA damage (assessed by the Comet assay), with positive findings observed only at near cytotoxic to cytotoxic doses, or with malathion of unspecified purity (Blasiak et al., 1999; Health Canada, 2010; Moore et al., 2010; Olakkaran et al., 2020). Chromosomal aberrations were observed in human peripheral leukocytes, but with test material of unspecified purity (Health Canada, 2010). An increase in micronucleated cells was found in cultured lymphocytes treated with high doses of malathion; however, in vivo studies with agricultural workers exposed specifically to malathion reported negative results for both micronuclei formation and glycophorin A mutations in peripheral lymphocytes of the cohorts examined (Titenko-Holland et al., 1997; Windham et al., 1998).

Although a large number of in vitro and in vivo studies using various rodent and human models reported positive findings, many of these studies lacked experimental details, or used test material of unknown or unspecified identity and/or purity; meanwhile others reported positive results only at high concentrations (i.e., cytotoxic doses) (Health Canada, 2010; WHO, 2017a). As such, the relevance of these findings is not clear (Health Canada, 2010).

In an 18-month study where $B6C3F_1$ mice were fed malathion at 100-16,000 ppm, an increased incidence of liver adenomas was observed in both sexes at 8 000 ppm (1,476 mg/kg per day for males, 1,707 mg/kg per day for females) and 16,000 ppm (2,978 mg/kg bw per day for males, 3,448 mg/kg bw per day for females) (Slauter, 1994). In another study where F344 rats were given 100-12,000 ppm of malathion in the diet for 24 months, an increased incidence of liver adenomas was also noted but only in females at 12,000 ppm (817 mg/kg bw per day) (Daly, 1996). These findings, however, are considered equivocal based on the incidence of tumours only at malathion concentrations that exceed the maximum tolerated dose, the absence of a dose-response relationship, the presence of tumours in only one sex in rats, the commonness of liver tumours in $B6C3F_1$ mice, and signs of metabolic saturation of the liver (Health Canada, 2010; WHO, 2017a). In the 24-month rat study, Daly (1996) also reported solitary rare nasal and oral tumours at 6,000 and 12,000 ppm in rats that could not be distinguished as treatment-related or caused by random occurrence (Health Canada, 2010). Further evaluations by peer reviewers and some regulatory agencies concluded that the nasal tumours resulted from irritation of the nasal epithelium from either volatilization or inhalation of very high concentrations of malathion from the feed (US EPA, 2000a; Jensen and Whatling, 2010; FAO/WHO, 2016).

Based on the weight of evidence, the PMRA has concluded that malathion is unlikely to possess carcinogenic potential for humans (Health Canada, 2010, 2012). The US EPA has classified malathion as having **"**suggestive evidence of carcinogenicity but not sufficient to assess human carcinogenic potential" (US EPA, 2009). In a recent re-evaluation of malathion by the International Agency for Research on Cancer (IARC), malathion was classified in Group 2A, as "probably carcinogenic to humans" (IARC, 2017).

2.6 Mode of action

Malathion increases oxidative stress markers and creates an imbalance in antioxidant status in different tissues. This causes tissue injuries, including lipid peroxidation, DNA damage,

and/or changes in antioxidant enzyme, which can explain the nephrotoxicity observed in rats and dogs (Akhgari et al., 2003; IARC, 2017; Akbel et al., 2018; Selmi et al., 2018).

In tissue, liver and plasma, malathion undergoes metabolic activation to form malaoxon. Malathion and malaoxon have the ability to inhibit PChE, EChE and BChE activity via phosphorylation of the active site of the enzyme (ATSDR, 2003; Krstic et al., 2008; Health Canada, 2010; Jensen and Whatling, 2010). The ChE enzyme is responsible for the hydrolysis of the neurotransmitter acetylcholine (ACh). Therefore, its inhibition causes ACh to accumulate in the synapses, overstimulating the nicotinic and muscarinic receptors in the central and/or peripheral nervous system. This overstimulation leads to smooth muscle contractions (e.g., abdominal cramps, glandular secretions, skeletal muscle twitching, and paralysis) and possible effects on learning, memory and other behavioral parameters (ATSDR, 2003; Health Canada, 2010; Jokanovic, 2018; Naughton and Terry Jr., 2018).

2.7 Selected key study

In its re-evaluation for the continuing registration of malathion (PACR2003-10), Health Canada (2010, 2012, 2019) identified the kidney as the most sensitive target organ across the database. The chronic oral toxicity/oncogenicity study in rats conducted by Daly (1996) was identified as the key study for the human health risk assessment of malathion in drinking water (Health Canada, 2019).

Groups of rats (90/sex/dose) were fed a diet of 0, 100/50 (reduced day 113), 500, 6,000 or 12,000 ppm (equivalent to 0, 2.4, 26, 327 or 677 mg/kg/bw per day for males and 0, 3.0, 32, 386 or 817 mg/kg bw per day for females) of malathion (97.1%) for 24 months (Health Canada, 2010). After 3 months, the lowest dose was reduced from 100 ppm to 50 ppm due to the observation of statistically significant EChE inhibition at 100 ppm in females (US EPA, 1997; Health Canada, 2010; WHO, 2017a). Rats were checked twice a day for toxicity and mortality and examinations were performed each week. Interim sacrifices took place after 3, 6 and 12 months (US EPA, 1997). Treatment-related clinical signs (i.e., anogenital staining) were observed only in females at the highest dietary dose (US EPA, 1997; Health Canada, 2010). Mortality was significantly increased in males at 6,000 and 12,000 ppm (starting at month 20 and 14, respectively) and in females at 12,000 ppm (closer to study completion), with deaths attributed in part to chronic nephropathy (US EPA, 1997; Health Canada, 2010; WHO, 2017a). Although a high incidence of chronic nephropathy was reported across all groups (including controls), a treatment-related increase in severity of the effect was observed in females exposed to ≥500 ppm and males exposed to ≥6,000 ppm, with males also demonstrating an earlier onset of the disease at interim sacrifice (US EPA, 1997; Health Canada, 2010). Decreased body weights and increased food consumption was recorded for both sexes at ≥6,000 ppm, along with increased absolute and relative liver weights and kidney weights. In both sexes, EChE and BChE inhibition was noted at ≥6,000 ppm, while PChE inhibition was noted at ≥500 ppm. Effects on erythrocyte and clinical chemistry parameters were observed in males and females exposed to the two highest doses. Lesions of the nasal mucosa (degeneration and hyperplasia of the olfactory epithelium), nasopharynx irritation (inflammation and hyperplasia of the respiratory epithelium) were reported in both sexes at ≥6,000 ppm (Health Canada, 2010).

An increase in the incidence of liver adenomas was noted in females at 12,000 ppm, but not in males. In both sexes, solitary oral and nasal tumours were observed; however, they could not be distinguished as either treatment-related or of random occurrence (oral tumours in females

at ≥6,000 ppm; nasal tumours in females at ≥6,000 ppm and in males at 12,000 ppm) (Health Canada, 2010).

An oral no-observed-adverse-effect level (NOAEL) of 3.0 mg/kg bw per day was identified based on a treatment-related increase in severity of chronic progressive nephropathy in female rats at the next dosage level of 32 mg/kg bw per day (Health Canada, 2010).

While sensitivity of the young has been demonstrated, the most sensitive endpoint following repeat exposure (behavioural effects) to young animals occurs at doses exceeding the NOAEL for chronic nephropathy. Chronic nephropathy is a disease related to ageing and has been observed following long-term exposure in adult rats (Health Canada, 2019).

3.0 Derivation of the health-based value

As noted above, the NOAEL of 3.0 mg/kg bw per day for increase in severity of chronic progressive nephropathy in female rats was selected as the basis for the current risk assessment. Using the NOAEL of 3.0 mg/kg bw per day, the acceptable daily intake (ADI) for malathion (Health Canada, 2010) is calculated as follows:

$$\text{ADI} = \frac{3.0 \text{ mg/kg bw per day}}{100}$$
$$= 0.03 \text{ mg/kg bw per day}$$

where:

- 3.0 mg/kg bw per day is the NOAEL based on chronic progressive nephropathy in female rats (Health Canada, 2010); and
- 100 is the uncertainty factor, selected to account for interspecies variation (×10) and intraspecies variation (×10).

Based on the ADI of 0.03 mg/kg bw per day, a health-based value (HBV) for malathion in drinking water was derived as follows:

$$\text{HBV} = \frac{0.03 \text{ mg/kg bw per day} \times 74 \text{ kg} \times 0.20}{1.53 \text{ L/day}}$$
$$= 0.29 \text{ mg/L (290 ug/L)}$$

where:

- 0.03 mg/kg bw per day is the ADI calculated using a NOAEL of 3.0 mg/kg bw per day (Health Canada, 2010);
- 74 kg is the adult body weight (Health Canada, in preparation);
- 1.53 L per day is the daily volume of tap water consumed by an adult (Health Canada, in preparation); and
- 0.20 is the default allocation factor since drinking water is not a major source of exposure to malathion and there is evidence of malathion in other exposure sources (i.e., food) (Krishnan and Carrier, 2013).

4.0 Analytical and Treatment Considerations

4.1 Analytical methods to detect malathion

Standardized methods available for the analysis of malathion in source and drinking water and their respective MDLs are summarized in Table 3. MDLs are dependent on the sample matrix, instrumentation, and selected operating conditions and will vary between individual laboratories. These methods are subject to a variety of interferences, which are outlined in the respective references.

A number of accredited laboratories in Canada were contacted to determine MDL and MRLs for malathion analysis and the MDLs were in the same order of magnitude as that reported in Table 3. The MRLs ranged between 0.02 to 5 µg/L for Gas Chromatography with Mass Spectrometry Detection (GC/MS) (AGAT Laboratories Ltd., 2019; ALS Environmental, 2019; CARO Analytical Services – Richmond Laboratory, 2019; Element Materials Technology Canada Inc., 2019; and SGS Environmental Services, 2019).

The MDLs or MRLs from provincial and territorial data range from 0.0001 to 15 µg/L (see Section 1.3).

Drinking water utilities should discuss sampling requirements with the accredited laboratory conducting the analysis to ensure that quality control procedures are met and that MRLs are low enough to ensure accurate monitoring at concentrations below the MAC. Sample processing considerations for the analysis of malathion in drinking water (e.g., sample preservation, storage) can be found in the references listed in Table 3. Additionally, a non-standardized method to analyse malathion in water based on high performance liquid chromatography with tandem mass spectrometry is presented in Rocha et al. (2015).

It is important to note that quenching is critical if an oxidant is present in samples in order to reduce additional degradation of malathion. Malathion has limited stability due to hydrolysis, with decreased half-life at increased pH and temperature (Wolfe et al., 1977; EFSA Scientific Report, 2006). As such, cooling of the samples and rapid analysis are recommended.

Table 3. Standardized methods for the analysis of malathion in water

Method (Reference)	Methodology	MDL (µg/L)	Interferences/comments
EPA 527 Rev. 1.0 (US EPA, 2005)	Capillary column gas chromatography/mass spectrometry (GC/MS)	0.057[a]	Method and matrix interferences; Contamination carryover
EPA 1699 (US EPA, 2007)	High Resolution GC/MS	0.0003 (296 pg/L)	Method and matrix interferences
EPA 8141B Rev. 2 (US EPA, 2000b)	Gas Chromatography with Flame Photometric Detector (GC/FPD)	5.5	Method and matrix interferences
EPA 8270D Rev. 4.0 (US EPA, 1998)	GC/MS	50[b]	Method and matrix interferences; Contamination carryover
O-1104 (USGS, 1983)	GC/FPD	0.01[c]	Method and matrix interferences; Sulfur and organosulfur will interfere
O-1126-95 (USGS, 1995)	GC/MS	0.005	Method and matrix interferences
O-1402-01 (USGS, 2001)	GC/FPD	0.005	Method and matrix interferences; Sulfur and organosulfur and

Method (Reference)	Methodology	MDL (µg/L)	Interferences/comments
			unknown organophosphate compounds will interfere
O-3104 (USGS, 1983)	GC/FPD	0.01[c]	Method and matrix interferences; Sulfur and organosulfur compounds will interfere
O-3402-03 (USGS, 2003)	Gas Chromatography (Unspecified Detector)	0.0040	Method and matrix interferences; Sulfur and organosulfur and unknown organophosphate compounds will interfere

[a] Detection limit.
[b] Estimated quantitation limit.
[c] MDL is estimated.

4.2 Treatment considerations

Treatment technologies available to effectively decrease malathion concentrations in drinking water include activated carbon, membrane processes, oxidation and advanced oxidation processes. Published data on malathion removal in water using these technologies indicates a large range of removal efficiencies (less than 50% up to approximately 100%) (Chian et al., 1975; Roche and Prados, 1995; Kiso et al., 2000; Duirk et al., 2009; Zhang and Pagilla, 2010; Beduk et al., 2012; Chamberlain et al., 2012; Fadaei and Dehghani, 2012; Sorour and Shaalan, 2013; Jusoh et al., 2014; Li et al., 2016). At the residential scale, certified treatment devices relying on reverse osmosis (RO) or activated carbon adsorption are expected to be effective for removal of malathion.

4.2.1 Municipal-scale

The selection of an appropriate treatment process for a specific water supply will depend on many factors, including the raw water source and its characteristics, the operational conditions of the selected treatment method and the utility's treatment goals. Bench or pilot testing is recommended to ensure the source water can be successfully treated and optimal process design is established.

When using oxidation or advanced oxidation processes (AOP) for pesticide removal in drinking water, it is important to be aware of the potential for formation of by-products due to degradation of the target compound (Ikehata and Gamal El-Din, 2006; Beduk et al., 2012; Li et al., 2019). Malathion has several degradation by-products that may form through oxidation (see Section 4.2.1.4), or advanced oxidation processes (see Section 4.2.1.5), including malaoxon, which is of health concern. The primary objective should be removal of the pesticide with the secondary objective being the minimization of by-product formation. In addition, water utilities should consider the potential for the formation of disinfection by-products depending on the oxidant selected and the source water quality.

4.2.1.1 Conventional treatment

Conventional filtration (chemical coagulation, clarification, and rapid sand filtration) and chlorine disinfection may reduce malathion concentrations through oxidation during the disinfection step depending on the oxidant (Roche and Prados, 1995; Duirk et al., 2009; Beduk et al., 2012; Chamberlain et al., 2012). However, degradation processes like oxidation result in the formation of by-products, such as malaoxon (see Section 4.2.1.4).

A bench-scale study evaluated chemical coagulation and sedimentation treatment technologies for the removal of both malathion and malaoxon (Matsushita et al., 2018). The study used river water and the results showed no removal (See Table 4).

Table 4. Malathion and malaoxon removal via coagulation, flocculation and sedimentation (Matsushita et al., 2018)

Parameter	Influent (µg/L)	Coagulant	Dose	Removal	Process Description
Malathion	10	Polyaluminum chloride	1.0 and 1.4 mg/L	0	Bench-scale: River water at 20˚C; 1L; final pH of 7.0 Dosed with coagulant; rapid stir (61 rpm) for 1 min; slow stir (13 rpm) for 10 min; rest for 60 min
Malaoxon	10			0	

A bench-scale study was conducted to evaluate the cumulative removal of malathion through coagulation, flocculation and filtration followed by chlorination (see Table 5) (Costa et al., 2018). The first part of this study differed from the previous study with the addition of a filtration step and showed 62.21% removal of malathion. The removal increased further after chlorination and the authors noted the formation of malaoxon.

Table 5. Removal of malathion through coagulation, flocculation, filtration followed by chlorination (Costa et al., 2018)

Influent (µg/L)	Treatment Type	Cumulative Removal	Process Description	Overall Description
0.48 mg/L	Coagulation, flocculation, filtration	62.21 ± 0.01%	Dosed with 20 mL aluminum sulphate at 1% (w/v); rapid mix (100 rpm) for 3 min; slow stir (50 rpm) for 10 min; rest for 15 min; filtration by gravity with 125 mm filter paper	Bench-scale: Jar tests Ultra-pure water; 1L at 100 NTU; pH 10.5 Coagulation, flocculation, filtration followed by chlorination Note: after post chlorination, malaoxon was detected (concentration not provided)
	Chlorination	73.2 ± 0.2%	Chlorine (dose = 5 mg/L)	

4.2.1.2 Activated carbon adsorption

Activated carbon adsorption is a widely used technology to reduce the concentration of micropollutants, including a wide range of pesticides, in drinking water (Haist-Gulde and Happel, 2012; van der Aa et al., 2012). Activated carbon can be applied in two ways: slurry applications using powdered activated carbon (PAC) or fixed-bed reactors with granular activated carbon (GAC) (Chowdhury et al., 2013).

Data generated through bench-scale testing to determine adsorption coefficients for pesticides is useful in predicting whether activated carbon adsorbs a particular pesticide (US EPA, 2011). In general, pesticides with an adsorption capacity constant (e.g., Freundlich coefficient) greater than 200 $\mu g/g(L/\mu g)^{1/n}$ are considered to be amenable to removal by carbon adsorption (Speth and Adams, 1993; Speth and Miltner, 1998; US EPA, 2011). However, it is important to note, that the presence of natural organic matter (NOM) adds complexity to activated carbon treatment because NOM competes directly for adsorption sites or fouls the carbon by blocking pores (Chowdhury et al., 2013). Since the capacity of activated carbon can be affected by many factors, including the compound's ionic character and the solution pH, appropriate testing (e.g., jar tests, rapid small-scale column tests, etc.) should be conducted to

confirm removal.

Powdered activated carbon

Many pesticides have been found to strongly adsorb to PAC (Chowdhury et al., 2013). The use of PAC offers the advantage of providing virgin carbon when required (e.g., during the pesticide application season) (Miltner et al., 1989). The removal efficiency of PAC depends on the PAC characteristics (type and particle size), dose, contact time, contaminant adsorbability and NOM presence (Gustafson et al., 2003; Summers et al., 2010; Haist-Gulde and Happel, 2012; Chowdhury et al., 2013).

A bench-scale study was conducted to determine the adsorption of malathion to PAC, as well as that of malaoxon (See Table 6) (Matsushita et al., 2018). With a PAC dose of 10 mg/L, similar removal efficiencies of 69 and 76% were observed for malathion and malaoxon, respectively. Thus, both substances have good adsorbability on activated carbon.

Table 6. Malathion and malaoxon removal via PAC (Matsushita et al., 2018)

Parameter	Influent (µg/L)	PAC Dose	pH	Remaining ratio	Removal Efficiency (%)[a]	Process Description
Malathion	10	10 mg/L	7.0	0.24 ± 0.01	76%	Bench-scale: River water 10 minute contact time
Malaoxon	10			0.31 ± 0.03	69%	

[a] Calculated from remaining ratio.

Granular activated carbon

The use of GAC is an effective approach for treating organic contaminants that are regularly found in source water at concentrations of concern (Chowdhury et al., 2013). The capacity of GAC to remove pesticides by adsorption depends on the filter velocity, empty bed contact time (EBCT), the GAC characteristics (type, particle size, reactivation method), the adsorbability of the contaminant, and the filter run time (Haist-Gulde and Happel, 2012). In addition, because GAC fixed-bed adsorbers are typically operated on a continuous basis, the GAC can become fouled (or preloaded) with NOM and it may be completely or partially ineffective for pesticide removal (Knappe et al., 1999; Summers et al., 2010; Haist-Gulde and Happel, 2012; Chowdhury et al., 2013).

Column experiments were conducted on two different GACs (palm shell activated carbon (PSAC) and coconut shell activated carbon (CSAC)) (Jusoh et al., 2014). The authors found that the malathion removal efficiency for CSAC was greater than that for PSAC (see Table 7). The authors also concluded that the adsorption capacity increased as flow rate decreased. In other words, removal efficiency increased with longer EBCT.

Table 7. Malathion removal via GAC (Jusoh et al., 2014)

Influent (µg/L)	EBCT (min)	Removal		Process Description
		CSAC[a]	PSAC[b]	
7	2.95	28.6%	18.6%	Bench-scale column experiments: Column diameter = 1.3 cm; Column height = 120 cm; Flow rate of 0.00012 m^3/hr; Adsorbent particle size = 1.0 mm; Temperature = 30˚C NOTE: The treated volume of water is not presented
	3.93	41.4%	31.4%	
	4.91	50.0%	42.9%	
	11.76	64.2%	47.1%	
	15.7	71.4%	60.0%	
	19.6	82.9%	71.4%	

[a] Coconut shell activated carbon.
[b] Palm shell activated carbon.

4.2.1.3 Membrane filtration

In general, nanofiltration (NF) and RO are effective pressure-driven membrane processes for the removal of pesticides from drinking water (Van der Bruggen and Vandecasteele, 2003; US EPA, 2011). The effectiveness of NF and RO for pesticide removal is dependent on the membrane characteristics, pesticide properties, feed water composition, operating conditions and membrane fouling (Van der Bruggen and Vandecasteele, 2003; Plakas and Karabelas, 2012).

Since the main mechanism for pesticide removal using NF and RO membranes is size exclusion, the molecular weight cut-off (MWCO) of the membrane is an important characteristic. Based on the molecular weight of malathion (217 Da), membranes with a MWCO varying between 200 and 400 Da are considered appropriate for malathion. In addition to the sieving effect, retention of small pesticide molecules by larger pore size membranes can be influenced by the physicochemical interactions between the pesticide and the membrane surface (Plakas and Karabelas, 2012).

Bellona et al. (2004) presented a flow-chart using the characteristics of the pesticide in water (e.g., molecular weight, log K_{ow}, molecular diameter) and those of the membrane (e.g., MWCO, pore size) which could be used to determine the potential for removal of malathion by membrane filtration. It is important to perform appropriate testing prior to full-scale implementation with membrane and source water under the proposed operating conditions to ensure that adequate malathion removal is occurring.

Malathion removal was investigated through several bench-scale wastewater studies (see Table 8). Chian et al. (1975) used two different membranes and both achieved greater than 99% malathion rejection. A second bench-scale study by Kiso et al. (2000) investigated malathion removal using four membranes. The malathion removal using the two poly(vinyl alcohol)/ polyamide membranes was high (greater than 88%), whereas the removal was much lower for the membranes composed from sulfonated polyethersulfone (less than 42%). Another study had similarly high malathion removal at a trans-membrane pressure of 1120 kPa and showed improved rejection with increased trans-membrane pressure (Zhang and Pagilla, 2010). A bench-scale study by Sorour and Shaalan (2013) showed increased rejection with increased initial malathion concentration.

Table 8. Malathion removal via reverse osmosis (RO) and nanofiltration (NF) from wastewater studies

Influent	Rejection	Membrane Type	Process Description	Reference
1057.8 µg in 150 mL solution	99.65%	NS-100	Bench-scale study: Stainless steel static test cell Aqueous solution prepared from demineralized water Room temperature; Pressure = 40.8atm (600psig) NS-100: Cross-linked polyethylenimine membrane; Average permeate flux = 49 ml/cm^2/day (12 gfd) CA: Cellulose acetate membrane; Average permeate flux = 32 ml/cm^2/day (8 gfd)	Chian et al. (1975)
	99.16%	CA		
0.5 – 1.5 mg/L	99.64%	Memb-1	Bench-scale study; Flat sheet type membranes Memb-1: Poly(vinyl alcohol)/polyamide; NaCl rejection =92%; [a]J_w=0.988m/d; P=1MPa Memb-2: Poly(vinyl alcohol)/polyamide; NaCl rejection =60%; [a]J_w=1.689m/d; P=1MPa Memb-3: Sulfonated polyethersulfone; NaCl rejection =51%; [a]J_w=2.435m/d; P=1MPa Memb-4: Sulfonated polyethersulfone; NaCl rejection =15%; [a]J_w=6.205m/d; P=0.5MPa	Kiso et al. (2000)
	88.1%	Memb-2		
	42.0%	Memb-3		
	41.4%	Memb-4		
10 mg/L	61%[b] (P=560kPa)	NF-A	Bench-scale; synthetic wastewater NF-A: Polypiperazine amide thin-film composite; $MgSO_4$ retention >99%; Product water flux = 58.4L/m^2·h	Zhang and Pagilla (2010)
	98%[b] (P=1680kPa)			
	78%[b] (P=560kPa)	NF90	Bench-scale; synthetic wastewater NF90: Polyamide thin-film composite; $MgSO_4$ retention >97%; Product water flux = 40.5L/m^2·h; Pore size = 0.55 ± 0.13nm; porosity = 17.1%	
	98%[b] (P=1680kPa)			
	55%[b] (P=560kPa)	NF270	Bench-scale; synthetic wastewater NF270: Polyamide thin-film composite; $MgSO_4$ retention >97%; Product water flux = 53.2L/m^2·h; Pore size = 0.71 ± 0.14nm; porosity = 11.7%	
	92%[b] (P=1680kPa)			
5.7mg/L	93.5%	NF Tubular ceramic membrane	Bench-scale study Membrane properties: Ceramic/TiO_2-Al_2O_3; Tubular configuration; 0.245 m^2 surface area; 1 kDa pore size Pressure = 5 bar	Sorour and Shaalan (2013)
17.1 g/L	99.4%			

[a] Pure water flux;
[b] Estimated from graph.

4.2.1.4 Oxidation and hydrolysis

Chemical oxidation and hydrolysis are the most important degradation pathways for the organophosphorus pesticides under drinking water treatment conditions (Durik et al., 2006; Newhart, 2006). Degradation of malathion in water is pH dependent and it degrades quickly in water with pH >7.0. The half-life range of malathion is 0.2 weeks in water at pH 8.0 compared to

21 weeks at pH 6.0 (Newhart, 2006). The studies examining degradation of malathion using various oxidants are presented in Table 9.

Common oxidation/disinfection processes showed a wide range of reactivity for malathion (Roche and Prados, 1995; Durik et al., 2009, 2010; Chamberlain et al., 2012). Bench-scale testing conducted with typical drinking water disinfection doses of chlorine (Cl_2) and ozone (O_3), have reported moderate to high removal of a low concentration of malathion (Chamberlain et al., 2012) (Table 9). The authors reported a greater than 50% removal of malathion using chlorination conducted at both pH levels of 6.6 and 8.6 and with an ozonation process at pH of 6.6. It was found that ozonation at pH 8.6 achieved a moderate removal ranging from 20 to 50%. Oxidants such as monochloramine (NH_2Cl), chlorine dioxide (ClO_2), permanganate (MnO_4), hydrogen peroxide (H_2O_2), and direct ultraviolet (UV) photolysis at 254 nm, achieved less than 20% removal of malathion. Hydrolysis tests conducted at pHs 2, 7 and 12 also reported similar results (Chamberlain et al., 2012). The application of direct UV photolysis was also reported as being ineffective for the degradation of malathion by Beduk, et al. (2012) and Li et al. (2019). Direct photolysis of organophosphorus pesticides using low- and medium-pressure UV lamps was reported to be very slow with a low quantum yield (Wu and Linden, 2008).

The degradation efficiency of malathion is influenced by several parameters, including water matrix, ozone dose and contact time (Roche and Prados, 1995; Beduk et al., 2012). In a bench-scale ozonation test, Roche and Prados (1995) studied the effect of water alkalinity on the oxidation efficiency of eleven pesticides, including malathion. Due to the inhibiting role of carbonate species, the removal of malathion was higher in water with a low alkalinity (specific data was not provided). Ozonation tests conducted by Beduk et al. (2012) reported an increase of malathion degradation rate with an increased ozone dose and pH level of the water. A direct ozone reaction (ozonolysis) was responsible for the degradation of malathion at a low pH, while a high pH of 9.0 involved a non-selective hydroxyl radical ($^{*}OH$) formation.

Duirk et al. (2009) examined the degradation of malathion in deionized water using hypochlorous acid (HOCl). The oxidation rate of malathion was rapid under the tested conditions and the oxidation efficiency strongly depends on the pH of the water. HOCl is a weak acid that dissociates to produce hypochlorite ion (OCl^-), with a dissociation constant (pK_a) of approximately 7.6 at 20°C. Chlorine species in the water shift from HOCl to hypochlorite ion (OCl^-), when the pH increased from neutral to alkaline. The study reported that OCl^- ion did not oxidize malathion to malaoxon (degradation by-product, discussed below in this section); however it accelerated the hydrolysis of malathion. Similar experiments investigated oxidation of malathion by chloramines using deionized water and pH range from 3.0 to 9.0 (Duirk et al., 2010). The initial malathion concentration was 0.5 µM and the initial monochloramine dose was 50 µM. Auto-decomposition of monochloramine is a pH-dependent process and allows for multiple chlorinated oxidants to coexist at neutral pH [(i.e., monochloramine (NH_2Cl), dichloramine ($NHCl_2$), and HOCl)] (Valentine and Jafvert1992). The reaction rate of monochloramine to degrade malathion was low. Dichloramine exhibited a reaction rate two orders of magnitude higher than monochloramine, but three orders of magnitude lower than hypochlorous acid. The authors reported that a 56% degradation of malathion was due mostly to the oxidation by dichloramine, when oxidation was conducted at a pH of 6.5. Above pH 8.0, alkaline hydrolysis was the primary degradation pathway for malathion, achieving 93% degradation (Duirk et al., 2010).

Organophosphorus pesticides contain a phosphorous/sulphur bond (P=S) that is highly reactive and easily degraded by oxidation, producing oxons having phosphorous/oxygen (P=O)

bonds as a primary degradation by-product (Magara et al., 1994; Kamel et al., 2009; Beduk et al., 2012). Malaoxon is more persistent than malathion and has a degradation kinetic of 4.3 - 5.6 lower than its parent molecule (Magara et al., 1992; Durik et al., 2010; Beduk et al., 2012; Li et al., 2019). Additionally, a study conducted by Aizawa and Magara, (1992) (as cited in Magara et al., 1994) reported that two other degradation by-products, ethyl chloromaleic acid and ethyl maleate, formed during chlorination of malathion. Newhart, (2006) also reported on several degradation by-products resulting from hydrolysis of malathion in alkaline aerobic conditions such as malathion alpha and beta monoacids, diethyl fumarate, diethyl thiomalate, O,O-dimethylphosphorodithioic acid, diethylthiomalate, and O,O-dimethylphosphorothionic acid. No treatment information was provided in the study.

Beduk et al. (2012) investigated malathion degradation by ozonation and the formation of malaoxon. While the malathion concentration of 200 µg/L was completely removed, malaoxon at a concentration of 12 µg/L was formed at an ozone dose of 1.5 mg/L and pH 9.5. Increasing the ozone dose to 2 and 2.5 mg/L caused the malaoxon formation to drop to 8 and 7 µg/L, respectively. The authors concluded that even high ozone doses were not efficient for complete removal of malaoxon. Duirk et al. (2010) reported that malaoxon was highly stable in the presence of chloramine at a pH of 8.5.

Table 9. Removal of malathion via oxidation

Oxidant	Influent (µg/L)	Oxidant Dose (mg/L)	Removal (%) or Reaction Rate ($M^{-1}h^{-1}$)	Process Description	Reference
Cl_2	1.5-3	2-5	>50% (pHs 6.6 and 8.6)	Bench-scale: buffered water (sodium phosphate); 23 ± 1°C and pHs of 6.6 and 8.6	Chamberlain et al. (2012)
O_3		1-2	> 50% (pH 6.6) 20-50% (pH 8.6)		
NH_2Cl		9-14	<20%		
MnO_4^-		3-5			
ClO_2		2-3			
H_2O_2		100			
UV_{254}		77-97 $mV \cdot s/cm^2$			
UV_{254}	200	-	4.4%	Bench-scale reactor: deionized water; medium pressure UV lamp; 90 min contact time	Beduk et al. (2012)
O_3	11.0	1	70.9%	Bench-scale: dechlorinated tap water spiked with pesticides; TOC = 2.1 mg/L; alkalinity = 240 mg/L $CaCO_3$; pH 8.3; ozone demand = 0.5 mg/L; cont. time of 10 min;	Roche and Prados (1995)
		2	89.1%		
		3	96.5%		
		4	>99%		
		5	>99%		
	200	1.5	~100% in: 20 min (pH 9.0); 30 min (pHs 6.5)	Bench-scale reactor: deionized water; pHs of 6.5 and 9.0. Malaoxon formation	Beduk et al. (2012)
$HOCl/OCl^-$	0.5 µM	0-100 µM	1.72 (± 0.36) $x10^6$/ 382 (± 0.26) $M^{-1}h^{-1}$	Bench scale: deionized water; 0.5 µM malathion, pH 6.5, T^0 25 ± 1˚C	Duirk et al. (2009)

4.2.1.5 Advanced Oxidation Processes

AOPs use chemical reactions to form hydroxyl radicals that are used to oxidize chemical compounds, such as pesticides (Crittenden et al., 2012). Several different advanced oxidation processes have been investigated for malathion degradation, including UV/hydrogen peroxide (H_2O_2); O_3/UV and O_3/H_2O_2/UV (see Table 10).

In laboratory tests, the presence of carbonate and sulphate ions was found to negatively impact the degradation of malathion when UV/H_2O_2 was used, with carbonate having the most impact (Fadaei, et al., 2012). The authors reported that malathion degradation was highest in distilled water, followed by tap water and then river water. This observed difference in malathion degradation was due to hydroxyl scavenger property of bicarbonate and sulphate ions and the presence of organic carbon in natural waters. An increase of pH and hydrogen peroxide concentration increased the degradation rate for malathion.

Beduk et al. (2012) investigated the degradation of malathion and subsequent formation of malaoxon in aqueous solution using photocatalytic ozonation (O_3/UV and O_3//UV/ H_2O_2). Efficient removal of both malathion and the formed malaoxon was found for O_3/H_2O_2/UV after 10 and 30 minutes' reaction time, respectively.

A bench-scale study by Roche and Prados (1995) achieved a greater than 99% degradation of malathion for all applied doses of O_3 with H_2O_2 added at a constant ratio of 0.4 g H_2O_2/g O_3. The results in Table 10 indicate that approximately 100% degradation of malathion was achieved with 1.0 mg O_3/L and an addition of 0.4 mg H_2O_2/L, as compared to the process with ozone alone requiring 4.0 mg O_3/L. A similar study by Li et al. (2019), showed a much higher reaction rate (two orders of magnitude) for UV/H_2O_2 oxidation as compared to direct UV photolysis. The degradation reaction by direct UV photolysis involved a photon adsorption, while the UV/H_2O_2 reaction involved formation of hydroxyl radical. Li et al. (2019) also evaluated the formation of by-products. The study reported that each AOP was found to form their own respective grouping of degradation by-products. Based on total organic carbon (TOC) analysis, low mineralization was achieved for malathion under the studied processes. Malathion was converted to degradation by-products rather than being mineralized to CO_2 and water.

Prior to full-scale application, appropriate pilot-scale or bench-scale testing would need to be conducted evaluating malathion removal as well as the degradation products.

Table 10. Removal of malathion via advanced oxidation processes

Process	Infl. (µg/L)	Initial Oxidant Dose (mg/L)	Catalyst	Removal (%) or Reaction Rate (cm^2/mJ)	Process Description and By-Product Information	Reference
UV/ H_2O_2	200, 400 and 600	150 w medium pressure mercury lamp	10 mg/L H_2O_2	Average removal: 77.88 ± 23.96%	Distilled water: pHs 3.0, 7.0 and 9.0; T = 25 ± 1˚C; contact time 180 sec;	Fadaei et al. (2012)
			30 mg/L H_2O_2	Average removal: 82.17 ± 24.24%		
			30 mg/L H_2O_2	~ 45% (in 60 sec) ~ 65% (in 180 sec)	Tap water spiked 200 µg/L malathion; turbidity 1 NTU; pH 7.44; alkalinity 210 mg/L as $CaCO_3$; HCO_3^- 256 mg/L;	

Process	Infl. (µg/L)	Initial Oxidant Dose (mg/L)	Catalyst	Removal (%) or Reaction Rate (cm^2/mJ)	Process Description and By-Product Information	Reference
					SO_4^{2-} 79 mg/L	
			30 mg/L H_2O_2	~ 40% (in 60 sec) ~ 60% (in 180 sec)	River water spiked 200 µg/L malathion; turbidity 12.5 NTU; pH 7.46; alkalinity 290 mg/L $CaCO_3$; HCO_3^- 354 mg/L; SO_4^{2-} 68 mg/L	
	15 µM	0.58 mW/cm^2	No H_2O_2	$6.5x10^{-4}cm^2/mJ$	Bench-scale reactor: aqueous solution pH 7.0; T = 20 ± 0.5˚C	Li et al. (2019)
			0.3 mM H_2O_2	$133.6x10^{-4}cm^2/mJ$		
O_3/UV	200	2.0 mg/L O_3	UV 254 nm	~100% (in 12 min)	Bench-scale reactor: No complete degradation of malaoxon: 13 µg/L in 10 min; 2 µg/L after 90 min	Beduk et al. (2012)
O_3/UV/ H_2O_2			UV 254 nm; H_2O_2 (20, 40 and 100 mg/L)	~100% (in 10 min)	Bench-scale reactor: Optimum: 40 mg/L H_2O_2 Malaoxon: 100% removal (in 30 min)	
O_3/H_2O_2	11.0	1, 2, 3, 4 and 5 mg/L O_3	0.4, 0.8, 1.2, 1.6 and 2.0 mg/L H_2O_2 (H_2O_2/O_3 = 0.4 g/g)	>99% for all doses	Bench-scale: dechlorinated tap water spiked with pesticides; TOC = 2.1 mg/L; alkalinity = 240 mg/L $CaCO_3$; pH 8.3; ozone demand = 0.5 mg/L; ozone demand = 0.5 mg/L	Roche and Prados (1995)

4.2.1.6 Combined technologies

As discussed in the oxidation section 4.2.1.4, formation of by-products such as malaoxon may occur through processes like chlorination. A bench-study by Li et al. (2016) investigated both the removal of malathion and the resulting formation of malaoxon. The authors illustrated that the removal efficiency by coagulation and a combination of coagulation and PAC was better for malathion (5% and 38%, respectively) than malaoxon (2% and 24%, respectively). The authors then examined the impacts of various pre-chlorination doses on overall malathion removal throughout the treatment process by investigating the gross removal of both malathion and malaoxon after the various stages. A treatment train consisting of pre-chlorination, PAC-assisted coagulation-sedimentation-filtration, and post chlorination was used with varying doses of pre-chlorination (0 to 3 mg/L) (See Table 11). The best total gross removal of both malathion and malaoxon was for the scenario in which no pre-chlorination occurred. Without pre-chlorination, malathion was not oxidized to the less well-removed malaoxon, resulting in overall better gross removal. As the pre-chlorination dose increased, malaoxon formed, causing the overall removal to decline.

Table 11. Removal of malathion and malaoxon through PAC/coagulation (Li et al., 2016)

Influent (µg/L)	Pre-CCl dose (mg/L)	Gross Removal of Malathion and Malaoxon (%)				Performance
		Pre-Cl	PAC-CSF[a]	Post-Cl	Total	
10	0	0.0	37.5	5.0	42.5	Bench-scale: Raw river water (pH 7.3; conductivity=267µS/cm; turbidity= 4.15 NTU; DOC=4.37mg/L; UV_{254}= 0.127cm^{-1}; Alkalinity=77.1mg/L; Na^{+}=6.3mg/L; K^{+}=2.2mg/L; Ca^{2+}=48mg/L; Mg^{2+}=4.6mg/L; SO_4^{2-}=30.2mg/L; Cl^{-}=18.6mg/L; F^{-}=0.7mg/L) 10 mg/L PAC; 120 µM Al_2SO_4 Rapid mixing: 250 rpm for 1 minute; Slow mixing: 30 rpm for 15 min; Settling for 30 min; Post-chlorination 1 mg/L for 30 minutes.
	0.25	-0.2	32.0	7.4	39.2	
	0.5	1.0	27.7	7.1	35.8	
	0.75	2.5	23.3	7.4	33.2	
	1	-0.7	19.9	7.6	26.8	
	1.5	4.7	16.2	3.3	24.2	
	2	8.4	16.1	0.4	24.9	
	3	8.5	15.1	0.2	23.8	

[a] PAC-CSF: powdered activated carbon assisted coagulation-sedimentation-filtration

4.2.2 Residential-scale

In cases where malathion removal is desired at the household level, for example, when a household obtains its drinking water from a private well, a residential drinking water treatment unit may be an option for decreasing malathion concentrations in drinking water. Before a treatment unit is installed, the water should be tested to determine the general water chemistry and malathion concentration in the source water.

To verify that a treatment unit is effective, water entering and leaving the treatment unit should be sampled periodically and submitted to an accredited laboratory for analysis. Units can lose removal capacity through use and time and need to be maintained and/or replaced. Consumers should verify the expected longevity of the components in the treatment unit according to the manufacturer's recommendations and service it when required. Systems classified as residential scale may have a rated capacity to treat volumes greater than that needed for a single residence, and thus, may also be used in small systems.

Health Canada does not recommend specific brands of drinking water treatment units, but it strongly recommends that consumers use units that have been certified by an accredited certification body as meeting the appropriate NSF International Standard/American National Standard (NSF/ANSI) for drinking water treatment units. The purpose of these standards is to establish minimum requirements for the materials, design and construction of drinking water treatment units that can be tested by a third party. This ensures that materials in the unit do not leach contaminants into the drinking water (i.e., material safety). In addition, the standards include performance requirements that specify the removal that must be achieved for specific contaminants (e.g., reduction claim) that may be present in water supplies. Certification organizations (i.e., third party) provide assurance that a product conforms to applicable standards and must be accredited by the Standards Council of Canada. Accredited organizations in Canada include:

- Groupe CSA
- NSF International
- Water Quality Association
- UL LLC
- Bureau de normalisation du Québec (available in French only)
- International Association of Plumbing and Mechanical Officials

- Truesdail Laboratories, Inc

An up-to-date list of accredited certification organizations can be obtained from the Standards Council of Canada.

The drinking water treatment technologies that are expected to be effective for malathion removal at the residential-scale include adsorption and RO. Currently, malathion is not included in the performance requirements of NSF/ANSI standards. However, consumers can use a treatment unit that is certified to the standards for RO or adsorption to ensure that the material safety has been tested.

Water that has been treated using RO may be corrosive to internal plumbing components. Therefore, these units should be installed only at the point of use. As large quantities of influent water are needed to obtain the required volume of treated water, these units are generally not practical for point-of-entry installation.

5.0 Management Strategies

All water utilities should implement a risk management approach, such as the source-to-tap or water safety plan approach, to ensure water safety (CCME, 2004; WHO, 2011, 2012). These approaches require a system assessment to characterize the source water, describe the treatment barriers that prevent or reduce contamination, identify the conditions that can result in contamination, and implement control measures. Operational monitoring is then established, and operational/management protocols are instituted (e.g., standard operating procedures, corrective actions and incident responses). Compliance monitoring is determined and other protocols to validate the water safety plan are implemented (e.g., record keeping, consumer satisfaction). Operator training is also required to ensure the effectiveness of the water safety plan at all times (Smeets et al., 2009).

5.1 Monitoring

Malathion can be present in groundwater and surface water in areas where it is being used depending on the type and extent of its application, environmental factors (e.g., amount of precipitation, soil type, hydrogeological setting, etc.) and environmental fate (e.g., mobility, leaching potential, degradation, etc.) in the surrounding area. Water utilities should consider the potential for malathion to enter source water (e.g., raw water supply to the drinking water system) based on site-specific considerations.

When it is determined that malathion may be present and monitoring is necessary then surface and groundwater sources should be characterized to determine the concentration of malathion. This should include monitoring of surface water sources during periods of peak use and rainfall events and/or monitoring of groundwater annually. Where baseline data indicate that malathion is not present in source water, monitoring may be reduced.

Where treatment is required to remove malathion, operational monitoring should be implemented to confirm whether the treatment process is functioning as required. The frequency of operational monitoring will depend on the water quality, fluctuations of the raw water concentrations and the treatment process. Responsible authorities should be aware of the impact of natural organic matter on activated carbon systems, as it may impact water quality objectives for malathion removal.

Where treatment is in place for malathion removal, compliance monitoring (i.e., paired samples of source and treated water to confirm the efficacy of treatment) should be conducted at a minimum on an annual basis. When routine operational monitoring indicates the potential for contaminant breakthrough, such as with GAC, monitoring should be conducted at least quarterly to plan for change-out of media. When a degradation process, like oxidation, is utilized, monitoring of by-product formation should also be considered.

6.0 International Considerations

Other national and international organizations have drinking water guidelines, standards and/or guidance values for malathion in drinking water. Variations in these values can be attributed to the age of the assessments or to differing policies and approaches, including the choice of key study and the use of different consumption rates, body weights and source allocation factors (Table 12).

The Australian National Health and Medical Research Council (NHMRC) has set a guideline value of 0.07 mg/L for malathion in drinking water based on EChE inhibition in rats (NHMRC and NRMMC, 2011). The US EPA does not have a maximum contaminant level (MCL) for malathion (US EPA, 2009). The World Health Organization (WHO) concluded that malathion occurs in drinking water at levels well below those of health concern and therefore has not established a formal guideline value for malathion (2004, 2017b).

The European Union (EU) does not have a specific chemical parametric value for individual pesticides. Instead, the EU has a value of 0.1 µg/L for any individual (single) pesticide, and a value of 0.5 µg/L for total pesticides found in drinking water. In establishing these values, the EU did not consider the science related to each pesticide, such as health effects. Instead, the values are based on a policy decision to keep pesticides out of drinking water (EU, 1998).

Table 12. Comparison of international drinking water values for malathion

Agency (Year)	Value (mg/L)	Key Endpoint (Reference)	NO(A)EL (mg/kg bw per day)	UF	ADI (mg/kg bw/day)	bw (kg)	DW Intake (L/day)	AF (%)	Comments
Health Canada - proposed MAC (2020)	0.29	Increase in severity of chronic kidney disease in a 2-year toxicity and carcinogenicity study in rats (Daly, 1996)	3 (NOAEL)	100	0.030	74	1.53	20	
US EPA (2009; 2018)	0.5 (non-regulatory lifetime health advisory)	EChE inhibition in offspring from the comparative ChE multiple dose oral study in rats (US EPA, 2009)	7.1 ($BMDL_{10}$)	100	0.07 (RfD)	70	2	20	US EPA has set a non-regulatory lifetime health advisory rather than a MCL for malathion in drinking water, which is calculated from

Agency (Year)	Value (mg/L)	Key Endpoint (Reference)	NO(A)EL (mg/kg bw per day)	UF	ADI (mg/kg bw/day)	bw (kg)	DW Intake (L/day)	AF (%)	Comments
									its associated Drinking Water Equivalent Level (DWEL) of 2 mg/L, obtained from its RfD (US EPA, 2018).
WHO (2004; 2017b)	0.9 (non-regulatory HBV)	Decreased survival, reduced body weight and decreased AChE activity in a 2-year toxicity and carcinogenicity study in rats (Daly, 1996).	29 (NOAEL)	500	0.3	60	2	10	WHO has set a non-regulatory HBV rather than a formal guideline for malathion in drinking water (WHO, 2017b).
Australia (NHMRC and NRMMC, 2011)	0.07	Red blood cell ChE inhibition in two-year rat study (Daly, 1996)	2 (NOEL)	100	0.02	70	2	10	No reference for the two-year rat study is provided in NHMRC and NRMMC, 2011 although description is consistent with Daly, 1996.
EU (1998)	0.1 µg/L	The EU has a value of 0.1 µg/L for any individual (single) pesticide, and a value of 0.5 µg/L for total pesticides found in drinking water. In establishing these values, the EU did not consider the science related to each pesticide, including health effects. Instead, the values are based on a policy decision to keep pesticides out of drinking water.							

AF – Allocation factor
$BMDL_{10}$ – Benchmark Dose Lower Confidence Limit associated with a 10% response
bw – Body weight
DW – Drinking water
DWEL – Drinking water equivalent level
NOEL – No observed effect level
RfD – Reference dose
UF – Uncertainty factor

7.0 Rationale

Malathion is a registered insecticide and acaricide used on a wide variety of sites including agricultural and non-agricultural sites. Despite its common use in Canada, data provided by provinces and territories that monitor for malathion in source and drinking water indicate that when detected, levels of malathion are well below the proposed MAC. The kidney has been identified as the most sensitive target organ for malathion toxicity. Although no human

studies have investigated the effects of malathion on the kidney, animal studies conducted in rats and dogs have consistently shown nephrotoxicity following malathion exposure.

Health Canada, in collaboration with the Federal-Provincial-Territorial Committee on Drinking Water, is proposing a MAC of 0.29 mg/L (290 µg/L) for malathion in drinking water based on the following considerations:

- An HBV of 0.29 mg/L (290 µg/L) based on an increase in severity of chronic nephropathy in female rats.
- Analytical methods are available to accurately measure malathion at concentrations well below the proposed MAC.
- Treatment technologies are available to effectively decrease malathion at concentrations well below the proposed MAC.

The MAC is protective of potential health effects from malathion exposure. As part of its ongoing guideline review process, Health Canada will continue to monitor new research in this area, including the outcomes of PMRA's evaluations, and recommend any change to this guideline technical document that it deems necessary.

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Appendix A: List of abbreviations

ACh	Acetylcholine
AChE	Acetylcholine esterase
ADI	Acceptable daily intake
AHS	Agricultural Health Study
AOP	Advanced oxidation processes
ATSDR	Agency for Toxic Substances and Disease Registry
BChE	Brain cholinesterase
bw	Body weight
CAS	Chemical Abstracts Service
CDW	Committee on Drinking Water
CFIA	Canadian Food Inspection Agency
ChE	Cholinesterase
CSAC	Coconut shell activated carbon
DCA	Dicarboxylic acid
EChE	Erythrocyte cholinesterase
EFSA	European Food Safety Authority
EBCT	Empty bed contact time
EPA	Environmental Protection Agency
EU	European Union
FAO	Food and Agriculture Organization of the United Nations
F1	First generation
GAC	Granular activated carbon
GC/FPD	Gas chromatography with flame photometric detector
GC/MS	Gas chromatography with mass spectrometry detection
GD	Gestational day
HBV	Health-based value
IARC	International Agency for Research on Cancer
LD_{50}	Median lethal dose
LOD	Limit of detection
MAC	Maximum acceptable concentration
MCA	Monocarboxylic acid
MCL	Maximum contaminant level
MDL	Method detection limit
MRL	Method reporting limit
MWCO	Molecular weight cut-off
NCI	National Cancer Institute
NF	Nanofiltration
NHL	Non-Hodgkin lymphoma
NHMRC	National Health and Medical Research Council (Australia)
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect level
NOM	Natural organic matter
NRMMC	National Resource Management Ministerial Council (Australia)
PAC	Powdered activated carbon

PACR	Proposed acceptability for continuing registration
PChE	Plasma cholinesterase
PND	Postnatal day
PMRA	Pest Management Regulatory Agency
PSAC	Palm shell activated carbon
RO	Reverse osmosis
TOC	Total organic carbon
UDS	Unscheduled DNA synthesis
US EPA	United States Environmental Protection Agency
USGS	United States Geological Survey
UV	Ultraviolet
WHO	World Health Organization

Appendix B: Canadian water quality data

Table B1. Levels of malathion in Canadian aquatic sources and air from the National Water Quality Surveillance Program (2003–2005)

Jurisdiction (Year Sampled)	No. Detects/ Samples	MDL (ng/L)	Range (ng/L)	
			Min	Max
BC – Lower Fraser Valley and Okanagan Basin (2003-2005)	7/96	0.062	<0.062	75.1
ON (2003)	1/162	14.7	143	143
ON (2004)	2/228	14.7	31.7	449
ON (2005)	3/160	14.7	10.4	611
ON – 10 isolated lakes (2003-2005)	3/163	0.001	<0.001	2.20
QC (2003)	0/49	20	Not available	Not available
QC (2004)	0/69	4-20	Not available	Not available
QC (2005)	0/62	20	Not available	Not available
AB, SK, MB – 8 sites (2003)	0/13	14.7	Not available	Not available
AB, SK, MB – 15 sites (2003-2004)	0/30	14.70	<14.70	<14.70
ON – 4 sites (2004-2005)	0/12	0.000	<0.000	Not available

Note: Adapted from Environment Canada, 2011
MDL – method detection limit