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# ***Metribuzin in Drinking Water***

Guideline Technical Document  
for Public Consultation

Consultation period ends  
September 11, 2020

Canada 

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## Purpose of consultation

This guideline technical document outlines the evaluation of the available information on metribuzin with the intent of updating the guideline for metribuzin in drinking water. The purpose of this consultation is to solicit comments on the proposed guideline, on the approach used for its development, and on the potential impacts of implementing them.

The existing guideline on metribuzin, developed in 1986, based its maximum acceptable concentration (MAC) of 0.08 mg/L (80 µg/L) on liver toxicity in dogs. This document proposes to retain the MAC of 0.08 mg/L (80 µg/L) for metribuzin in drinking water, based on liver toxicity in dogs.

This document is available for a 90-day public consultation period.

Please send comments (with rationale, where required) to Health Canada via email:

[HC.water-eau.SC@canada.ca](mailto:HC.water-eau.SC@canada.ca)

or

Water and Air Quality Bureau, Health Canada  
269 Laurier Avenue West, A.L. 4903D  
Ottawa, ON K1A 0K9

All comments must be received before September 11, 2020. Comments received as part of this consultation will be shared with members of the Federal-Provincial-Territorial Committee on Drinking Water (CDW), along with the name and affiliation of their author. Authors who do not want their name and affiliation shared with CDW members should provide a statement to this effect along with their comments.

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

## Proposed guideline

*A maximum acceptable concentration (MAC) of 0.08 mg/L (80 µg/L) is proposed for metribuzin 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 metribuzin completed by Health Canada's Pest Management Regulatory Agency (PMRA) and supporting documents.

## Exposure

Metribuzin is a pre-and post-emergent herbicide used to control broadleaf weeds and grasses in agriculture. In 2016 (the most recent year for which data are available), more than 100,000 kg of metribuzin (as an active ingredient) was sold in Canada. Metribuzin is released into the environment as surface runoff following agricultural spraying (particularly within two weeks of soil application), as tile drain effluent, from accidental discharge or as spray drift. It has the potential to leach into groundwater or move into surface water.

Data provided by provinces and territories that monitor for metribuzin indicate that metribuzin is not commonly found in source or drinking water in Canada. However, low levels of metribuzin have been found in source and treated drinking water in a few Canadian provinces during targeted monitoring programs in agricultural areas where metribuzin is being applied. Although metribuzin is used on food crops, it is rarely detected in foods.

## Health effects

In repeat-dose animal studies, metribuzin primarily targeted the liver, and to a lesser extent, the thyroid but did not cause birth defects, reproductive effects or an increase in cancer. Of the available studies in humans, there was no relationship between exposure to metribuzin and the incidence of cancer or Parkinson's disease. The proposed MAC of 0.08 mg/L (80 µg/L) is based on liver effects seen in a two-year dog study.

## Analytical and treatment considerations

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

At the municipal level, treatment technologies that are available to effectively decrease metribuzin concentrations in drinking water include oxidation, activated carbon adsorption, and membrane filtration. These technologies are capable of achieving treated water concentrations well below the proposed MAC. Although metribuzin may be removed using common oxidants used for disinfection (e.g., chlorine), utilities should be aware of the potential formation of degradation by-products.

In cases where metribuzin 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 metribuzin 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 metribuzin removal is occurring.

### **Application of the guideline**

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

The proposed guideline is protective against health effects from exposure to metribuzin 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 metribuzin concentrations are above the proposed MAC, then an investigation to determine the most appropriate way to reduce exposure to metribuzin should be conducted. This may include use of an alternate water supply or installation of treatment. Where treatment is already in place and an exceedance occurs, an investigation should be conducted to verify treatment and determine if adjustments are needed to lower the treated water concentration below the proposed MAC.

### **International considerations**

Other national and international organizations have drinking water guidelines, standards and/or guidance values. 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.

Australia's National Health and Medical Research Council has set a guideline value of 0.07 mg/L for metribuzin in drinking water. The United States Environmental Protection Agency (U.S. EPA) does not have a regulatory value for metribuzin. The U.S. EPA considers regulating metribuzin in drinking water would have little impact on human health risk reduction as its occurrence in public water systems and the number of people potentially exposed through drinking water is low. The World Health Organization (WHO) has not set a specific guideline value for metribuzin.

The European Union (EU) does not have a specific 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, including health effects. Instead, the values are based on a policy decision to keep pesticides out of drinking water.

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## 1.0 Exposure Considerations

### 1.1 Sources and uses

Metribuzin or 4-amino-6-(1,1-dimethylethyl)-3-(methylthio)-1,2,4-triazine-5(4H)-one is a pre- and post-emergent herbicide used to control broad-leaf weeds and grasses in agricultural crops by inhibiting photosynthesis (CCME, 1999; Health Canada, 2005). More than 100,000 kg active ingredient of metribuzin was sold in Canada in 2016 (Health Canada, 2016).

Metribuzin is released into the environment as surface runoff following agricultural spraying (particularly within two weeks of soil application), as tile drain effluent, from accidental discharge or as spray drift and it has the potential to leach into groundwater or move into surface water (Bastien and Madramootoo, 1992; U.S. EPA, 1998; CCME, 1999; U.S. EPA, 2003; Health Canada, 2005). Leaching from soil is influenced by topography, precipitation and site-specific soil characteristics (Health Canada, 2019a). Under sandy soil conditions, metribuzin is 'highly' to 'very highly' mobile and likely to leach (CCME, 1999; U.S. EPA, 2003; European Food Safety Authority (EFSA), 2010). Leaching is hindered in soils with high clay and/or high organic matter content as metribuzin moderately adsorbs to soil with adsorption decreasing as soil pH increases or as organic matter content decreases (Bowman, 1991; CCME, 1999; U.S. EPA, 2003; EFSA, 2010; Rigi et al., 2015). Microbial degradation to desamino-diketo-metribuzin (DADK), diketo-metribuzin (DK) and carbon dioxide is one of two principal routes of removal of metribuzin from soil with metribuzin being moderately persistent under aerobic conditions (half-life of 40-106 days) and highly persistent under anaerobic conditions (half-life of 112-439 days) (U.S. EPA, 2003; EFSA, 2010). The other degradation route from soil and surface water is photodegradation (half-life of 4.3 hours to 2.5 days) which produces desamino-metribuzin (DA), although this route is only relevant in the top 1 millimeter of soil exposed to direct sunlight or in shallow, clear surface water with good light penetration (U.S. EPA, 2003; EFSA, 2010). Both DADK and DK are persistent and very mobile in soil (U.S. EPA, 1998).

In groundwater, metribuzin mainly breaks down into the same metabolites (DADK, DK, DA) as in soil and these metabolites are present at an order of magnitude less than the parent compound metribuzin (Lawrence et al., 1993). Metribuzin in groundwater has a half-life of 350 days in a shallow aquifer (Perry, 1990). Metribuzin resists hydrolysis with an extrapolated half-life of 1,317 days at 20°C and pH 9 (EFSA, 2010). Based on its vapour pressure (5-10 mmHg at 20 °C), Henry Law constant ( $2.0 \times 10^{-5}$  Pa m<sup>3</sup>/mol) and photo-oxidative degradation in the atmosphere (21 hours), metribuzin is not expected to volatize from either water or land surfaces or undergo long range airborne transport (CCME, 1999; U.S. EPA, 2003; EFSA, 2010).

### 1.2 Substance identity

Metribuzin (C<sub>8</sub>H<sub>14</sub>N<sub>4</sub>OS) is a white crystalline solid belonging to the asymmetric triazinone class of chemicals (U.S. EPA, 1998; Health Canada, 2005).

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

Property	Metribuzin	Interpretation
CAS#	21087-64-9	
Molecular weight (g/mol)	214.3	
Water solubility (g/L)	1.2	Highly soluble in water
Vapour pressure (volatility)	5 to 10 mmHg at 20°C	Low volatility, unlikely to contaminate air
Henry's Law constant	$2.0 \times 10^{-5}$ Pa m <sup>3</sup> /mol <sup>a</sup>	Low volatilization potential
octanol: water partition coefficient (Log K <sub>ow</sub> )	1.6 at pH 4-9, 20 °C <sup>a</sup>	Unlikely to bioaccumulate

Unless otherwise indicated, information is from U.S. EPA, 2003.

<sup>a</sup>EFSA, 2010.

### 1.3 Exposure

Media-specific exposure data are limited to levels in water and food. Canadian water monitoring data from the provinces and territories (municipal and non-municipal supplies), Health Canada's Pest Management Regulatory Agency (PMRA) and Environment Canada (Environment Canada, 2011) (Appendix B) were available for metribuzin while food data was available from the United States (U.S.).

Water monitoring data provided by the provinces and territories indicate that metribuzin levels are below the method reporting limit (MRL) or method detection limit (MDL) in the majority of samples. This includes samples from a variety of water supplies in Canada, including surface water and groundwater as well as treated and distributed drinking water where monitoring occurred (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 du Québec, 2019; Nova Scotia Environment, 2019; Government of Ontario, 2019; Prince Edward Island (P.E.I.) Department of Communities, Land and Environment, 2019).

Provinces that conducted monitoring in which all samples were reported below the MDLs are reported in Table 2. This provides information on the number and types of samples each province collected over a specified time period in which no metribuzin was detected. In addition, data provided by First Nations and Inuit Health Branch for various regions in Canada (Manitoba, Ontario, Quebec and Atlantic region) indicated that metribuzin levels were below the MDLs in all samples (n=821; MDLs 0.01-5 µg/L) collected between 2014 and 2018 (Indigenous Services Canada, 2019).

Water monitoring data from provinces that conducted sampling where concentrations above the detection limit were reported are summarized in Table 3. Monitoring conducted in Prince Edward Island (P.E.I.) found low concentrations ranging from 0.04 to 0.28 µg/L for municipal wells and 0.03 to 1.21 µg/L for non-municipal/private wells (P.E.I. Department of Communities, Land and Environment, 2019). Quebec reported three data sets representing samples collected from both municipal surface and groundwater supplies as well as samples collected as part of two special projects evaluating groundwater quality in potato growing regions and small systems/private wells. Detectable concentrations were low with a concentration range in municipal systems of 0.03 and 0.06 µg/L and a range in groundwater from the special projects monitoring between 0.01 and 1.7 µg/L (Ministère de l'Environnement et de la Lutte contre les changements climatiques du Québec, 2019).

Monitoring for metribuzin is not currently conducted in New Brunswick, Newfoundland and Labrador, Saskatchewan and Yukon (New Brunswick Department of Health, 2019; Newfoundland and Labrador Municipal Affairs and Environment, 2019; Saskatchewan Water Security Agency, 2019; Yukon Environmental Health Services, 2019).

**Table 2.** Summary of non-detect monitoring data for metribuzin

<b>Jurisdiction</b> (MDL $\mu\text{g/L}$ )	<b>Monitoring Period</b>	<b>Water Type</b> (Municipal: ground/surface – raw, treated, distributed)	<b># Detects/</b> <b>samples</b>
British Columbia (2.5 - 5)	2013-2018	Surface – raw	0/18
Manitoba (0.2)	2015-2018	Surface – ambient	0/396
Nova Scotia (0.25 - 7)	2007-2018	Ground – raw	0/72
		Ground – treated	0/34
		Surface – raw	0/35
		Surface – treated	0/40
		Distributed	0/1
Ontario (0.05)	2008-2012	Ground – raw	0/214
		Ground – treated	0/48
		Surface/ground – raw	0/564
		Surface/ground – treated	0/583
		Surface/ground – distribution	0/1

**Table 3.** Summary of metribuzin detections in select provinces in Canada

Jurisdiction (MDL µg/L)	Monitoring Period	Water Type (Municipal: ground/surface – raw, treated, distribution and Non-Municipal: ground)	# Detects/ samples	Maximum Conc. (µg/L)
P.E.I. (0.03)	2004-20017	Ground-raw (municipal)	12/665	0.28
		Ground-raw (non-municipal)	27/614	1.21
Québec (0.01 – 0.9)	2012-2018	Ground – distribution (municipal)	0/578	
		Surface – distribution (municipal)	3/1708	0.06
		Ground – raw <sup>a</sup> (municipal)	1/46	0.06
		Ground – treated <sup>a</sup> (municipal)	0/17	
		Ground – distribution <sup>a</sup> (municipal)	1/5	0.02
		Ground – raw <sup>b</sup> (municipal)	0/82	
		Ground – raw <sup>b</sup> (non-municipal)	14/132	1.70

<sup>a</sup> Potato Project 2017-2018: Results of metribuzin analyses in raw, treated or distributed groundwater from nine drinking water supplies.

<sup>b</sup> Small Systems Project 2012-2018: Results of metribuzin analyses found in raw groundwater from 25 water supplies.

Health Canada's PMRA (Health Canada, 2019a) evaluated several Canadian surface and groundwater monitoring studies that were conducted in P.E.I., British Columbia, Alberta, Quebec, Manitoba, New Brunswick, Ontario and Nova Scotia. A large amount of monitoring data was available for metribuzin in Canada but only a few studies were from potential sources of drinking water. A total of 3,820 groundwater samples were analyzed for metribuzin. There were 259 detections (7% detection frequency), with a maximum detected concentration in groundwater of 7.5 µg/L in P.E.I. during the 1988-1989 sampling period. The data from the P.E.I. sites are considered to be a worst case scenario, as metribuzin was used in the fields over a 3 year period and the wells were located downslope or within 300 meters of treated fields. A total of 10,393 surface water samples were analyzed for metribuzin. Metribuzin was detected in 849 of the samples (8% detection frequency). The two highest concentrations detected were 195 µg/L and 87 µg/L. These two concentrations were detected in P.E.I. in 2008 and one of the detections was sampled during a runoff event. In P.E.I., all drinking water is sourced from groundwater, and detections of metribuzin in P.E.I. surface water were not considered relevant sources of drinking water. Overall, available monitoring data on metribuzin indicate that the maximum concentrations in Canadian drinking water sources were 7.5 µg/L in groundwater and 6.1 µg/L in surface water. The highest detections were not observed in areas of highest metribuzin use (i.e., Saskatchewan and Ontario), but were detected in areas considered to be most vulnerable to leaching and runoff due to high incidents of precipitation, sandy soil textures and shallow groundwater tables.

Using annual total precipitation by ecodistricts and the percent of total sand in agricultural areas in Canada, the following can be inferred:

- Eastern Canada receives higher precipitation than Western Canada;
- the majority of soils in the agricultural areas of Western Canada have less than 50% sand, while soils in Eastern Canada are more coarse, with a higher sand content (>69%);
- compared to Western Canada, Eastern Canada generally has a shallower groundwater table; and

- the potential to detect metribuzin in groundwater in Saskatchewan is low because of its medium to fine textured soils.

Based on its higher precipitation, its coarse and sandy soil texture, and its shallower groundwater table, Eastern Canada is relatively more vulnerable to leaching of metribuzin than Western Canada (Health Canada, 2019a).

Although metribuzin is applied to food crops, it is rarely detected in food samples and does not tend to accumulate in food (Bray et al., 2008). Canadian food residue data were unavailable. Monitoring data conducted by the United States Department of Agriculture's Pesticide Data Program and collated by Bray et al. (2008) did not find any residues of metribuzin in 2,586 dairy products (milk, heavy cream, butter) sampled from 2003 to 2005 (limit of detection ranged from 0.3 to 6.0 ppb). Metribuzin was detected in only 13 of 26,487 fruits and vegetables sampled between 2000 and 2005 and was not detected in 4,362 barley grain, soybeans and wheat flour sampled between 2002 and 2005 (Bray et al., 2008). Metribuzin was not detected in meats (poultry n=1564, pork n= 704, and beef n=1835) (Bray et al., 2008).

## 2.0 Health Considerations

All pesticides, including metribuzin, are regulated by Health Canada's 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 (U.S. EPA). As such, this health assessment is primarily based on PMRA's evaluations (Health Canada, 2005, 2006) and supporting documentation. Additionally, any reviews and relevant literature available since PMRA's evaluations were completed were also considered.

### 2.1 Kinetics

**Absorption:** Metribuzin is rapidly and almost completely absorbed (95% to 100% based on excretion data) within thirty-six hours following ingestion with peak blood and tissue levels being achieved within 4 hours (Bleeke et al., 1985; Office of Environmental Health Hazard Assessment (OEHHA), 2001; EFSA, 2010). Based on a study in rats, dermal absorption of metribuzin is unlikely to occur (Löser and Kimmerle, 1972).

**Distribution:** Metribuzin and its metabolites are widely distributed following absorption with the highest concentrations found in the thyroid and liver followed by kidneys and then other tissues (heart, fat, ovaries, brain, muscle, plasma and testes) (OEHHA, 2001; EFSA, 2010). Thyroid tissue contained 10-times more metribuzin than liver tissue (OEHHA, 2001).

**Metabolism:** Based on studies in Wistar rats, metabolism of metribuzin is extensive and occurs rapidly through several pathways (deamination, hydroxylation at the t-butyl side chain, hydrolytic or aminolytic cleavage of the thioalkyl moiety, and conjugation), some of which can act in combination, producing numerous metabolites in urine, feces and tissues (Bleeke et al., 1985; Cain et al., 1987; OEHHA, 2001; EFSA, 2010; Estonia and Germany, 2018). Cytochrome P450 may be involved in the initial metabolism, yielding reactive intermediates such as metribuzin sulfoxide or deamonometribuzin sulfoxide which then react with glutathione (GSH) (Bleeke et al., 1985; OEHHA, 2001). Conversion to mercapturic acid derivatives appears to follow conjugation with GSH (Estonia and Germany, 2018). At very high levels, or in the absence of GSH or other non-protein sulfhydryls, metabolites can bind to proteins (OEHHA, 2001). Metabolites were similar in urine and feces and include DA, DK, demethylmetribuzin (DM), tert-butylhydroxy-metribuzin, and N-acetylcysteine-metribuzin (N-AC-metribuzin) as

well as many unidentified metabolites (OEHHA, 2001; EFSA, 2010; Estonia and Germany, 2018).

**Elimination:** Metribuzin and its metabolites are rapidly excreted in the urine and feces, with up to 96% being eliminated within four days (Bleeke et al., 1985; Cain et al., 1987; Mathew et al., 1998). Species, strain and sex differences in the proportions and types of metabolites eliminated in excreta were observed (OEHHA, 2001). In studies using radiolabelled (<sup>14</sup>C) metribuzin, male albino rats eliminated almost equal amounts of <sup>14</sup>C in the urine and feces (Bleeke et al., 1985); Wistar rats excreted 55.8% to 71.5% in the feces, 27.3% to 43.4% in the urine and 0.1% in expired air (Cain et al., 1987; EFSA, 2010); and male mongrel dogs excreted twice as much <sup>14</sup>C label in urine compared to feces (Baychem, 1972). For all tissues, the elimination half-lives ranged from 18.4 to 33.6 hours and were generally shorter in males than females (OEHHA, 2001; EFSA, 2010).

## 2.2 Health effects

The toxicity database for metribuzin is well-characterized, covering several endpoints and various types of exposure (see U.S. EPA, 1998, 2003; OEHHA, 2001; EFSA, 2010; Estonia and Germany, 2018 for more thorough reviews). In animals, metribuzin was not acutely toxic and was well-tolerated in repeat-dose studies. It also did not cause birth defects or reproductive effects. It was not carcinogenic in animal studies using rats (Wistar and Fischer 344) and mice (CD1) or in epidemiological studies. The liver and the thyroid have been identified as the target organs in animals.

## 2.3 Effects in humans

No human effects were discussed in Health Canada's assessments by PMRA or their supporting documents, as no human health studies were available in the published literature at that time (U.S. EPA, 1998, 2003; Health Canada, 2005, 2006). Studies were available from the more recent literature concerning both cancer and non-cancer endpoints, and are included in this assessment.

**Agricultural Health Study:** The Agricultural Health Study (AHS) is a large, questionnaire-based prospective study (over 89,000 participants) investigating cancer and non-cancer endpoints in a cohort of licensed pesticide applicators and their spouses in Iowa and North Carolina. 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 (questionnaire-based), 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 analysis of the AHS data. A case-control analysis by Andreotti et al. (2009) did not find an association between metribuzin and the development of pancreatic cancer after controlling for age, smoking and diabetes. Alavanja et al. (2003), examining AHS data from 1993 to 1997, found overall cancer incidence in pesticide applicators to be significantly less than expected for 45 common pesticides

including metribuzin when compared to incidence among males in the general populations of Iowa and North Carolina. The study also did not find an association between metribuzin use and prostate cancer incidence. Similarly, Delancey et al. (2009) did not find an association between metribuzin use and overall cancer incidence but did suggest a potential association between metribuzin use as measured by intensity-weighted lifetime exposure days and certain lymphohematopoietic malignancies (defined as lymphomas, myelomas, and leukemias) when the low-exposure group was the referent. However, these findings were not consistent across exposure metrics and reference groups (low-exposure vs. no exposure groups), and may have resulted from the smaller sample size in the low exposure group or from a residual confounder. A more recent non-AHS cohort study involving more than 300,000 farmers from France, Norway and the US failed to associate metribuzin exposure with Non-Hodgkin's lymphoma (NHL), leukemia, and lymphoma (Leon et al., 2019). A pooled analysis of three case-control studies from the 1980s also did not find an association between “ever” use of metribuzin by farmers and NHL (De Roos et al., 2003).

A population-based case-control study using telephone interviews was conducted as part of the Nebraska Health Study II (Lee et al., 2005). It found a significant association between metribuzin exposure and the risk of glioma among male but not female farmers. Weaknesses of the study included the low number of glioma cases (n=9), the proportion of proxy respondents (4 of 9), recall bias, and the potential for differential misclassification (Lee et al., 2005).

**Non-Cancer:** Examining non-cancer endpoints, Hoppin et al. (2002) did not find an association between metribuzin use and wheeze among pesticide applicators based on AHS data collected from 1994 to 1997 although a follow-up study using 2005 to 2010 data found an elevated, but not statistically significant association between metribuzin use and allergic wheeze (Hoppin et al., 2017). Using AHS data up to 2003, Kamel et al. (2006) did not find a strong association between metribuzin use and Parkinson's disease. Goldner et al. (2013) did not find an association between metribuzin use by male pesticide applicators in the AHS and thyroid disease.

## 2.4 Effects in animals

Repeat exposure studies in rats, mice and dogs showed metribuzin primarily affected the liver and the thyroid although other effects have also been noted (Löser and Mirea, 1974; Löser and Mohr, 1974; Hayes, 1981; Thyssen, 1981; Flucke and Hartmann, 1989; Christenson and Wahle, 1993). Metribuzin showed low acute toxicity based on oral LD<sub>50</sub> values of 2345 mg/kg (female) and 2200 mg/kg (male) in Wistar II rats, 711 mg/kg (female) and 698 mg/kg (male) CF<sub>1</sub> mice, >500 mg/kg (male) in rabbits and 250 mg/kg (male) in guinea pigs, the most sensitive species (Löser and Kimmerle, 1972). Health effects included laboured breathing and sedation (Löser and Kimmerle, 1972). Dermal LD<sub>50</sub> values of >20,000 mg/kg in rabbits and >500 mg/kg in Wistar II rats, and inhalation values of >0.648 mg/L (maximum obtainable concentration was used) and >885 mg/m<sup>3</sup> both in rats have been reported; animals showed no signs of toxicity (Crawford and Anderson, 1972; Löser and Kimmerle, 1972; Shiotsuka, 1986; Breckenridge et al., 2009).

**Liver effects:** The liver was the main target organ in chronic studies using dogs, mice and rats, as well as in subchronic and short-term studies using dogs, rats, and rabbits. Effects consisted of changes in liver enzymes, histopathological changes, and increased absolute and relative liver weights.

Chronic oral studies were conducted in beagles, mice and two species of rats. In a study by Löser and Mirea (1974), beagles were fed 25-1500 ppm of metribuzin daily for two years. At the highest dose, dogs had changes in liver histopathology, increased relative liver weights and increased liver enzymes including serum glutamate-oxaloacetate transaminase (SGOT), serum glutamate-pyruvate transaminase (SGPT), alkaline phosphatase, and bromosulphthalein (BSP) retention. CD1 mice fed 200-3200 ppm metribuzin for two years had increased relative liver weights but only in the high dose group (Hayes, 1981). Histopathological changes in the liver were seen in Wistar rats (25-300 ppm) and F344 rats (30-900 ppm) fed metribuzin for up to two years but only at 300 ppm and above (Löser and Mohr, 1974; Christenson and Wahle, 1993).

Two oral subchronic studies also showed similar hepatic effects. In beagles fed  $\leq 500$  ppm of metribuzin for 90 days hepatic effects including dose-dependent increases in liver weight, liver to body weight ratio and liver to brain weight ratio as well as a small decrease in SGOT and SGPT at 500 ppm males only (Chaisson and Cueto, 1970). Increased liver weights were also observed in high-dose (1500 ppm) Wistar rats fed 50-1500 ppm for 3 months although liver pathology was unremarkable (Löser et al., 1969).

Short-term 21-day studies via dermal exposure (New Zealand rabbits) and inhalation (Wistar TNO/W 74 albino rats) also showed liver effects including: a dose-dependent increase in cholesterol in rabbits, increased liver enzymes N-demethylase and cytochrome P450 in rabbits and rats, as well as increased O-demethylase levels and increased liver weight in rats (Thyssen, 1981; Flucke and Hartmann, 1989).

In a two-generation reproduction study using Crl:CD BR rats, liver effects (hypertrophy of the hepatocytes of the centrilobular and mid zonal regions) were seen in high-dose males (750 ppm) and mid- and high-dose females (150 and 750 ppm, respectively) (Porter et al., 1988).

**Thyroid effects:** Thyroid effects included changes in thyroid weights and in levels of circulating thyroid hormones and were seen in rats, dogs and rabbits.

Increased absolute and relative thyroid weights (in males only), as well as increased thyroxine (T4) and decreased triiodothyronine (T3) were seen in a chronic study in which Fischer 344 rats were fed 30-900 ppm of metribuzin daily for 104 weeks (Christenson and Wahle, 1993). Similarly, thyroid weights were increased in high-dose beagles fed metribuzin (25-1500 ppm) daily for two years and in high-dose Wistar rats fed metribuzin (50-1500 ppm) daily for 3 months (Löser et al., 1969; Löser and Mirea, 1974).

Short-term studies showed increased absolute and relative thyroid weights at  $720 \text{ mg/m}^3$  in Wistar TNO/W 74 albino rats exposed to  $32-720 \text{ mg/m}^3$  of metribuzin as an aerosol daily for 6 hours and showed decreased T3 levels at  $1000 \text{ mg/kg bw per day}$  in male New Zealand rabbits exposed dermally to  $40-1,000 \text{ mg/kg bw per day}$  of metribuzin for 3 weeks (Thyssen, 1981; Flucke and Hartmann, 1989).

In a developmental toxicity study, mid-dose (70 ppm) and high-dose (200 ppm) pregnant CrL:CD BR rats gavaged with 25-200 mg/kg bw per day of metribuzin on gestation days 6 to 18 had decreased T4 levels while high-dose rats had increased thyroid weight (Kowaski et al., 1986).

**Reproductive/developmental toxicity:** No fetotoxicity was observed in rats and rabbits gavaged with metribuzin (rats: 25-200 mg/kg bw per day; rabbits: 10-85 mg/kg bw per day) on gestation days 6-18 and rats fed metribuzin (5-100 mg/kg bw per day) on gestation days 6-15 despite maternal toxicity (decreased body weight gain and increased thyroid weights) (Machemer, 1972; Kowaski et al., 1986; Clemens and Hartnagel, 1989).

In a 3-generation reproduction study, no treatment-related effects on mating, gestation, lactation or pup development were seen in FB30 rats fed 35-300 ppm of metribuzin (Löser and Siegmund, 1974). No reproductive effects were seen in a 2-generation reproduction study in which Cr:CD BR rats were fed 30-150 ppm of metribuzin; however, high dose F0 and F1 generations consumed less food, had decreased body weight gain and hypertrophy of the liver (Porter et al., 1988).

## 2.5 Genotoxicity and carcinogenicity

Metribuzin was not mutagenic in a range of *in vitro* and *in vivo* tests. Negative *in vitro* studies (both with and without activation) included: Ames assays using *Salmonella typhimurium* and *Escherichia coli*, an SOS Chromotest using *E. coli*, Chinese hamster ovary (CHO)/Hypoxanthine-guanine phosphoribosyl transferase (HGPRT mutation assay, and an unscheduled DNA synthesis assay in rat primary hepatocytes (Inukai and Iyatomi, 1977; Yang, 1986). An *in vitro* test using CHO cells was clastogenic but only in the presence of S9; the U.S. EPA determined clastogenicity was not of concern as there was no evidence of mutagenicity in *in vivo* tests (Murli, 1990; U.S. EPA, 1998). Negative *in vivo* tests included three dominant lethal mutation tests in male and female mice gavaged with metribuzin, and a cytogenetic study assessing spermatogonia in Chinese hamsters (Machemer and Lørke, 1974a, 1974b).

No increase in the incidence of tumours was seen in CD1 mice fed 200-3200 ppm of metribuzin for 2 years (Hayes, 1981). Both Fischer 344 rats fed 30-900 ppm for 52 or 104 weeks and Wister rats fed 25-300 ppm showed no evidence of carcinogenicity (Löser and Mohr, 1974; Christenson and Wahle, 1993).

The U.S. EPA has classified metribuzin as - D; not classifiable as to human carcinogenicity based on the unavailability of human data and inadequate evidence from animal studies (U.S. EPA, 2003) while the International Agency for Research on Cancer (IARC) has not reviewed the carcinogenicity of metribuzin.

## 2.6 Mode of action

Based on an intraperitoneal study in mice and an oral study in rats, metribuzin increases oxidative stress and alters antioxidant status causing hepatotoxicity by depleting the liver GSH content and binding to liver proteins (Bleeke et al., 1985; Chiali et al., 2013). In the liver, microsomal mixed-function oxidase (MFO) metabolizes metribuzin to a reactive intermediate, likely metribuzin sulfoxide or deaminometribuzin sulfoxide which then reacts with available thiols (especially GSH), or, in their absence, with proteins and other macromolecules (Bleeke et al., 1985).

The principal urinary metabolites of metribuzin are mercapturic acids, which arise via metribuzin sulfoxide or deaminometribuzin sulfoxide reacting with reduced glutathione (GSH) (Bleeke et al., 1985). Sulfoxidation therefore appears to activate metribuzin to an electrophilic metabolite which, in the absence of GSH, binds to tissue proteins producing hepatotoxicity (Bleeke et al., 1985).

## 2.7 Selected key study

Health Canada (2019a, 2019b) has identified the liver as the most sensitive target organ across the database based on a 2-year feeding study in dogs. In a 2-year feeding study conducted by Löser and Mirea (1974), four beagle dogs/sex/group were administered 0, 25, 100, or 1,500 ppm (0, 0.83, 3.5, or 55.6 mg/kg bw per day) of metribuzin (Bay 94 337 technical 99.5%) in the

diet. Mortality rates were observed in the high-dose (1,500 ppm or 0.83 mg/kg/bw per day) group at 75% in both males and females. The clinical tests performed after twelve months of metribuzin exposure suggested the presence of liver dysfunction in the dogs. Elevated activities of liver enzymes such as SGOT, SGPT, ornithine-carbamyl transferase (OCT) and alkaline phosphatase along with an increase in BSP (bromsulphthalein) retention were reported in the males beginning at 3.5 mg/kg bw per day. Increased SGPT, OCT and serum protein levels were observed in high-dose females. Increased mucopolysaccharide droplets in the liver and hepatic necrobiosis were observed in mid- and high-dose males and females. There were no major changes in kidney function. An increase in thyroid weight was observed in the high-dose groups of both sexes.

The 2-year dog toxicity study no-observed-effect-level (NOEL) of 0.83 mg/kg body weight (bw) per day for males and females with a standard uncertainty factor of 100 was used to establish the acceptable daily intake (ADI) of 0.0083 mg/kg bw per day. At the lowest-observed-effect-level (LOEL) of 3.5 mg/kg bw per day, increased ornithine carboxytransferase was observed in males and increased mucopolysaccharide droplets in the liver and hepatic necrobiosis were observed in males and females.

### 3.0 Derivation of the health-based value

As noted above, the NOEL of 0.83 mg/kg bw per day for liver effects in dogs was selected as the basis for the current risk assessment. Using this NOEL, the ADI (Health Canada, 2019a) was calculated as follows:

$$\begin{aligned} \text{ADI} &= \frac{0.83 \text{ mg/kg bw per day}}{100} \\ &= 0.0083 \text{ mg/kg bw per day} \end{aligned}$$

where:

- 0.83 mg/kg bw per day is the NOEL, based on liver effects in beagles; and
- 100 is the uncertainty factor, selected to account for interspecies variation ( $\times 10$ ), intraspecies variation ( $\times 10$ ).

Based on the ADI of 0.0083 mg/kg bw per day, a health-based value (HBV) for metribuzin in drinking water was derived as follows:

$$\begin{aligned} \text{HBV} &= \frac{0.0083 \text{ mg/kg bw per day} \times 74 \text{ kg} \times 0.20}{1.53 \text{ L/day}} \\ &= 0.08 \text{ mg/L (80 } \mu\text{g/L}) \end{aligned}$$

where:

- 0.0083 mg/kg bw per day is the ADI calculated using a NOEL of 0.83 mg/kg bw per day (Health Canada, 2019a, 2019b);
- 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 for drinking water (Krishnan and Carrier, 2013).

## 4.0 Analytical and Treatment Considerations

### 4.1 Analytical methods to detect metribuzin

Standardized methods available for the analysis of metribuzin in source and drinking water and their respective MDLs are summarized in Table 4. MDLs are dependent on the sample matrix, instrumentation, and selected operating conditions and will vary between individual laboratories. The MDLs or MRLs from provincial and territorial data are in the range of 0.01 to 7 µg/L (British Columbia Ministry of Health, 2019; Manitoba Sustainable Development 2019; Ministère de l'Environnement et de la Lutte contre les changements climatiques du Quebec, 2019; Nova Scotia Environment, 2019; Indigenous Services Canada, 2019; P.E.I. Department of Communities, Land and Environment, 2019).

Additional analytical methods that are not currently standardized are available for the measurement of metribuzin in water. These methods are based on high performance liquid chromatography with either mass spectrometry or ultraviolet detection (Flores-Garcia et al., 2011; Sinha et al., 2011; Rocha et al., 2015). Similar MDLs to the standard methods listed below have been reported and these methods are suitable for use in commercial laboratories (Haiste-Gulde and Sacher, 2019).

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 maximum acceptable concentration (MAC). Sample processing considerations for the analysis of metribuzin in drinking water (e.g., sample preservation, storage) can be found in the references listed in Table 4. It is important to note that quenching is critical if an oxidant is present in samples in order to prevent additional degradation of metribuzin prior to analysis.

**Table 4.** Standardized methods for the analysis of metribuzin in drinking water

Method <sup>a</sup> (Reference)	Methodology	MDL ( $\mu\text{g/L}$ )
EPA 507 Rev. 2.1 (U.S. EPA, 1995a)	Liquid-liquid extraction and capillary column gas chromatography (GC) with a nitrogen-phosphorus detector	0.029
EPA 508.1 Rev. 2.0 (U.S. EPA, 1995b)	Liquid-solid C-18 cartridge or disk extraction and gas chromatography with an electron capture detector (GC/ECD)	0.009
EPA 525.2 Rev. 2.0 (U.S. EPA, 1995c)	Liquid-solid C-18 cartridge or disk extraction and GC with mass spectrometry (GC/MS)	0.062 - 0.22
EPA 551.1 Rev. 1.0 (U.S. EPA 1995d)	Liquid-liquid extraction and GC/ECD	0.005 - 0.041

<sup>a</sup> All methods are subject to matrix interferences caused by contaminants that are co-extracted from the sample and present in solvents, reagents, and glassware. Interfering contamination may also occur when a sample containing low concentrations of analytes is analyzed immediately following a sample containing relatively high concentrations of analytes.

## 4.2 Treatment considerations

Treatment technologies that are available to effectively decrease metribuzin concentrations in drinking water include oxidation, activated carbon adsorption, and membrane filtration. Published data on metribuzin removal in water using these technologies indicate that between 50 to 98% removal can be achieved (Miltner et al., 1989; Hofman et al., 1997; Chen et al., 2004; Chamberlain et al., 2012). At the residential scale, certified treatment devices relying on reverse osmosis or activated carbon adsorption are expected to be effective for removal of metribuzin.

### 4.2.1 Municipal-scale treatment

Since metribuzin concentrations are low in source water, treatment technology data reported in the literature generally have low influent concentrations ( $< 50 \mu\text{g/L}$ ). Information on the removal efficiencies and the operational conditions from these studies are reported below as they provide an indication of the effectiveness of specific treatment technologies for metribuzin removal. The selection of an appropriate treatment process 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.

#### 4.2.1.1 Conventional treatment

Conventional filtration (chemical coagulation, clarification, and rapid sand filtration) and chlorine disinfection may reduce metribuzin concentrations through oxidation during the disinfection step (Miltner et al., 1989; Blomquist et al., 2001). Conventional clarification and filtration processes alone are not effective for the removal of metribuzin. Monitoring of metribuzin in full-scale treatment plants found no statistically significant removal of low levels of metribuzin ( $< 5 \mu\text{g/L}$ ) through clarification and filtration. Additional coagulation/flocculation jar tests confirmed no removal of metribuzin (initial concentration of  $45 \mu\text{g/L}$ ) from river water using an aluminum sulphate dose of  $30 \text{ mg/L}$  (Miltner et al., 1989).

#### 4.2.1.2 Oxidation

Chemical oxidation of metribuzin using chlorine, chlorine dioxide ( $\text{ClO}_2$ ), permanganate ( $\text{MnO}_4^-$ ) and ozone ( $\text{O}_3$ ) can be effective treatment methods for removing metribuzin from water depending on a variety of factors including oxidant dose, contact time, disinfectant demand, temperature and pH. Data for several oxidants that are effective are reported in Table 5.

Miltner et al. (1989) conducted monitoring at full-scale treatment plants and reported 94% removal of low levels of metribuzin in the post-filtration chlorination step. These results are supported by bench-scale studies that provide further evidence that metribuzin can be effectively removed using chlorine oxidation (Miltner et al., 1989; Chamberlain et al., 2012; Hu et al., 2017). Hu et al. (2017) studied the reaction of chlorine and metribuzin (initial concentration of 1000  $\mu\text{g/L}$ ) under varying conditions including chlorine dose, pH, and bromide and ammonium concentrations. The authors noted that degradation rates increased with increasing temperature, decreasing pH, increasing bromide concentration, and decreasing ammonium concentration.

Bench-scale testing conducted with other oxidants including  $\text{ClO}_2$ ,  $\text{MnO}_4^-$  and  $\text{O}_3$  have reported moderate to high removal of low levels of metribuzin (Miltner et al., 1989; Chamberlain et al., 2012). Chamberlain et al. (2012) reported greater than 50% removal of 1.5 - 3  $\mu\text{g/L}$  of metribuzin using a  $\text{ClO}_2$  dose and contact time that is typical for drinking water disinfection.  $\text{MnO}_4^-$  and  $\text{O}_3$  removals ranged from 20% to greater than 50% depending on the pH. The same study reported that oxidation with monochloramine and ultraviolet was not effective for removal of metribuzin.

Overall, these studies demonstrate that depending on the influent metribuzin concentration and other water quality parameters, drinking water treatment plants using chlorination and other oxidants (e.g.,  $\text{ClO}_2$ ,  $\text{O}_3$ ,  $\text{MnO}_4^-$ ) are capable of lowering metribuzin concentrations below the MAC during typical treatment plant operations (Miltner et al., 1989; Chamberlain et al., 2012).

When using oxidation processes for pesticide removal in drinking water, it is important to be aware of the potential formation of by-products due to degradation of the target compound (Ikehata and Gamal El-Din, 2006; Chamberlain et al., 2012). Removal of the target pesticide alone does not ensure that the treatment is efficient and that full mineralization (to carbon dioxide, inorganic ions and water) has been achieved. In addition, water utilities should consider the potential formation of disinfection by-products based on the oxidant selected and the source water quality. Several authors have reported the presence of potential degradation products from the oxidation of metribuzin. Miltner et al. (1989) reported the presence of additional chromatographic peaks following chlorine oxidation of metribuzin (degradation by-products were not identified). Hu et al. (2017) reported that chloroform, 1,1,1-trichloroacetone, dichlororoacetonitrile were formed (less than 1% molar yield) following chlorination of metribuzin. To examine whether the target pesticides were degraded and mineralized, several authors have monitored the decline of organic carbon content (either total or dissolved) and/or chemical oxygen demand (COD) (Ikehata and Gamal El-Din, 2006; Beduk et al., 2012; Li et al., 2019). Pilot-scale testing is an important step for water utilities considering oxidation processes for pesticide removal in drinking water.

**Table 5.** Removal of metribuzin via oxidation

Oxidant	Influent (µg/L)	Oxidant Dose (mg/L)	Removal	Process Description	Reference
Chlorine	2.41	2.95	94 %	Full-scale: Conventional surface water treatment. Chlorine applied post filtration (Chlorine dose: 2.95 mg/L; residual: 2.23 mg/L).	Miltner et al. (1989) <sup>a</sup>
	60.1	3.1	96 %	Bench-scale: Chlorine residual: 1.8 mg/L following 6 hr reaction time.	
	1.5 – 3	2 - 5	20-50 %	Bench-scale: Experiments conducted under typical surface water disinfection conditions: CT: 107-173 mg·min/L pH 6.6 and 8.6	Chamberlain et al. (2012) <sup>b</sup>
Chlorine dioxide	60.1	5.9	100%	Bench-scale: Chlorine residual: 3.8 mg/L following 6 hr reaction time.	Miltner et al. (1989)
	34.4	2.0	60%	Bench-scale: Chlorine residual: 0.4 mg/L following 2 hr reaction time.	
	1.5 - 3	2 -3	.>50%	Bench-scale: CT: 38 - 73 mg·min/L pH 8.6	Chamberlain et al. (2012) <sup>b</sup>
Ozone	1.5 - 3	1 - 2	> 50%	Bench-scale: CT: 0.2 - 0.3 mg·min/L; pH 6.6	Chamberlain et al. (2012) <sup>b</sup>
Permanganate	1.5 – 3	3 - 5	20-50%	Bench-scale: CT: 134 - 64 mg·min/L pH 8.6	Chamberlain et al. (2012) <sup>b</sup>

<sup>a</sup> Removal estimates may have been impacted due to lack of quenching following sample collection.

<sup>b</sup> CT = disinfectant concentration (C) x time (T) at 23 ± 1°C. Experiments were conducted at pH of 6.6 and 8.6.

Data only reported for the pH where removal was greater than 20%.

#### 4.2.1.3 Activated carbon adsorption

Activated carbon adsorption is a widely used technology to reduce the concentration of micropollutants, including 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 or fixed bed reactors with granular activated carbon (Chowdhury et al., 2013).

Although there is limited full-scale data published regarding the use of activated carbon specifically for metribuzin adsorption, it is expected to be effective for metribuzin removal based on its physical-chemical properties (e.g., solubility, molecular size, polarity, etc.) and published research on adsorption capacity. Data generated through bench-scale testing to determine adsorption coefficients for pesticides is useful in predicting whether activated carbon adsorbs a particular pesticide (U.S. EPA, 2011). In general, pesticides with an adsorption capacity constant (e.g., Freundlich coefficient) greater than 200 µg/g(L/µg)<sup>1/n</sup> are considered to be amenable to removal by carbon adsorption (Speth and Miltner, 1989; Speth and Adams, 1993; U.S. 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, 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 powdered activated carbon (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 type and dose, the contact time, the PAC characteristics (type, particle size), the adsorbability of the contaminant and the presence of NOM (Gustafson et al., 2003; Summers et al., 2010; Haist-Gulde and Happel, 2012; Chowdhury et al., 2013).

Miltner et al. (1989) compiled data from a full-scale PAC application and jar tests to estimate PAC capacity versus pesticide concentration and calculated a Freundlich adsorption coefficient of  $61.7 \text{ mg/g(L/mg)}^{1/n}$  ( $61,700 \text{ }\mu\text{g/g(L/}\mu\text{g)}^{1/n}$ ) in a natural river water. In this study, higher or similar adsorption of metribuzin compared with similar pesticides such as atrazine was observed. The authors concluded that PAC applied at dosages typically used for taste and odour control would also be sufficient for removal of several pesticides (including metribuzin) if moderate percent removal is required. Similarly, Frank et al. (1991) reported that a seasonal PAC dose of 5 mg/L completely removed metribuzin (mean influent concentration of 1.7  $\mu\text{g/L}$ ) from a surface water supply.

#### Granular activated carbon

The use of granular activated carbon (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 partially ineffective for metribuzin removal (Knappe et al., 1999; Summers et al., 2010; Haist-Gulde and Happel, 2012; Chowdhury et al., 2013). Miltner et al. (1989) evaluated metribuzin removal in a full-scale sand-replacement GAC bed. The GAC bed was 18 inches deep, 30 months old and had an EBCT of 2.81 minutes at a loading rate of 4 gpm/ft<sup>2</sup> (9.8 m/hr). The mean influent metribuzin concentration was 0.89  $\mu\text{g/L}$  and the mean removal was 57% over a period of 11 sample days. This removal efficiency was similar to those observed for other triazine herbicides including atrazine, cyanazine and simazine.

#### *4.2.1.4 Membrane filtration*

In general, nanofiltration (NF) and reverse osmosis (RO) are effective pressure-driven membrane processes for the removal of pesticides from drinking water (Van der Bruggen and Vandecasteele, 2003; U.S. EPA, 2011). The effectiveness of RO and NF 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.

Bellona et al., (2004) present a flow-chart using the parameters of the pesticide in water (e.g., molecular weight,  $\log K_{ow}$ , molecular diameter) and those of the membrane (e.g., MWCO, pore size) to determine the potential for removal. This chart could aid in the choice of a possible membrane for metribuzin removal. Based on the molecular weight of metribuzin (217 Da), membranes with a MWCO varying between 200 and 400 Da is considered appropriate for metribuzin. 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).

**Table 6.** Metribuzin removal via reverse osmosis and nanofiltration

Influent ( $\mu\text{g/L}$ )	Rejection	Membrane Type	Process Description	Reference
10	87-97%	Polyamide NF	-Bench-scale: groundwater (total alkalinity 120 mg/L as $\text{CaCO}_3$ ). - Membrane MWCO of 300 Da. - Test conditions: Spiral wound configuration, 15 or 50% recovery; flux 10 or 15 gsfd.	Chen et al. (2004)
4.5	85%	Cellulose-acetate RO	- Bench-scale: surface water pre-treated with coagulation, sedimentation, filtration, and ultra-filtration.	Hofman et al. (1997) <sup>a</sup>
	98%	Composite polyamide RO	- Test conditions: All membranes in 4x40 spiral wound configuration, 9% recovery.	
	99%	Ultra-low pressure RO	- At 80% recovery, initial concentration of 1.4 $\mu\text{g/L}$ and composite polyamide RO: 93% rejection estimated from modelling data.	
2.53	59%	Cellulose - acetate RO	Bench-scale: surface water pre-treated with coagulation, sedimentation, filtration.	Fronk and Baker (1990) <sup>a</sup>
	76%	Polyamide RO	Test conditions: Pressure: 150 - 200 psi, 9-13 % recovery, permeate flux: 7.58 - 23 gal/min.	
	100%	Thin film composite RO		

<sup>a</sup> MWCO data not available for this study.

Bench-scale studies have shown that RO and NF are effective for the removal of metribuzin from drinking water (Fronk and Baker, 1990; Hofman et al., 1997; Chen et al., 2004). Studies using a variety of membrane types and operating conditions for metribuzin removal are reported in Table 6. These data demonstrate that rejections of metribuzin ranging from 59 to 99% can be achieved. In general, thin film composite and ultra-low pressure RO membranes achieved the highest rejection (99-100%) of metribuzin (Fronk and Baker, 1990; Hofman et al., 1997). Chen et al. (2004) found that rejection of metribuzin using a spiral-wound polyamide NF membrane was also effective (up to 97%) under optimum conditions (e.g., high flux and low recovery).

#### 4.2.2 Residential-scale treatment

In cases where metribuzin 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 metribuzin concentrations in drinking water. Before a treatment unit is installed, the water should be tested to determine the general water chemistry

and metribuzin 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.

Health Canada does not recommend specific brands of drinking water treatment units, but 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. 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 (i.e., reduction claim) that may be present in water. Certification organizations provide assurance that a product conforms to applicable standards and must be accredited by the Standards Council of Canada (SCC). Accredited organizations in Canada (SCC, 2019) include:

- CSA Group;
- NSF International;
- Water Quality Association;
- UL LLC;
- Truesdail Laboratories Inc.
- Bureau de Normalisation du Québec; and
- International Association of Plumbing and Mechanical Officials.

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

The drinking water treatment technologies that are expected to be effective for metribuzin removal at the residential-scale include:

- reverse osmosis (RO); and
- adsorption.

Currently, metribuzin 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 reverse osmosis or adsorption to ensure that the material safety has been tested. These standards are NSF/ANSI Standard 58 Reverse Osmosis Drinking Water Treatment Systems and NSF/ANSI Standard 53 Drinking Water Treatment Units - Health Effects (NSF/ANSI, 2018a,b). In addition, units that have been certified for the removal of a similar pesticide, such as atrazine are more likely to be effective for the removal of metribuzin.

Water that has been treated using reverse osmosis may be corrosive to internal plumbing components. Therefore, these units should be installed only at the point-of-use (POU). Also, 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 drinking 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

Metribuzin 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 metribuzin to enter source water (e.g., raw water supply to the drinking water system) based on site-specific considerations.

When it is determined that metribuzin may be present and monitoring is necessary then surface and groundwater sources should be characterized to determine the concentration of metribuzin. 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 metribuzin is not present in source water, monitoring may be reduced.

Where treatment is required to remove metribuzin, 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 metribuzin removal.

Where treatment is in place for metribuzin 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 quarterly. When a degradation process, like oxidation, is utilized, monitoring of by-product formation should also be considered.

## 6.0 International Considerations

This section presents drinking water guidelines, standards and/or guidance from other national and international organizations. 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.

Australia has set a guideline value of 0.07 mg/L for metribuzin in drinking water (National Health and Medical Research Council (NHMRC) (Australia) and Natural Resources Management Ministerial Council (NRMMC) (Australia), 2011) based on a NOEL of 2 mg/kg bw per day for decreased heart weights from a 2-year rat study. The U.S. EPA does not have a regulatory value for metribuzin. It concluded that regulation of metribuzin in drinking water would have little impact on human health risk reduction as its occurrence in public water systems

and the numbers of people potentially exposed through drinking water are low (U.S. EPA, 2003). The World Health Organization (WHO) has not set a specific guideline value for metribuzin.

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.

## 7.0 Rationale

Metribuzin is registered in Canada to control broadleaf weeds and grasses in agriculture. Despite its common use in Canada, data provided by provinces and territories that monitor for metribuzin in source and drinking water indicate that when detected, levels of metribuzin are well below the proposed MAC. The liver is considered the target organ for metribuzin toxicity. Although no human studies have investigated the effects of metribuzin on the liver, animal studies conducted in several species (rats, mice, rabbits and dogs) have consistently shown liver toxicity following metribuzin exposure.

Health Canada, in collaboration with the Federal-Provincial-Territorial Committee on Drinking Water, is proposing to reaffirm a MAC of 0.08 mg/L (80 µg/L) based on the following considerations:

- An HBV of 0.08 mg/L (80 µg/L) based on liver effects in beagle dogs;
- Metribuzin can be accurately measured at concentrations well below the proposed MAC; and
- Drinking water treatment technologies are available to remove metribuzin to below the proposed MAC.

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

## 8.0 References

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## Appendix A: List of acronyms

ADI	Acceptable daily intake
AHS	Agricultural Health Study
ANSI	American National Standards Institute
BSP	Bromosulphthalein
CAS#	Chemical Abstracts Service registry number
CCME	Canadian Council of Ministers of the Environment
CHO	Chinese hamster ovary
COD	Chemical oxygen demand
DA	desamino-metribuzin
DADK	desamino-diketo-metribuzin
DK	diketo-metribuzin
ECD	Electron capture detector
EFSA	European Food Safety Authority
EU	European Union
GAC	Granular activated carbon
GC	Gas chromatography
GSH	Glutathione
HBV	Health-based value
HGPRT	Hypoxanthine-guanine phosphoribosyl transferase
IARC	International Agency for Research on Cancer
LD <sub>50</sub>	median lethal dose
LOEL	Lowest-observed-effect level
MAC	Maximum acceptable concentration
MDL	Method detection limit
MFO	Microsomal mixed-function oxidase
MRL	Method Reporting Limit
MS	Mass spectrometry
MWCO	Molecular weight cutoff
N-AC-metribuzin	N-acetylcysteine-metribuzin
NF	Nanofiltration
NHMRC	National Health and Medical Research Council (Australia)
NOEL	No-observed-effect level
NOM	Natural organic matter
NRMMC	Natural Resources Management Ministerial Council (Australia)
NSF	NSF International
OCT	Ornithine-carbamyl transferase
OEHHA	Office of Environmental Health Hazard Assessment
PAC	Powdered activated carbon
P.E.I.	Prince Edward Island
PMRA	Pest Management Regulatory Agency
POU	Point-of-use
SCC	Standards Council of Canada
RO	Reverse Osmosis
SGOT	Serum glutamate-oxaloacetate transaminase

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SGPT	Serum glutamate-pyruvate transaminase
T3	Triiodothyronine
T4	Thyroxine
UL	Underwriters Laboratory
U.S.	United States
U.S. EPA	United States Environmental Protection Agency
WHO	World Health Organization

## Appendix B: Canadian water quality data

**Table B1.** Levels of metribuzin 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)		25 <sup>th</sup> percentile (ng/L)	Median (ng/L)	75 <sup>th</sup> percentile (ng/L)
			Min	Max			
<b>Tap Water</b>							
AB, SK, MB – rural communities (2004-2005) <sup>a</sup>	?/29		8.11	<20.70			
<b>Surface Water</b>							
BC – Lower Fraser Valley and Okanagan Basin (2003-2005)	22/93	0.015	<0.015	2.74			
ON (2003)	17/161	20.7	21.0	1230			
ON (2004)	29/224	20.7	23.0	668			
ON (2005)	14/183	20.7	23.1	1210			
ON – 10 isolated lakes (2003-2005)	49/163	0.001	<0.001	23.1			
QC (2003)	1/50	20	<20	20			
QC (2004)	0/69	6-20					
QC (2005)	0/62	20					
NB (2003-2005)	10/57	30-300					
P.E.I. (2003-2005)	2/82	50-80					
NS (2003-2005)	0/48	30					
<b>Rivers</b>							
AB, SK, MB – 8 sites (2003)	0/63	20.7					
<b>Reservoir Water</b>							
AB, SK, MB – 15 sites (2003-2004)	1/198	20.7	<20.7	185			
<b>Groundwater</b>							
P.E.I. (2004)	2/122		100	180			
P.E.I. (2005)	3/112			190			
<b>Air</b>							
ON – 4 sites (2004-2005)	9/12	0.000	<0.001	0.039	0.007	0.012	0.030
ON – 4 sites (2004-2005) <sup>b</sup>	8/12	0.001	<0.001	0.225	<0.001	0.022	0.060

MDL = method detection limit

? = Number of detects not given

<sup>a</sup>The mean value was 20.30 ng/L

<sup>b</sup>Represents transformation product endosulfan-sulphate

Note: Adapted from Environment Canada, 2011