Chlorpyrifos Special Registration Review

Scoping document

The Minnesota Department of Agriculture
Pesticide and Fertilizer Management Division
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Minnesota Department of Agriculture mission statement
To enhance Minnesotans' quality of life by ensuring the integrity of our food supply, the health of our environment, and the strength of our agricultural economy.

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1. Executive summary

The Minnesota Department of Agriculture (MDA) is the lead state agency for pesticide and fertilizer regulatory functions in Minnesota. To better understand the effects of pesticides on the environment and human health in Minnesota, the MDA conducts special registration reviews. Special registration reviews summarize information about specific pesticides, and in some cases, describe a variety of opportunities for state-specific actions to mitigate adverse effects of pesticides. The Commissioner of Agriculture has directed the Pesticide and Fertilizer Management Division to conduct an in-depth special registration review of chlorpyrifos. To begin the special registration review, this draft scoping document has been written in collaboration with the Minnesota Department of Health, Minnesota Pollution Control Agency, and the University of Minnesota, to introduce and outline the topics for consideration. After a public comment period on this document the MDA will publish a final scoping document and begin the special registration review.

Chlorpyrifos is a pesticide commonly sold and used in Minnesota in both restricted use and non-restricted use products. It is a neurotoxic chemical capable of affecting a wide range of animals including many arthropod pests but also humans and non-target organisms. As a highly effective pesticide against a broad taxonomic range of pests, chlorpyrifos is used in a variety of important agricultural crops in Minnesota. For example, chlorpyrifos is used to manage soybean aphids which can reduce soybean yield up to 40%. Chlorpyrifos is one pest management option among others, but in some cases, it is a critical pesticidal option when resistance to other pesticides arises.

Chlorpyrifos exposure can lead to acetylcholinesterase (AChE) inhibition and neurodevelopmental effects in humans. The Environmental Protection Agency's (EPA) latest human health risk assessment for chlorpyrifos concluded that dietary, residential, occupational, and aggregate exposures to chlorpyrifos were all risks of concern for humans. The calculated chlorpyrifos exposure levels in food for infants, children, youth, and adult females were 93, 140, and 110, and 62 times higher than the acceptable level of exposure, respectively. Due to concerns about the risks to human health, chlorpyrifos has been banned in some other countries, and some states in the United States (US).

According to the EPA's chlorpyrifos ecological risk assessment, chlorpyrifos is classified as very highly toxic to aquatic organisms such as fish and aquatic invertebrates, very highly toxic to birds, and moderately toxic to mammals. The EPA determined all endangered and threatened species in the US could potentially be exposed to chlorpyrifos and the modeled levels of exposure resulted in threshold exceedances for most endangered taxa.

Pesticides are monitored in groundwater and surface waters by the MDA. From 2008 to 2018, the MDA has detected chlorpyrifos in Minnesota surface waters above the chronic water quality standard in 83 samples, including 18 detections above the maximum (i.e., acute) water quality standard. As of March 2020, 13 surface water bodies in Minnesota were proposed for designation by the MPCA or designated as impaired by the EPA due to chlorpyrifos water quality standard violations. Twelve of the violations were the result of exceedances of the maximum standard. In 2012, the Commissioner of Agriculture designated chlorpyrifos as a "surface water pesticide of concern."

The MDA, in collaboration with the University of Minnesota and other stakeholders, has been providing education about environmental issues arising from chlorpyrifos use to pesticide applicators and growers in Minnesota. Education and outreach efforts by the MDA increased following the designation of chlorpyrifos as a surface water pesticide of concern.

Proposed topics for consideration for the chlorpyrifos special registration review include:

- State, federal, and other countries' regulation and legislation
- Sales and use
- Fate and transport
- Environmental monitoring and water designations
- Human health risks
- Ecological risks
- Benefits of use
- Chlorpyrifos and climate change
- Alternatives to chlorpyrifos
- Minnesota Department of Agriculture's education and outreach

The public comment period for the draft scoping document for the chlorpyrifos special registration review will close on September 17, 2020. During the review of chlorpyrifos, the MDA may provide information about review related topics through the "Nonpoint-source Pesticide Information" list serv (https://public.govdelivery.com/accounts/MNMDA/subscriber/new). Once the review is complete, the Commissioner of the Agriculture will issue a determinization of the review's findings along with opportunities for action.

2. Introduction

The Minnesota Department of Agriculture (MDA) is the lead state agency for pesticide and fertilizer regulatory functions in Minnesota under the Pesticide Control Law (Minn. Stat. Chapter 18B). One of those functions is to protect the environment and human health from harmful exposure to pesticides. The MDA has developed a procedure to conduct special registration reviews to increase scrutiny of new and existing pesticide registrations. Special registration reviews result in a greater understanding of potential unreasonable adverse effects of pesticides on the environment or human health in Minnesota and describe a variety of opportunities for state-specific actions. The reviews are not intended to be redundant of analyses and decisions reached by the United States (US) Environmental Protection Agency (EPA) during federal registration. Previously, the MDA has completed in-depth special registration reviews for several other pesticides which can be found on the MDA's website (www.mda.state.mn.us/pesticide-special-registration-reviews). The scope of these special registration reviews varies depending on the potential education, outreach, and regulatory needs identified by the MDA.

Chlorpyrifos is widely used in Minnesota to manage a variety of arthropod pests. Most formulations of chlorpyrifos are restricted use pesticides. Chlorpyrifos is also a source of contamination in multiple surface water bodies in Minnesota and can pose a substantial risk to human health and the environment. Thus, the Commissioner of Agriculture directed the Pesticide and Fertilizer Management Division to conduct a special registration review of chlorpyrifos. This in-depth review of chlorpyrifos will outline potential unreasonable adverse effects of chlorpyrifos on human health and the environment and

summarize the benefits of chlorpyrifos use in Minnesota. To mitigate adverse effects, the review will identify potential state-specific actions and their possible consequences. The review may take a year or more to complete. This draft scoping document is the first step in conducting this special registration review. The purpose of the scoping document is to define the focus and topics for consideration within the special registration review. Public comments on the scoping document will be taken for 60 days. The MDA will consider all appropriately submitted public comments. Following the public comment period, the MDA will publish a revised scoping document which will be used to guide the review. The MDA will collaborate with the Minnesota Department of Health (MDH), Minnesota Pollution Control Agency (MPCA), University of Minnesota (U of MN), and other stakeholders that can provide technical expertise for the scoping document and/or the special registration review.

Potential state-specific actions will depend on the findings of the special registration review. Outcomes from previous special registration reviews include clarification of label provisions and enforcement designed to protect humans, non-target organisms, and the environment; targeted enforcement and education; and applicator guidance and education to enhance pesticide stewardship.

3. Background

Chlorpyrifos (O,O-diethyl O-(3,5,6-trichloro-2-pyridinyl)-phosphorothioate) is an active ingredient in the organophosphate class (1B) of insecticides. Chlorpyrifos is toxic to a wide range of arthropods and interferes with the normal functioning of their nervous systems by binding to acetylcholinesterase (AChE), preventing the breakdown of acetylcholine. Subsequent accumulation of acetylcholine causes over stimulation of nerves which can result in paralysis and death.

Chlorpyrifos products are registered to manage arthropods such as insects, ticks, and mites on or in agricultural crops, nursery plants, ornamentals, wood structures, cattle, and other habitats. In Minnesota, chlorpyrifos is used on soybeans (*Glycine max* (L.) Merr.), sugar beets (*Beta vulgaris* L.), wheat (*Triticum aestivum* L.), sunflower (*Helianthus annuus* L.), and other crops to manage agricultural pests. Chlorpyrifos is applied by aerial- and ground-based methods and is also used in insect bait stations and as a seed treatment. Chlorpyrifos formulations include: emulsifiable, flowable, and soluble concentrates, impregnated material, and granular products. As of March 2020, there were 48 pesticide products with chlorpyrifos as an active ingredient registered in Minnesota. In February 2020, a major manufacturer of chlorpyrifos products, Corteva Agriscience, announced it would stop producing chlorpyrifos-containing products by the end of 2020 [1]. Chlorpyrifos is manufactured by other companies such as Adama, Inc., FMC Corporation, Gharda Inc., Makhteshim-Agan of North America, Inc. and Platte Chemical company.

Chlorpyrifos methyl, another chlorpyrifos organophosphate pesticide, is a separate standalone active ingredient from chlorpyrifos. It has not been sold in Minnesota in the past five years and is not labeled for outdoor use. Therefore, chlorpyrifos methyl will not be a part of this special registration review.

4. Topics for consideration

Topics for consideration reflect the scope of the special registration review for chlorpyrifos. Each topic will be reviewed to better understand Minnesota-specific concerns and opportunities for action. Preliminary information about the topics for consideration and proposals of what the special registration review will contain are presented below.

4.1 State, federal, and other countries' regulation and legislation

Chlorpyrifos was first registered for use in the US in 1965 by the EPA [2]. Since then, several changes to the registration have occurred. Chlorpyrifos registrants voluntarily entered into an agreement with the EPA in 2000 to eliminate most homeowner uses, phase out termiticides, and discontinue use on tomatoes. In 2002, the EPA implemented requirements to reduce allowable chlorpyrifos application rates per season on some crops, increase the required amount of personal protective equipment when applying chlorpyrifos, and maintain buffer zones around areas treated with chlorpyrifos to protect water quality, fish, and wildlife. Further registration changes by the EPA occurred in 2012 when aerial application rates were lowered and "no-spray" buffer zones around public spaces were required. In October 2015, the EPA proposed to revoke all tolerances, or the maximum acceptable residue levels, for chlorpyrifos on or in food [3]. This decision was reversed by the EPA in March of 2017 [4].

Additional application requirements for chlorpyrifos exist and differ depending on the product. For example, for multiple formulations of chlorpyrifos applied as a liquid, wind speeds should be between 3 and 10 mph for the duration of the application, nozzles must produce medium or coarse droplets, spray must not be allowed to drift from the application site, and the appropriate buffer zone distances around aquatic sites and sensitive areas must be maintained.

Through the Pesticide Registration Review program, the EPA reviews all registered pesticides at least every 15 years, as mandated by the Federal Insecticide, Fungicide, and Rodenticide Act. Under this requirement, the EPA began a registration review of chlorpyrifos in 2009. The EPA intends to complete the ongoing registration review and assessment by the statutory deadline of October 1, 2022. Prior to 2009, the registration of chlorpyrifos was reviewed in 2002 and in 2006 as part of an organophosphate cumulative risk assessment which resulted in the continuation of its registration.

In 2007, the Natural Resources Defense Council (NRDC) and Pesticide Action Network North America (PANNA) submitted a petition to the EPA to revoke all tolerances and cancel all registrations for chlorpyrifos. The EPA denied this petition in 2019 [5]. Several states and environmental organizations have challenged this decision in federal court [6].

Several US states have banned the use of chlorpyrifos. Hawaii prohibited the use of chlorpyrifos starting January 1, 2019; however, chlorpyrifos can be used in Hawaii through December 31, 2022 with a permit from the Hawaii Department of Agriculture. The California Department of Pesticide Regulation (CDPR) has banned use of chlorpyrifos in California after December 31, 2020. The governor of New York directed the New York Department of Environmental Conservation to ban chlorpyrifos for all uses, except spraying apple tree trunks by December 2020, and ban apple tree trunk applications after July 2021. The Maryland Department of Agriculture has started developing regulations to phase out chlorpyrifos use in 2020.

Other countries have increased restrictions on the use of chlorpyrifos, for example, the European Commission discontinued chlorpyrifos use in European Union countries starting in February 2020 and Australia suspended use of chlorpyrifos in public areas, homes, and gardens in 2019.

The special registration review of chlorpyrifos will expand upon the information presented here about state, federal, and other countries' chlorpyrifos regulations. In addition, current mandatory and precautionary label requirements in the US will be summarized to further outline how chlorpyrifos is used.

4.2 Sales and Use

The MDA collects data on the sales of pesticide products in Minnesota. Based on this sales data, an estimated total of 1,042,000 lb of chlorpyrifos active ingredient were sold in Minnesota in 2018 (Fig. 1). This was the greatest quantity of an insecticidal active ingredient sold in Minnesota in 2018.

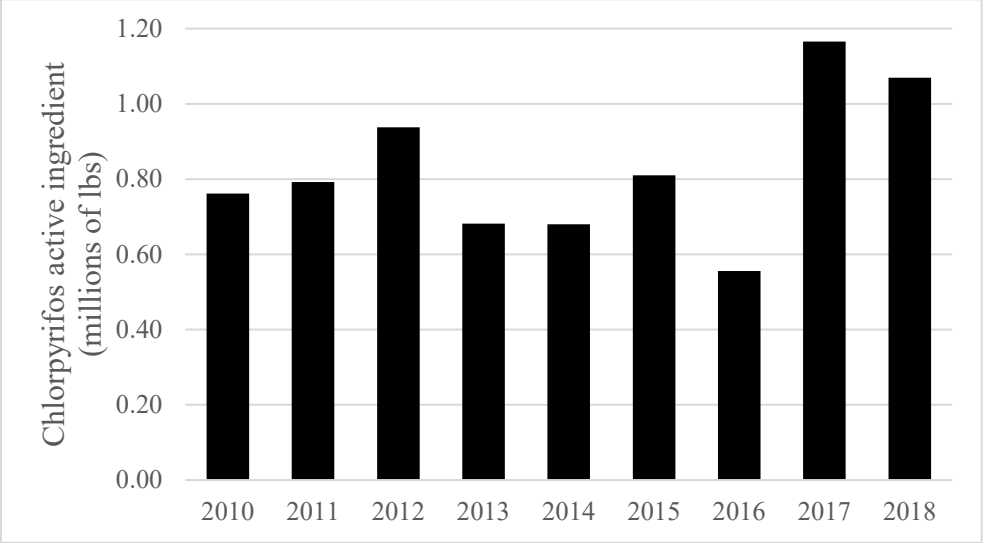

Figure 1. Pounds of chlorpyrifos active ingredient sold in Minnesota from 2010-2018. Sales data were provided to the MDA by pesticide dealers and pesticide registrants.

The United States Geological Survey (USGS) and the United States Department of Agriculture (USDA) National Agricultural Statistics Service (NASS) collect national data on pesticide use. According to a USGS survey, in 2017 Minnesota had the 3rd highest use of chlorpyrifos in the US, following California and North Dakota [7]. Based on USDA NASS and Minnesota Agricultural Statistics Service (MASS) surveys, chlorpyrifos was applied on approximately 11% of soybean acres in 2018 [8], 9% of wheat acres in 2013 [9], 1% of hay acres and corn (*Zea mays* L.) acres in 2015 [10] in Minnesota. NASS and MASS do not collect pesticide use data for all crops; however, chlorpyrifos is used on a notable portion of acres for other crops in Minnesota such as sugar beets and dry beans (approximately 15% of sugar beet acres [11] and 15% of dry bean (*Phaseolus vulgaris* L.) acres [12]).

The special registration review will provide a summary of the various uses of and products containing chlorpyrifos in Minnesota. Using publicly available data, chlorpyrifos sales trends will be analyzed and the potential impact of loss of certain chlorpyrifos products from the market will be discussed.

4.3 Fate and transport

When pesticides enter the environment, they can move and degrade by a variety of pathways. How pesticides move is largely determined by their physical and chemical properties, as is the length of time they persist after application. Site-specific conditions, such as weather and soil type, are also key in determining their fate, along with the formulation applied (e.g., liquid vs. granular), method of application (e.g., ground- or aerial-based), and other use factors (e.g., rate and timing).

Chlorpyrifos has a low solubility in water and binds strongly to soil through adsorption, which limits its mobility. Being relatively immobile in soil, leaching to groundwater is not expected; however, there is potential for chlorpyrifos to move with runoff, primarily with eroded sediment, and enter surface water [13]. Once in surface water, chlorpyrifos may persist in the water column or partition to sediment, again due to its high adsorption affinity.

Spray drift and volatilization are additional transport pathways from ground and aerial spray applications of chlorpyrifos [14,15]. Spray drift of aerosols can occur during the application process as fine spray droplets move away from the treated area. Volatilization of chlorpyrifos predominantly occurs from leaf surfaces shortly after foliar application, though volatilization from surface water and soil is also possible [16]. The resulting vapors can disperse and move offsite through atmospheric transport. While spray drift is generally limited to short distances from the application site, volatilization can result in long range transport.

The persistence of chlorpyrifos in different soils varies, and its half-life can range from a few days to over 100 days. Microbial degradation is considered a major route of chlorpyrifos dissipation in soil, though photodegradation at the soil surface and abiotic hydrolysis may also occur [13]. Chlorpyrifos can undergo abiotic hydrolysis, biodegradation, and photodegradation in aquatic environments, while oxidation and photolysis are key degradation processes in air and on foliar surfaces.

The major degradate of chlorpyrifos is 3,5,6-trichloro-2-pyridinol (TCP). TCP can form through biotic or abiotic hydrolysis in soil and water and on foliar surfaces. Compared to chlorpyrifos, TCP is more mobile and persistent in soils when not exposed to light. TCP is also a degradate of the herbicide triclopyr.

Chlorpyrifos oxon is a minor degradate that forms from the oxidation of chlorpyrifos in the environment. It can form in the air or enter the air via volatilization from treated crops. Like chlorpyrifos, it can move offsite through atmospheric transport; however, it is less stable than the parent in the environment. Chlorpyrifos oxon can also be formed when water containing chlorpyrifos is treated by chlorination [17].

The environmental fate of chlorpyrifos will be further described as part of the special registration review. The review will summarize the transport and degradation of chlorpyrifos in relation to Minnesota-specific use patterns, transport pathways, and conditions (e.g., climate and soil). The formation and fate of key chlorpyrifos degradates will also be addressed.

4.4 Environmental monitoring and water designations

The MDA is charged with monitoring pesticides in groundwater and surface water under Minnesota Statute (Minn. Stat. Chapter 18B, 18C, 18D, and 103H). The MDA began monitoring for chlorpyrifos in

groundwater in 1985 and in surface water in 1991 across Minnesota. Monitoring for chlorpyrifos oxon began in 2012 in Minnesota. Water quality monitoring data can lead to official designations that indicate unacceptable levels of contamination by a pesticide such as listing a water body as "impaired" for chlorpyrifos. The MDA is not charged with air and soil monitoring for pesticides.

4.4.1 Water monitoring

In 2008, the MDA Laboratory Services reduced the method reporting limit (MRL) for chlorpyrifos from 100 ng/L to 40 ng/L. From 2008 to 2018, the MDA analyzed 6,769 samples collected from rivers, lakes and wetlands (surface waters) for chlorpyrifos [18]. The MDA detected chlorpyrifos in surface waters above the Minnesota chronic water quality standard (41 ng/L) in 83 samples, including 18 detections above the maximum (i.e., acute) water quality standard (83 ng/L). The chronic water quality standard is "the highest water concentration or fish tissue concentration of a toxicant or effluent to which aquatic life, humans, or wildlife can be exposed indefinitely without causing chronic toxicity," and the maximum water quality standard is the "highest concentration of a toxicant in water to which aquatic organisms can be exposed for a brief time with zero to slight mortality" (Minn. Rules 7050.0218). Monitoring data from 25 river locations has indicated at least one chlorpyrifos detection above Minnesota's chronic water quality standard, including 14 detections above the maximum water quality standard. Three chlorpyrifos detections above the Minnesota chronic water quality standard, and below the Minnesota maximum water quality standard, occurred in two lakes. Only one chlorpyrifos detection (61.8 ng/L) has occurred in a non-agricultural watershed.

Samples are primarily collected May through August, and detections of chlorpyrifos in surface waters occur most frequently in August. Most detections have occurred in samples collected during base flow conditions (i.e., stable, lower flow) versus stormflow conditions (i.e., increased flow often following rainfall generated runoff or snowmelt). Chlorpyrifos oxon has never been detected in surface water by the MDA. Neither chlorpyrifos nor chlorpyrifos oxon has been detected by the MDA in groundwater. The MDA has detected chlorpyrifos six times in rainfall since 2008 at concentrations as high as 612 ng/L [18].

The USGS also monitors for chlorpyrifos and chlorpyrifos oxon in groundwater and surface water in Minnesota. The USGS has detected chlorpyrifos in surface water, but not above Minnesota's water quality standards [18]. The USGS has not detected chlorpyrifos in groundwater or chlorpyrifos oxon in surface or ground water in Minnesota.

As of March 2020, 13 surface water bodies in Minnesota were proposed for designation by the MPCA or designated as impaired by the EPA due to chlorpyrifos water quality standard violations (Fig. 2) [19]. A water body is designated as "impaired" on the Clean Water Act's 303(d) list if it fails to meet one or more water quality standards. The MPCA is responsible for proposing water bodies to be designated as impaired and provides a list of impaired waters to the EPA for approval. For a water body to be listed as impaired because of a pesticide, a detection above the maximum standard only needs to occur once, or the water body needs to have two exceedances of the chronic standard within three years. In response to chlorpyrifos surface water impairments, a Chlorpyrifos Response Plan was developed. For details, see section 4.10 of this document.

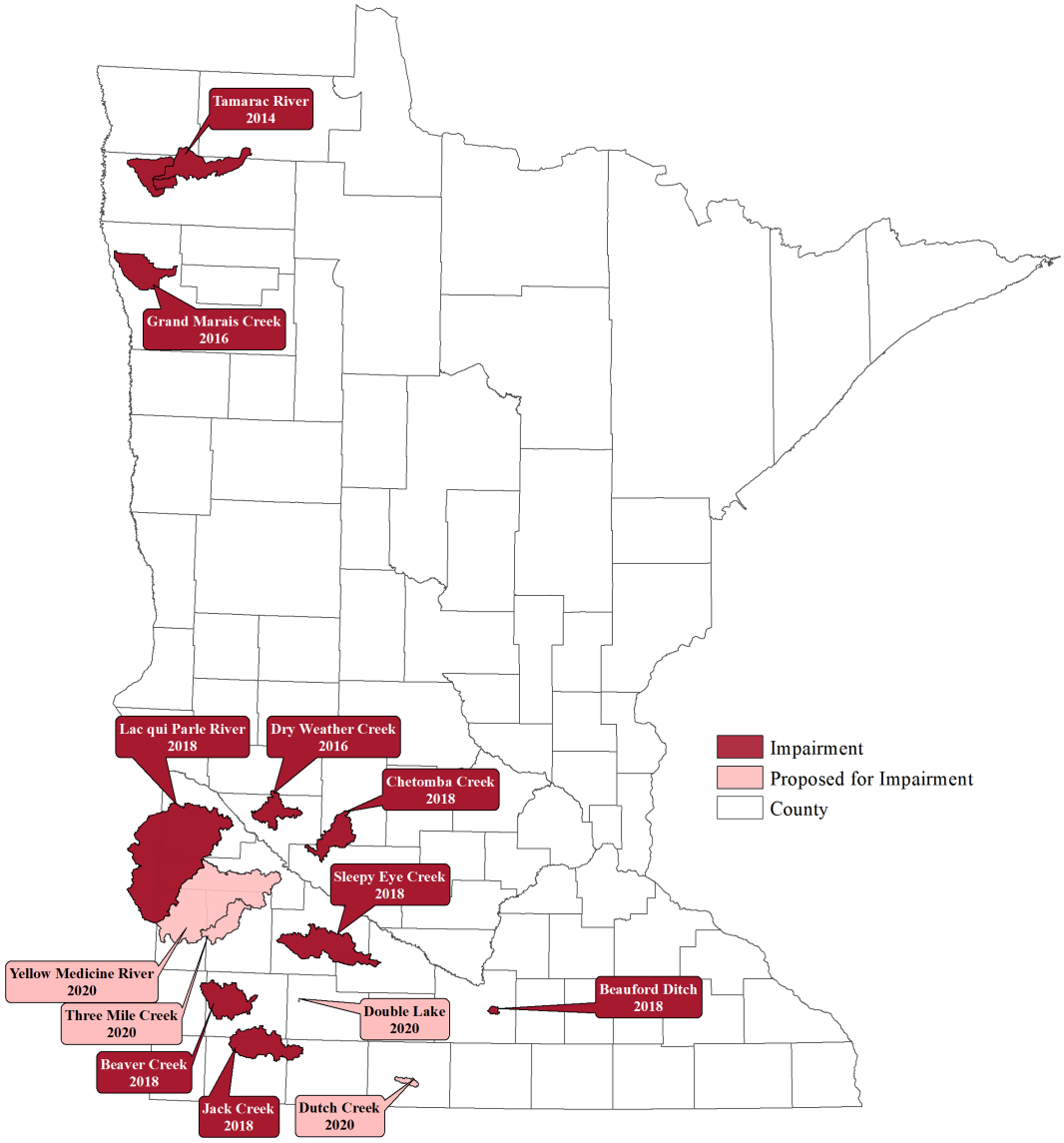

Figure 2. Minnesota watersheds (colored shapes) containing water bodies that have been designated or are proposed for designation as impaired due to chlorpyrifos as of March 2020. The year a water body was first designated or proposed for designation, if it has not been designated, is located under the name of the water body.

In 2012, the Commissioner of Agriculture designated chlorpyrifos as a "surface water pesticide of concern" [20]. Surface water pesticide of concern is a designation given to pesticides that are detected in surface water at concentrations of concern relative to a water quality reference value as laid out in the Pesticide Management Plan (PMP). This designation resulted in development of chlorpyrifos best management practices (BMPs). For details, see section 4.10 of this document.

4.4.2 Air monitoring

While chlorpyrifos and chlorpyrifos oxon are not monitored in air in Minnesota by state agencies, data exists from other US states and organizations. For example, the California Air Resources Board

conducted a study in San Joaquin County on a walnut orchard for chlorpyrifos and its oxon in air [21], and the Washington Department of Health in collaboration with the University of Washington School of Public Health conducted air monitoring studies in the North Central and Yakima Valleys for chlorpyrifos and its oxon [22]. Additionally, PANNA has conducted air monitoring for select pesticides in central Minnesota [23].

The special registration review will include an overview of relevant chlorpyrifos monitoring data in surface waters, groundwater, precipitation, and air. Chlorpyrifos detections in Minnesota water will be analyzed and compared to sales and use data.

4.5 Human health risks

The EPA conducts human health risk assessments when approving new pesticides or new uses of registered pesticides and when periodically reviewing already registered pesticides. These risk assessments estimate the nature of and potential for harmful effects of pesticides on human health. Scientific data is reviewed to evaluate the toxicity, hazards, dose-response, and expected exposure to characterize the risk of a pesticide to humans. Most recently, the EPA conducted a preliminary human health risk assessment for chlorpyrifos in 2011, followed by revised human health risk assessments in 2014 and 2016 that incorporated new information, models, and selection of different critical toxicological effects and adjusted uncertainty factors [24–26]. The Minnesota Department of Health (MDH) also occasionally conducts health risk assessments on pesticides. In 2013, MDH developed water guidance for chlorpyrifos and chlorpyrifos oxon based on its nomination to the Contaminants of Emerging Concern Initiative [27].

4.5.1 Toxicity and hazards

Chlorpyrifos is considered moderately toxic (category II) to humans on acute oral, dermal, and inhalation bases. It is readily absorbed into the bloodstream through the gastrointestinal tract if it is ingested, through the lungs if it is inhaled, or through the skin if there is dermal exposure. Following intake, some chlorpyrifos is stored in fat tissues and eventually moves out of the fat tissue and is eliminated, primarily through urine, from the body. The minor metabolite, chlorpyrifos oxon is considerably more toxic to humans than chlorpyrifos.

Chlorpyrifos is a neurotoxic chemical metabolized in the human body to the more toxic and potent AChE inhibitor chlorpyrifos oxon. The activation of chlorpyrifos to its oxon metabolite is required for inhibition of the critical enzyme AChE. AChE is found in nerve endings and the membrane of red blood cells. Two toxicological endpoints, AChE inhibition and neurodevelopmental effects, have been used by the EPA for hazard characterization of chlorpyrifos and its oxon. Accumulation of acetylcholine in neural junctions due to the inhibition of AChE by chlorpyrifos oxon results in the acute signs and symptoms of cholinergic overstimulation (e.g., cramps, muscular weakness, paralysis, death). However, for the purposes of risk assessment, these acute effects are not used to develop protective exposure levels. Instead, the selection of dose levels that protect against red blood cell AChE inhibition were typically used as a more sensitive and more available biomarker compared to brain AChE inhibition. However, as the revised human health assessments by the EPA make clear, the use of AChE inhibition is no longer considered the most sensitive effect on which to base human health risk assessments.

Studies on the effects of chlorpyrifos on the developing brain of laboratory animals as well as epidemiologic research results from human prospective birth cohort studies indicate that gestational and/or postnatal exposure may cause persistent behavioral effects in offspring and children. Multiple biologically plausible hypotheses and pathways describing the mechanistic aspects of neurodevelopmental effects of chlorpyrifos have been investigated by researchers including cholinergic and non-cholinergic systems, signaling pathways, proteins, and others. The EPA reviewed these pathways and concluded that no one pathway has sufficient data to be considered more credible than the others. Therefore, the values derived from a human health risk assessment must provide protection against AChE-based toxicity pathways in addition to numerous other possible toxicity pathways leading to developmental neurotoxicity.

Potential adverse neurodevelopmental effects in infants and children as a result of prenatal exposure to chlorpyrifos has been documented. Starting in 2008, the EPA reviewed available literature and research on chlorpyrifos, with a particular focus on effects seen in women and children following chlorpyrifos exposures. For the human health risk assessments in 2011, 2014, and 2016 the EPA reviewed the latest experimental data related to AChE inhibition, cholinergic and non-cholinergic adverse outcomes, including neurodevelopmental studies on behavior and cognition effects. The agency performed an in-depth analysis of the available chlorpyrifos biomonitoring data and critically reviewed epidemiologic studies from three major children's health cohort studies in the US (i.e., The Mothers and Newborn Study of North Manhattan and South Bronx performed by the Columbia Children's Center for Environmental Health at Columbia University; the Mt. Sinai Inner-City Toxicants, Child Growth and Development Study; and the Center for Health Assessment of Mothers and Children of Salinas Valley conducted by researchers at University of California Berkeley). This intensive review over the last decade has resulted in the human health risks assessments discarding AChE inhibition as the key effect, in favor of modeling time-weighted average blood concentrations using complex models based on neurodevelopmental outcomes seen in the epidemiological studies.

It is unlikely chlorpyrifos is carcinogenic to humans based on studies on rats and mice and an absence of a mutagenicity concern. Slight genetic alterations in yeast and DNA damage to bacteria were found, but chlorpyrifos was not mutagenic in mammalian cells or bacteria. Immunotoxicity, even at the highest dose tested, was not found in the guideline study.

4.5.2 *Dose-response*

The most recent revised human health risk assessment from the EPA in 2016 has selected neurodevelopmental outcomes as documented in the epidemiological studies as the critical effect. The derivation of updated risk values involves the use of a physiologically-based pharmacokinetic and pharmacodynamic model to estimate a time weighted average blood level associated with adverse neurodevelopmental outcomes. This blood concentration (0.004 µg/L) is designated as a lowest-observed-adverse-effect-level (LOAEL) for neurodevelopmental effects in humans.

As reported in the EPA's 2016 human health risk assessment, the steady state population adjusted doses for exposure to chlorpyrifos by food only ($ssPAD_{food}$) are 0.000002, 0.0000017, 0.0000012, 0.0000012 mg/kg/day for infants, children, youth, and adult females, respectively. The $ssPAD_{food}$ represents the daily

dose that protects against adverse effects for a specific population. Chlorpyrifos oxon is not found on food, so the EPA did not conduct an analysis for it.

4.5.3 Exposure assessment and risk characterization

Humans can be exposed to chlorpyrifos by eating food that has chlorpyrifos residue or drinking water from sources contaminated with chlorpyrifos. Chlorpyrifos oxon is not considered by the EPA to be a residue of concern in food or feed, however it is considered the primary residue of concern in drinking water. For chlorpyrifos, the EPA has calculated the exposure by food to be 0.000186, 0.000242, 0.000128, and 0.000075 mg/kg/day for infants, children, youth, and adult females, respectively. These exposure levels are 93, 140, and 110, and 62 times higher than the acceptable $ssPAD_{food}$ for infants, children, youth, and adult females, respectively. The MDH established health-based guidance values (HBVs) for chlorpyrifos and chlorpyrifos oxon in 2013 across multiple exposure durations. The water guidance values for short-term chronic and subchronic exposure to address potential human health risks from exposure to chlorpyrifos and its oxon in drinking water are 600 and 400 ng/L, respectively. These values were calculated prior to the EPA's revised human health risk assessments so they do not incorporate the updated modelling or more sensitive neurodevelopmental effects of chlorpyrifos.

In residential settings, humans can be exposed to chlorpyrifos from applications made on golf courses, or for adult mosquito management, through volatilization and/or spray drift from any application of chlorpyrifos, or through incidental oral exposure such as if a child touches a contaminated surface and then puts their hand in their mouth. In occupational settings, humans can be exposed when handling chlorpyrifos prior to, during, or after application if re-entering a treated area. Chlorpyrifos oxon residues were not analyzed for residential exposure by the EPA. Chlorpyrifos oxon is not considered an occupational residue of concern by the EPA; however, no additional data has been submitted in response to the EPA's recommendation to address uncertainties regarding the formation and decay of chlorpyrifos oxon in greenhouses.

In 2006, prior to the EPA's latest three chlorpyrifos human health risk assessments, the EPA conducted an Organophosphorus Cumulative Risk Assessment [28]. In that risk assessment the EPA found that there was a reasonable certainty of no harm to major populations subgroups from cumulative exposure to all substances that have a common mechanism of toxicity to chlorpyrifos (i.e., organophosphates) from dietary, residential, or other non-occupational exposure. An updated cumulative risk assessment for organophosphates has not been conducted since 2006.

The risk characterization of chlorpyrifos based on the EPA's 2016 revised human health risk assessment is clear. Individually, as well as in aggregate, dietary, residential, and occupational exposures to chlorpyrifos were all considered by the EPA in 2016 to be risks of concern. While the EPA is required to assess aggregate exposures and risks (chlorpyrifos exposure from multiple routes), this was not performed due the risks from food exposure alone being in excess of the steady-state population adjusted dose.

The special registration review will provide greater detail about human health risk assessments including a review of the different methods used for establishing acceptable levels of exposure across the population. The EPA's tolerances, or the maximum acceptable residue levels, for chlorpyrifos on or in food will be summarized. The potential impacts of chlorpyrifos at concentrations being found in

Minnesota on human health will be examined. Additionally, the special registration review will assess whether MDH should revise their health-based guidance values for chlorpyrifos.

4.6 Ecological risks

The EPA conducts ecological risk assessments when approving new pesticides or new uses of registered pesticides and when periodically reviewing already registered pesticides. Ecological risk assessments consider the risk of the pesticide to a variety of species, while biological evaluations focus on endangered or threatened (listed) species and/or designated critical habitats. Scientific data is used to determine what plants and animals are at risk, estimate their potential exposure, and evaluate whether exposure levels are likely to cause harm in order to characterize the risk posed by a pesticide to the environment. The EPA published a preliminary problem formulation for ecological risk and environmental fate, endangered species and drinking water assessment for chlorpyrifos in 2008 [13], and a biological evaluation for chlorpyrifos in 2017 [16].

4.6.1 Terrestrial organisms

Terrestrial organisms such as mammals, birds, and invertebrates may be exposed to chlorpyrifos and its degradates through multiple routes of exposure including contact, inhalation, and dietary. Contact and inhalation exposure can occur during or after an application within the target site. Contact and inhalation exposure may also take place outside of the treated area, if drift occurs. Dietary exposure can occur when terrestrial organisms ingest food, such as plants and prey, or water containing chlorpyrifos or by ingesting treated seeds or chlorpyrifos granules directly.

Chlorpyrifos is categorized by the EPA as moderately toxic to mammals (rat lethal dose [LD_{50}] = 97 mg/kg; house mouse LD_{50} = 60 mg/kg) and highly to very highly toxic to birds (house sparrow LD_{50} = 10 mg/kg; common grackle LD_{50} = 5.6 mg/kg) on an acute oral basis. Chlorpyrifos is considered by the EPA to be highly toxic to terrestrial invertebrates based on acute contact LD_{50} values of 0.059 µg/bee for honeybees. While toxicity data on terrestrial plants is limited, the EPA does note that chlorpyrifos shows some phytotoxicity to terrestrial plants.

The major degradate of chlorpyrifos, TCP, is less toxic than the parent for mammals and birds, and it is not considered as a degradate of concern to terrestrial organisms by the EPA. Chlorpyrifos oxon is considered a degradate of concern; however, limited toxicity data available to assess the potential effects of chlorpyrifos oxon on terrestrial organisms.

4.6.2 Aquatic organisms

Aquatic organisms including freshwater fish, invertebrates, and plants can be exposed to chlorpyrifos or its degradates, chlorpyrifos oxon and TCP, through contaminated surface water bodies such as lakes, ponds, rivers, and streams. Chlorpyrifos may bioaccumulate in organisms, which poses additional risk to organisms higher in the food chain. Chlorpyrifos may represent a hazard to benthic organisms because of its persistence in sediments.

According to the EPA, chlorpyrifos is classified as very highly toxic to fish (bluegill sunfish lethal concentration [LC_{50}] = 1.8 µg/L) and aquatic invertebrates (water flea LC_{50} = 0.10 µg/L) on an acute

basis. There is potential for chlorpyrifos to bioaccumulate from continuous exposure; however, when exposure ceases, it can rapidly depurate from fish. Although chlorpyrifos is designed to target arthropods, it shows toxicity (e.g., reduced growth) to aquatic plants as well (alga EC_{50} = 140 µg/L).

The major degradate of chlorpyrifos, TCP, is orders of magnitude less toxic than the parent for freshwater fish and invertebrates; therefore, it is not considered as a degradate of concern to aquatic organisms. Chlorpyrifos oxon, in contrast, is considered a degradate of concern by the EPA and is of similar or greater toxicity than chlorpyrifos to many aquatic species. For example, the oxon is 8.5 times more toxic than chlorpyrifos to sheepshead minnows and 100 times more toxic than chlorpyrifos to aquatic phase amphibians. However, according to the EPA, data gaps exist for oxon toxicity to aquatic organisms.

4.6.3 Endangered species

The EPA was required to conduct a biological evaluation of chlorpyrifos to examine its potential effects on federally endangered and threatened (listed) species and/or designated critical habitats. Due to the multitude of chlorpyrifos use patterns, the EPA determined all listed species' ranges and critical habitats overlap with potential areas of chlorpyrifos exposure. All the modeled chlorpyrifos uses and use patterns resulted in threshold exceedances for most endangered taxa. The Minnesota Zoo has partnered with the US Fish and Wildlife Service to monitor for pesticides including chlorpyrifos in federally listed critical prairie habitat for Poweshiek skipperlings and Dakota skippers in Minnesota since 2014 [29]. They found chlorpyrifos in critical prairie habitats in summer samples across all years (2014-2019). Levels of chlorpyrifos ranged from trace amounts (i.e., <1 part per billion [ppb]) to 2290 ppb.

Greater detail about the potential exposure and toxicity of chlorpyrifos and chlorpyrifos oxon to terrestrial and aquatic organisms in Minnesota will be included in the special registration review. Specifically, the potential impacts of chlorpyrifos at concentrations being found in Minnesota on terrestrial and aquatic organisms will be examined. Additionally, risk to endangered species in Minnesota will be explored.

4.7 Benefits of use

Chlorpyrifos is a highly effective pesticide (i.e., results in rapid and high levels of mortality) against a broad taxonomic range of pests (e.g., aphids, beetles, and mites) including important agronomic pests in Minnesota such as the soybean aphid (*Aphis glycines* Matsumura) which can reduce soybean yield up to 40% [30]. Compared to certain other available active ingredients, chlorpyrifos can be more effective. For example, foliar liquid applications of chlorpyrifos are more effective than pyrethroids to manage sugar beet root maggot (*Tetanops myopaeformis* Röder) in sugar beets [31]. Chlorpyrifos provides an additional pesticide class to be used in rotations for important agronomic pests in Minnesota, which is important because rotation between different pesticide classes can delay the development of pesticide resistance. Additionally, chlorpyrifos can be beneficial as an option for managing pests that have developed resistance to other classes of insecticides, such as pyrethroid resistant soybean aphids [32]. Other benefits of chlorpyrifos include its low risk of contaminating groundwater, low cost relative to certain alternative pesticides, the availability of multiple formulations for application, and the ability to tank mix it with other pesticides.

The current and potential future benefits of chlorpyrifos in managing major pests in Minnesota will be summarized in the special registration review.

4.8 Chlorpyrifos and climate change

World-wide, stress and yield loss from pests is expected to increase due to climate change [33,34]. The geographic and temporal occurrence and quantity of pests is greatly affected by climate conditions. Climate change will likely alter Minnesota's pest complex in multiple ways. The changing climate could change the type and/or increase the number of pests requiring management [35]. Often, there exists a lag between the appearance of a new pest and the development of efficient management strategies. Highly toxic pesticides like chlorpyrifos can be a reliable method of killing new and unfamiliar pests. Changing climate may also affect the phenology of pests [36], increasing the length of time a pest is active and requiring management. Climate change also has the potential to change the location and types of crops being grown in Minnesota. For example, between 2006 and 2012, the areas where soybean is grown in Minnesota has shifted further northward [37].

The special registration review will summarize potential impacts of climate change on Minnesota pests and cropping patterns as they relate to chlorpyrifos use.

4.9 Alternatives to chlorpyrifos

The availability of alternative pest management options is an important factor when weighing potential mitigating actions the MDA may take. Reviewing chlorpyrifos alternatives can also aid in anticipating possible consequences of proposed actions. Pest management options besides chlorpyrifos are available. For example, there are 36 conventional active ingredients other than chlorpyrifos registered in Minnesota for use against soybean aphids on soybeans and nine for use against sugar beet root maggot on sugar beets. Additionally, non-conventional (e.g., organic pesticides), and non-pesticidal (e.g., cultural control, biological control) pest management options are also available. Alternative management options may differ from chlorpyrifos in their efficacy, cost, safety, and ease of use.

Recent data about alternative pest management options to chlorpyrifos, with a focus on the Midwest, will be summarized in the special registration review.

4.10 Minnesota Department of Agriculture's education and outreach

Reviewing the MDA's current and past education and outreach efforts relating to chlorpyrifos provides context when considering potential actions. Education and outreach efforts represent a key step (i.e., prevention) in the MDA's approach to managing pesticides and water quality (as outlined in the PMP). Knowledge about current and previous education and outreach activities can also offer insight on possible consequences of proposed actions.

The MDA, in collaboration with the University of Minnesota and other stakeholders, has been providing education to pesticide applicators and growers about environmental issues arising from chlorpyrifos use in the state. Education and outreach efforts by the MDA increased following the designation of chlorpyrifos as a surface water pesticide of concern in 2012. Those efforts have included presentations and mailings to applicators, dealers, and other stakeholders. In addition, efforts were made to educate

applicators through licensing recertification training and label compliance assistance programs. BMPs for chlorpyrifos were developed in 2014, in response to the designation as a surface water pesticide of concern, to address its presence in Minnesota surface waters. The chlorpyrifos BMPs cover mandatory label requirements and voluntary recommendations such as using integrated pest management and rotating between different insecticides. A Chlorpyrifos Response Plan was developed in 2019 to address continued detections of chlorpyrifos in Minnesota surface waters and the continued designations of chlorpyrifos water quality impairments of surface water bodies in agricultural areas of Minnesota. The Chlorpyrifos Response Plan addresses current and potential future impairments by outlining specific education and outreach efforts that will be made in addition to regional and targeted monitoring and use inspections.

In the special registration review the MDA's current and past chlorpyrifos education and outreach efforts will be described. The review will also evaluate the effectiveness of these educational programs and explore opportunities to strengthen and expand education and outreach efforts.

5. Abbreviations

AChE	acetylcholinesterase
BMPs	best management practices
CARB	California Air Resources Board
CDPR	California Department of Pesticide Regulation
EPA	The Environmental Protection Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
HBV	health-based guidance value
LC_{50}	lethal concentration to kill 50%
LD_{50}	lethal dose to kill 50%
MASS	Minnesota Agricultural Statistics Service
MDA	The Minnesota Department of Agriculture
MDH	Minnesota Department of Health
MPCA	Minnesota Pollution Control Agency
NASS	National Agricultural Statistics Service
NRDC	Natural Resources Defense Council
PANNA	Pesticide Action Network North America
PMP	Pesticide Management Plan
ppb	parts per billion
$ssPAD_{food}$	Steady state population adjusted dose for exposure by food only
USDA	United States Department of Agriculture
USGS	United States Geological Survey
US	United States of America

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