Court File No. T-956-21

FEDERAL COURT

BETWEEN:

SAFE FOOD MATTERS INC.
and PREVENT CANCER NOW

Applicants

and

ATTORNEY GENERAL OF CANADA
and MINISTER OF HEALTH

Respondents

Court File No. T-1412-21

FEDERAL COURT

BETWEEN:

SAFE FOOD MATTERS INC.
and PREVENT CANCER NOW

Applicants

and

ATTORNEY GENERAL OF CANADA
and MINISTER OF HEALTH

Respondents

AFFIDAVIT OF MARGARET SEARS
(Affirmed November 2, 2021)

I, Margaret Sears, of the City of Ottawa, in the Province of Ontario, AFFIRM AS FOLLOWS:

1. I am the Chair of one of the applicants in this proceeding, Prevent Cancer Now ("**PCN**"). As such I have personal knowledge of the matters set out in this affidavit. Where I do not have such knowledge, I have set out the source of my information and belief and I believe the information to be true.

2. PCN is a Canadian non-profit corporation founded in 2007. PCN's mission is to eliminate preventable contributors to cancer through research, awareness, education and advocacy.

3. Our work covers a wide range of issues such as the effects of pest control products on the environment and human health; other toxic substances such as flame retardants, phthalates, triclosan and formaldehyde, to name a few; nuclear issues; cannabis regulation; and other issues. We comment regularly on scientific methods and rigour to recognize and assess toxic substances, including effects on hormone systems and other paths contributing to cancer; to protect vulnerable populations; and to address modern exposures. We regularly make submissions to regulatory agencies on a variety of topics with a view to primary cancer prevention. This includes submissions to various committees during legislative reviews. For example, PCN made submissions in 2019 to the federal Standing Committee on Agriculture and Agri-Food on healthy food related topics including pesticides, and to the Senate Agriculture and Forestry Committee on neonicotinoid pesticides in 2014.

4. I have an undergraduate degree in Chemical Engineering and Applied Chemistry from the University of Toronto, Master's and Doctorate degrees in Chemical Engineering from McGill University, and extensive work experience in medical scientific review methods and environmental health on a variety of environmental issues including bitumen emissions, toxic metals, chemical and environmental sensitivities, pesticides, indoor air quality and everyday exposures, and other topics. I have produced reports and conducted research on the human health implications of exposures to toxic substances with funding from the Canadian Institutes for Health Research (CIHR) and Social Science and Humanities Research Council, for health and medical

groups and government agencies and such as the Canadian Institute of Child Health, the Ontario College of Family Physicians, the Canadian Human Rights Commission, the Canadian Transportation Authority and the Canadian Committee on Indoor Air Quality. I have authored and co-authored a variety of peer-reviewed publications on environmental health and acted as guest co-editor of two special editions of medical journals on environmental health and clinical approaches. In 2013, I received the Carleton Lee Award from the American Academy of Environmental Medicine. My curriculum vitae is attached as **Exhibit "A"**.

5. PCN regularly makes submissions to the Pest Management Regulatory Agency of Health Canada ("**PMRA**") on consultations under the *Pest Control Products Act*. For example we made several submissions to the PMRA on the pollinator re-evaluations of neonicotinoid and glyphosate pesticides between 2014 and 2019, including being involved in a campaign opposing PMRA's proposal to increase maximum residue limits ("**MRLs**") in food for glyphosate. We also commented on significant PMRA policies such as the proposed cumulative risk assessment framework, and the PMRA's practice of using conditional registrations.

6. As part of this work, PCN publicly advocates for restrictions on the production and use of organophosphate pesticides, including Chlorpyrifos.

7. PCN has previously participated in consultations conducted by the PMRA on the Chlorpyrifos re-evaluation decision.

<u>The 2017 Proposed Cumulative Risk Framework</u>

8. On March 1, 2017, the PMRA released Regulatory Proposal PRO2017-01, Cumulative Risk Assessment Framework (the "**Proposed Cumulative Risk Assessment Framework**"), through which the PMRA proposed to develop a framework and methodology to assess the cumulative effects of pesticides that have a common mechanism of toxicity. The Proposed Cumulative Risk Assessment Framework was made available to the public for comment. This is attached as **Exhibit "B"**.

9. On April 14, 2017, PCN and six other non-profit organizations (the Canadian Association of Physicians for the Environment, Canadian Environmental Law Association, the David Suzuki Foundation, Ecojustice, Environmental Defence, and Équiterre) submitted a letter to the PMRA, offering recommendations on how to strengthen the Proposed Cumulative Risk Assessment Framework when evaluating the health risks of pesticides. The letter is attached to this affidavit as **Exhibit "C"**.

10. In summary, in this submission PCN and the other organizations recommended, among other things, that the PMRA should finalize and operationalize the risk assessment framework and utilize it in regulatory decision-making.

11. Despite the release of the Proposed Cumulative Risk Assessment Framework and the above recommendations, to date the PMRA has never finalized or implemented a cumulative risk assessment framework.

Work on Chlorpyrifos and Other Organophosphates

12. PCN has been making numerous submissions to the Government of Canada since 2014 (catalogued here: http://www.preventcancernow.ca/main/resources/cancer-prevention-submissions/). The first specifically regarding Chlorpyrifos was submitted in 2019 (http://www.preventcancernow.ca/wp-content/uploads/ChlorpyrifosSubmission.pdf), commenting on the environmental assessment and further commenting on omission of human health, and recommending that the insecticide be banned.

13. PCN, its founders and I myself have recognized that organophosphate insecticides (of which Chlorpyrifos is one) are harmful since our first work on pesticides bylaws. We noted the 2015 carcinogenicity findings of the International Agency for Research on Cancer (IARC) regarding four related organophosphate insecticides and one herbicide. Organophosphate insecticides, including Chlorpyrifos, were also investigated in the PCN analysis of pesticide use on Ontario golf courses, and were found to be commonly used.

14. In the media, I co-authored an opinion piece in the National Observer, "Canada has waited long enough to ban chlorpyrifos." Submissions regarding Chlorpyrifos are posted on the PCN website.

The 2019 Proposed Re-evaluation Decision

15. On May 31, 2019, the PMRA released Proposed Re-evaluation Decision PRVD2019-05, "Chlorpyrifos and Its Associated End-use Products: Updated Environmental Risk Assessment" (the "**Proposed Re-evaluation Decision**").

16. In the Proposed Re-evaluation Decision the PMRA proposed to largely discontinue registration of products containing Chlorpyrifos, but to maintain registration for certain uses, specifically:

- Standing water - temporary pools for larval mosquito control;
- Outdoor adult mosquito control;
- Structural indoor and outdoor (non-residential);
- Outdoor ornamentals (container stock only) for control of Japanese beetle larvae; and
- Greenhouse ornamentals.

17. On August 29, 2019, PCN made a submission to the PMRA in response to the Proposed Chlorpyrifos Re-evaluation Decision. The submission is attached to this affidavit as **Exhibit "D"**.

18. PCN submitted that Chlorpyrifos should be taken off the market immediately, given that it is excessively persistent and toxic, and that preferable alternatives exist. PCN specifically identified the human health risks from continued manufacture and use of products that contain Chlorpyrifos, such as the risks of brain damage in children, and that Chlorpyrifos is likely a carcinogenic substance.

19. PCN also noted that the European Food Safety Authority (the "**EFSA**") was unable to conduct risk assessments of Chlorpyrifos in August 2019, as

potential neurological and developmental effects were present even at low levels. As a result, PCN noted that the EFSA would discontinue the use of these pesticides immediately.

20. PCN also made submissions on safe alternatives to the remaining uses permitted for Chlorpyrifos containing products, such as alternatives for mosquito control, structural pest control, and ornamental plants.

21. PCN also referenced and relied on a 2018 article published in *PLOS Medicine*, entitled "Organophosphate exposures during pregnancy and child neurodevelopment: Recommendations for essential policy reforms", a copy of which is attached to this affidavit as **Exhibit "E"**. In the article, the authors, a collection of doctors and medical researchers from Canada and the US, detailed the evidence of risks of cognitive and neurodevelopmental disorders that result from prenatal exposure to organophosphate pesticides like Chlorpyrifos, and recommended the immediate phase out of organophosphate pesticides.

<u>The 2020 Final Re-evaluation Decision</u>

22. On December 10, 2020, the PMRA released decision RVD2020-14, "Chlorpyrifos and Its Associated End-use Products (Environment)" (the "**Final Re-evaluation Decision**").

23. The PMRA in the Final Re-evaluation Decision continued certain categories of uses of Chlorpyrifos based on environmental risk and discontinued other uses. In summary, the PMRA used different categories of uses with specific requirements for each category:

    (i) Uses requiring label amendments and new restrictions, which would require label amendments within a two-year implementation period, including uses for:

        a) Standing water – temporary pools for larval mosquito control;

        b) Outdoor adult mosquito control;

c) Structural indoor and outdoor (non-residential);

d) Outdoor ornamentals (container stock root immersion only) for control of Japanese beetle larvae;

e) Elm bark beetle and mountain pine beetle control;

f) Greenhouse ornamentals;

(ii) Garlic and canola uses: delayed cancellation; and

(iii) Other outdoor uses (for example on other crops): cancelled on a three-year phase-out.

24. There was no consultation in PVRD2019-05 on the proposed label amendments for elm bark beetle and mountain pine beetle control, this measure was new in the Final Re-Evaluation Decision.

25. On February 8, 2021, PCN, Safe Food Matters Inc. ("**SFM**"), and eight other organizations submitted to Minister of Health, the Honourable Patty Hadju, a Notice of Objection to the Final Re-evaluation Decision pursuant to section 35 of the *Pest Control Products Act* (the "*PCPA*" or the "Act"). The Notice of Objection is attached as **Exhibit D** to the affidavit of Mary Lou McDonald.

26. In the Notice of Objection, PCN and the other organizations submitted that the uses continued through the Final Re-evaluation Decision were not in compliance with the requirements of the *Pest Control Products Act*, specifically that the risk posed through further use was not "acceptable" as required by the Act.

27. The Notice of Objection explained that Chlorpyrifos is volatile or semi-volatile and can be transported long distances and had previously been evaluated by Health Canada as persistent.

28. The Notice of Objection raised concerns about indoor and outdoor non-residential structural uses of Chlorpyrifos. For example, according to PMRA regulatory documents, Chlorpyrifos may be used for pest control in

laboratories, warehouses, railroad boxcars, food granaries, cargo areas, livestock housing, and industrial plants. Non-residential structures also include pet kennels, and areas within multi-unit residential structures where the general public has no access such as furnace rooms, and storage areas.

29. The Notice of Objection raised concerns that the PMRA failed to assess the exposure to the environment from these uses. The limited range of applications did not necessarily lead to a valid assumption of limited exposure. For example, outdoor broadcast treatment (meaning treatment applied uniformly over the entire treated area) could result in the insecticide being transported into soil or foliage, or evaporated or blown on dust into the air, and thereby result in human exposure. Indoor use can result in volatilization into indoor air where it can be inhaled, and condensation resulting in re-deposition onto surfaces where it may be transferred to hands, food, or food preparation surfaces. For example, use is permitted in food processing plants and meat packing plants where many people work and where food can be exposed. The Notice of Objection raised concerns that human exposure from these uses was excluded from the risk assessment.

30. The Notice of Objection noted that many Canadians have concerns with the health risks associated with Chlorpyrifos and that any update to the human health risk assessment should be subject to public comment and consultation. Human health concerns regarding structural uses were expressed. The Notice of Objection also questioned the value of the use of Chlorpyrifos for this purpose as there are other alternatives.

31. The Notice of Objection raised concerns about the assumptions used by the PMRA in continuing to permit use in mountain pine and elm bark beetle control and whether it was effective for these uses. The Notice of Objection also questioned whether the PMRA had identified potential exposure to terrestrial organisms such as birds, bats and insects from mosquito control uses in temporary or vernal pools. Many of these issues are also raised in comments of other organizations on the proposed decision. I obtained the

joint comments from David Suzuki Foundation, Canadian Environmental Law Association, Canadian Association of Physicians, Environmental Defence and Équiterre, dated July 31, 2019. This document is attached as **Exhibit "F".**

32. In the Notice of Objection, PCN and the other organizations specifically criticized the PMRA's decision to divide the environmental risk assessment from an assessment of human health, pointing out that "Risks to the environment and health often overlap. Because the assessments are separated, there is room for relevant considerations to 'fall through the cracks.'"

33. PCN and its partner organizations also asked for a review panel, pursuant to s. 35(3) of the *PCPA*, to review the Final Re-evaluation Decision and to recommend whether the decision should be confirmed, reversed or varied.

PMRA Sales Reports on Chlorpyrifos

34. On June 24, 2018 I sent an email to the PMRA requesting pesticides sales reports since 2007. Interim requests had been made as reports were published, and as of June 2021 I had obtained reports for 2007-2008, 2009, 2010, 2012, 2013, 2014, 2015, 2016 and 2018. These are all that are listed on the PMRA website, and that were identified in response to an open-ended request.

35. Chlorpyrifos was among the top ten insecticides in every sales report. Relying on information within the PMRA Sales Reports, on June 10, 2021 I completed a summary table on relevant sales information for Chlorpyrifos insecticides. In the table I identified Chlorpyrifos' rank among the top ten insecticides based on total national sales by weight (in kilograms), and whether Chlorpyrifos was the only listed organophosphate insecticide in the top 10 insecticides sold for that year or if another organophosphate insecticide was also listed in the top 10. The summary table is attached to this affidavit as **Exhibit "G"**.

The PMRA Data Call-in Decision

36. After the final decision in the environmental portion of the Chlorpyrifos re-evaluation in December 2020, the PMRA took further steps to re-initiate the

human health re-evaluation of Chlorpyrifos. Two days after our notice of objection was filed, on February 10, 2021, the PMRA issued a "Data Call-in" for the Chlorpyrifos active ingredient ("Data Call-in"). This data call-in is included as **Exhibit "H"**.

37. The Data Call-in requested a variety of toxicology data and occupational and non-occupational exposure studies relevant to human health. The Data Call-in stated that this was "information required for re-evaluation".

38. A large number of the studies in the Data Call-in are over a decade old, and a significant number date back to the 1960s, '70s, '80s and '90s. The PMRA documents do not explain why the PMRA failed to request, receive or review this information earlier on in the re-evaluation process, which commenced in 1999 and included earlier partial re-evaluations of human health. The PMRA's re-evaluation policy requires that new information indicating an increased environmental risk be supplied by registrants. The information in the Data Call-in was required within 30 calendar days and was sent to two registrants: Adama Agricultural Solutions Canada Ltd. and Sharda Cropchem Limited.

39. On May 13, 2021, the PMRA released Re-evaluation Note REV2021-02, "Update on the Re-evaluation of Chlorpyrifos", under which the PMRA cancelled all remaining Chlorpyrifos uses and products, and ordered the existing stocks of all Chlorpyrifos products to be phased out on a three-year timeline. This decision is attached as **Exhibit F** to the Affidavit of Mary Lou McDonald and is described in paragraphs 15-16 of her affidavit.

40. Following the PMRA's decision in May 2021 to cancel Chlorpyrifos registrations with a three-year phase-out for existing stocks, PCN and SFM then commenced this judicial review application.

41. I was informed by my counsel on this judicial review application, and believe it to be true, that we were served with the Certified Tribunal Record ("**CTR**") for this application on August 17, 2021. Counsel has advised me that the CTR

contains a record of decision and briefing note for an MRL Trackers' Meeting on April 19, 2021.

42. I did not know that the PMRA made a new decision regarding Chlorpyrifos MRLs in April 2021 until I was advised by my counsel about the contents of the CTR. There is no documentation of this decision in the Public Registry for the Chlorpyrifos re-evaluation. I am not aware of any other public notice of this decision.

43. I make this affidavit in support of this judicial review application and for no improper or other purpose.

AFFIRMED REMOTELY by Margaret Sears stated as being located at the City of Ottawa, in the Province of Ontario, before me at the Municipality of Prince Edward County in the Province of Ontario, on November 2, 2021, in accordance with *O. Reg 431/20, Administering Oath or Declaration Remotely*.

Commissioner for Taking Affidavits
(or as may be)

Charlotte Ireland, LSO # P10772

MARGARET SEARS

This is **Exhibit "A"** referred to in the affidavit of
Margaret Sears affirmed remotely before
me in accordance with O. Reg 431/20,
Administering Oath or Declaration Remotely
this 2nd day of November, 2021.

Commissioner for Taking Affidavits
(or as may be)

Margaret (Meg) E. Sears (M.Eng., Ph.D.)

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Capabilities and Experience:

Broad interests include health and medicine, epidemiology and toxicology, chemistry, ecology, biology and chemical engineering. Specific interests in ongoing work include environmental health, and scientific evidence synthesis for hazard and risk assessment, and public policy. A current focus is on multi-factorial contributors to chronic disease, and filling data gaps in environmental health epidemiology.

Activities include researching, assessing, reviewing and reporting in the scientific literature, for government bodies, peer-reviewed publications, and civil society organizations. My work includes liaising with a broad network of scientific experts, physicians and others on topics related to environment and health. I also frequently observe and participate in stakeholder meetings regarding the Chemicals Management Plan, and participate in federal government consultations and other meetings on chemicals management and pesticides. In 2015, two reports from the Parliamentary Standing Committee on Health included my recommendations regarding pesticides, and health effects of radiofrequency radiation. The *Canadian Environmental Protection Act* Parliamentary Committee and the *Canadian Environmental Assessment Act* Panel recommendations include some of my recommendations, and I participated with Canadian Environmental Law Association staff and others, drafting proposed amendments to the *Canadian Environmental Protection Act (1999)*. I have written key documents regarding environmental sensitivities and worked with groups of affected individuals as well as health care professionals.

Experience includes working with groups of researchers on large scientific reports, including research question identification, literature searches, data extraction, analysis and review, writing, editing, managing references and maintaining version control. I chair the civil society organization *Prevent Cancer Now* and work with numerous academics and civil society organizations in Canada and internationally regarding toxic exposures. I have also twice been a medical journal guest editor. I have also conducted consultations among professionals, and citizens' groups, and prepared and presented scientific committee and tribunal submissions.

Public speaking includes lecturing at the Universities of Ottawa and Toronto, and Lakehead University, and numerous public presentations regarding topics in environmental health, as well as webinars on environmental public health, scientific review, policy change, and toxicant-specific topics.

Topics recently addressed include hazard and risk assessment per federal legislation, and more specifically epidemiology, toxicology (including pesticides), endocrine disruptors, toxic elements, systematic review in environmental health, and electromagnetic radiation in public and personal health.

Diverse laboratory and field experience in chemical engineering, applied chemistry, and microbiology including occupational health and safety, and microbiological and petrochemical industry research.

Academic Background

1986 Doctor of Philosophy, McGill University. Effects of growth conditions on biosorption by *Rhizopus* biosorbents.

1981 Masters of Chemical Engineering, McGill University. Measurement and mathematical modelling of biosorption of uranyl ion by biomass of the mould *Rhizopus arrhizus*.

1979 Bachelors of Applied Chemistry and Chemical Engineering, with Honours, University of Toronto.

Appointments

Senior Clinical Research Associate, presently working with Dr. Richard van der Jagt on the Environmental Health Information Infrastructure project; previously under Dr. David Moher at the Centre for Practice-Changing Research, Epidemiology, at the Ottawa Hospital Research Institute

Associate with University of Sherbrooke, working with Dr. Isabelle Gaboury and colleagues

Previously Adjunct Investigator at the Children's Hospital of Eastern Ontario (this type of appointment was discontinued)

Professional Membership

Canadian Paediatric Society, including Environmental Health Section.
Canadian Public Health Association
Ontario Public Health Association
International Network for Epidemiology and Policy

Awards and Grants

2013 Carleton Lee Award, American Academy of Environmental Medicine

2007-2009 Canadian Institutes of Health Research / Social Sciences and Humanities Research Council grant for a scoping review on the toxic elements arsenic, cadmium, lead and mercury.

1980-1985 Natural Sciences and Engineering Research Council scholarship for post-graduate studies

2007-2010 P.I. on NSERC / SSHRC grant, with Dr. Riina Bray, Medical Director WCH, UofToronto

Work Experience – University instruction

2012, 2014, 2017 University of Ottawa EVS 3131 (undergraduate) and Capstone Masters programs - Supervised and participated in student projects. Lectured on Environmental Health.

2010 – 2012 Lakehead University and the Northern School of Medicine - PUBL5213 Environmental and Occupational Public Health (Masters of Public Health). Lectured on toxicology and epidemiology, land use planning, evidence synthesis, pesticides, toxic metals and endocrine disruption, in a distance-learning course.

2011, 2012 Lectured on toxicology epidemiology and evidence synthesis, as well as pesticides, in ENV 341, at University of Toronto.

2009, 2010 Lectured on toxicology, epidemiology, evidence synthesis, pesticides and toxic metals in HSS3303 at the University of Ottawa.

Work Experience – selected

2020-21 Preparation of a Module (2020) and Update (2021) on COVID-19 in Buildings, for the Canadian Committee on Indoor Air Quality, National Research Council.

2019 Preparation of a Module regarding Indoor Environmental Quality, for the Canadian Committee on Indoor Air Quality, National Research Council.

2018 Preparation of a Module regarding Chemical Sensitivities, for the Canadian Committee on Indoor Air Quality, National Research Council.

2013-2014 – Health expert in the Proceeding of the Alberta Energy Regulator re. health effects of bitumen emissions in the Peace River area.

2012 Health expert in Fortis BC hearing re. Smart Meters

2004-on Systematic Reviews in the Centre for Practice Changing Research at the Ottawa Hospital Research Institute, under Dr. David Moher. Many aspects of evidence review and synthesis, and editorial responsibility for large medical scientific research reports.

2003-on Work with diverse medical researchers, on data analysis, presentation and writing, in Ottawa, Toronto and at the University of Sherbrooke.

2011 In conjunction with physicians associated with the Ontario College of Family Physicians, I conducted literature searches, synthesis of information and co-writing of a report regarding updating the Greig Record for child and adolescent primary care visits with Family Physicians.

I organized and spoke at a meeting to present Toxic Metals in Canadians scoping review findings and to gain insights from physicians, clinical and toxicological researchers, and public health officials.

2009 Co-authored "Air Travel and Chemical Sensitivities" for the Canadian Transportation Authority.

2008 Canadian Institutes of Health Research Primary Investigator - "Toxic Metals in Canadians and their Environments: Exposures, health effects, and physician and public health management strategies - A Scoping Review"

2008-on Occasionally assist Canadian Civil Society Organizations (e.g., the David Suzuki Foundation, Canadian Assoc. of Physicians for the Environment) with scientific review and writing of documents regarding environmental health topics, including pesticides and cosmetics.

Prepared affidavits with regard to health effects of herbicides (and contaminants) used at CFB Gagetown, NB.

Lectured on epidemiology, toxicology and synthesis of scientific evidence in environmental health, pesticides, toxic elements (particularly arsenic, cadmium, lead and mercury) as well as scientific writing, in undergraduate courses at the University of Ottawa and University of Toronto, and at the graduate level (Masters of Public Health) at Lakehead University.

2006 Prepared "A Medical Perspective on Environmental Sensitivities" for the Canadian Human Rights Commission, including research review, and consultation with physicians, architects and civil society organizations.

2002-on Writing, and assisting medical researchers and others with drafting of research documents.

- This work includes data extraction, review of data and statistics, review of the medical background information, literature review updates, and planning, drafting and version control.
- Articles have included systematic reviews, randomized controlled trials, other interventional and observational studies, and commentaries.
- Topics include pesticide assessment and 2,4-D, environmental sensitivities, medical ethics, medical education, diabetes in children, probiotics, sexuality and fertility following spinal cord injury, breast cancer care, child car-seats and booster-seats, nocturnal enuresis, omega-3 fatty acids and infant health, computerized physician order-entry systems in the context of bronchiolitis, childhood arthritis, models of medical practice and collaboration, lipid modifying agents, drug delivery, TPMT assessment in thiopurine therapy, morphine monitoring nursing practice, nutritional supplements and drugs for cardiovascular health, and online medical education.

2002 Drafted "Frequently Asked Questions" responses regarding breast milk contamination, flame retardants, West Nile virus and insect repellents, for the Canadian Institute of Child Health.

1979-80 Research engineer at Gulf Canada's research facility in Sheridan Pk., Mississauga. Constructed and operated small-scale laboratory simulation of heavy oil cracking, as well as mathematical modelling of enhanced oil recovery (akin to 4-phase hydrogeology).

1975-79 During summers prior to and during undergraduate studies, worked in UofT Chemical Engineering laboratories (including tar sands oil extraction), and at Imperial Oil Research laboratories.

Volunteer Activities

2017-20 Member of the Science Committee for the Canadian Public Health Association 2018 Conference Planning Committee

2017-20 Core leadership group and Conference planning for the Canadian Alliance for Regional Risk Factor Surveillance (CARRFS)

2015-on member of Waste Watch Ottawa, that brings strong evidence regarding waste management to Ottawa City Council

2011- on Board member (currently Chair) of *Prevent Cancer Now* (www.preventcancernow.ca). Advancing primary cancer prevention with scientific analyses, public education, and policy and law reform. Activities include scientific writing and editing of publicly available documents, media, public presentations regarding cancer prevention. PCN collaborates with many Canadian professional and ENGOs.

2011- on Member of the Sustainability Committee ("Green Team") at the Children's Hospital of Eastern Ontario, Ottawa.

2001-11 on Established, along with other mothers, the Ottawa Neuroblastoma Research Fund (CHEO)

2001- on Work with physicians and various organizations regarding pesticides and health.

2002- on (currently quiescent) Founding member of the Coalition for a Healthy Ottawa and the Canadian Coalition for Health and the Environment. We synthesized and promoted research on pesticides and health, as well as synthesis of scientific evidence, in efforts to reduce use of pesticides in urban areas, and for vector control, with these and other groups across Canada.

1995-8 Member of the Board of Directors of *Les Petits Ballets*, in charge of publicity.

1989-on (currently quiescent) Founding member and Secretary for the Wetlands Preservation Group of West Carleton, working for environmental protection before the Ontario Municipal Board, Environmental Assessment Advisory Committee, in court, and before the Sewell Commission on land use planning.

Peer-reviewed publications

Sears, M.E. for the Canadian Committee on Indoor Air Quality. "COVID-19 in Buildings." Module 15 (2020) and Update (2021). https://iaqresource.ca/en/iaq-guides/

Sears, M.E. for the Canadian Committee on Indoor Air Quality. "Indoor Environmental Quality (IEQ) and Productivity in Workplaces/ Achievement in Schools." Module 14 (2019). https://iaqresource.ca/wp-content/uploads/2020/09/CCIAQB-Module14-Eng.pdf

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Sears, Margaret E., and Stephen J. Genuis. Environmental Determinants of Chronic Disease and Medical Approaches: Recognition, Avoidance, Supportive Therapy, and Detoxification. J Environ Public Health. Article ID 356798 (2012): 1–15.

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Sears M. Toxic Metals Injuries. Paed Child Health. 2011;16(3):152.

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2020 Co-chair Canadian Alliance for Regional Risk Factor Surveillance (CARRFS) pre-CPHA conference symposium, online.

2019 Co-chair CARRFS collaborator session, CPHA conference, Ottawa.

2018 Core organizing committee for CARRFS pre-conference session, and speaker (**Escalating Chronic Disease in Young Canadians – surveillance for environmental links**) at the collaboration session during the Canadian Public Health Association conference, Montreal.

2017 Presentations and participation in an experts forum at The Hebrew University, hosted by the Israeli Institute for Advanced Studies, and the Environmental Health Trust. **"Wireless Radiation and Human Health."** Jerusalem, January 2017.

2015 **"Scientific Review to Support Public Policy Regarding Exposure to Radiation from Wireless Communications Devices."** Poster. International Bioelectromagnetics Conference. Alisomar, California. June 2015

2014 "**Search and ye shall find environmental health concerns: e.g. Peace River Proceeding1769924."** Invited Presentation. Under Western Skies Conference. Calgary. September 2014.

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Non-peer reviewed medical / scientific articles

Ongoing, submissions regarding policy and laws improvements, and scientific comments regarding substances and exposures to the Government of Canada and others, on behalf of *Prevent Cancer Now*. http://www.preventcancernow.ca/main/resources/cancer-prevention-submissions

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M.E. Sears, C.S. Findlay, N. Arya, L. Marshall, M. Sanborn, K.J. Kerr, J. Kasperski
[2007 – prepared on behalf of the Environmental Health Committee, Ontario College of Family Physicians; submitted to the Pest Management Regulatory Agency (PMRA) of Health Canada]

This is **Exhibit "B"** referred to in the affidavit of **Margaret Sears** affirmed remotely before me in accordance with O. Reg 431/20, Administering Oath or Declaration Remotely this 2nd day of November, 2021.

Commissioner for Taking Affidavits
(or as may be)

Regulatory Proposal PRO2017-01

Cumulative Risk Assessment Framework

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1.0 Executive Summary

This document describes the framework and methodology that Health Canada's Pest Management Regulatory Agency (PMRA) will use for assessing the cumulative effects of pesticides that have a common mechanism of toxicity. It supersedes Health Canada's 2001 Science Policy Note (SPN2001-01) on Guidance for Identifying Pesticides that have a Common Mechanism of Toxicity for Human Health Risk Assessment. The document also builds upon Health Canada's response to the Commissioner of the Environment and Sustainable Development 2015 audit on pesticide safety, whereby the PMRA indicated its intention to have methodology for cumulative assessment in place in the 2017-2018 fiscal year.[1] The document takes into account approaches taken by other chemical regulators and outlines general methods for cumulative risk assessment that are based on additive behaviors of these chemicals when combined. A step-wise approach for identifying pesticides that belong to a common mechanism group is presented including criteria for initial grouping and considerations for refining a common mechanism group. A flexible tiered framework for assessing the hazard and exposure components of an assessment is presented that will facilitate the refinement of these parameters in a cumulative risk assessment to the extent needed, thereby using resources efficiently. While the document summarizes elements of cumulative risk characterization, some of the uncertainties and challenges with respect to cumulative methodology in general are presented.

The PMRA will accept written comments on this proposal up to 45 days from the date publication of this document. Please forward all comments to Publications (please see contact information indicated on the cover page of this document).

2.0 Introduction

For the purpose of this policy, cumulative assessment is aimed at identifying the risks associated with co-exposures to two or more chemicals that cause a common toxic effect(s) by the same, or essentially the same, sequence of major biochemical events (that is, a common mechanism of toxicity). Concurrent exposure routes (oral, dermal, inhalation) and pathways (for example, diet, drinking water, residential use) to chemicals that share a common mechanism of toxicity are assessed to determine the potential for cumulative effects, based on the likelihood that people may be exposed to more than one of these chemicals at the same time. Cumulative assessment is undertaken to explore the possibility that low-level exposures to specific multiple chemicals could lead to the same or increased health risk relative to a higher level of exposure to any of these chemicals individually.

The consideration of the cumulative effects of pesticides was mandated in the modernization of Canadian pesticide legislation and reflects the application of modern science. Specifically, sections 7, 11 and 19 of the *Pest Control Products Act* (PCPA, 2006) requires the consideration of "available information on…cumulative effects of the pest control product and other pest control products that have a common mechanism of toxicity" in evaluating the health risks of a pesticide. In some scientific circles, exposure to multiple chemicals by multiple routes and pathways is referred to as combined exposure to multiple chemicals rather than cumulative

[1] http://www.hc-sc.gc.ca/cps-spc/pest/part/protect-proteger/pesticide-safety-securite-pesticide/index-eng.php

exposure; however, the terminology used through this document reflects that used in the PCPA for the assessment of pesticides. The scope of this policy does not extend to the consideration of mixtures of chemicals that may result in cumulative effects through disparate mechanisms of toxicity; however, it is worth acknowledging that this is an area of interest in the international regulatory community to be closely monitored.

Assessing the cumulative effects of pesticides to human health differs from aggregate assessment, which considers the risk from exposure (non-occupational) to a single chemical via all relevant routes and exposure pathways. Aggregate risk assessments have been fully implemented in the review of both new and re-evaluated pesticides and are supported by policy (Health Canada, 2003).

Currently, the PMRA is completing individual assessments for pesticides within the same common mechanism group through its re-evaluation program. It is essential that toxicological and exposure assessments of individual chemicals are up-to-date prior to undertaking the complex task of cumulative assessment. Cumulative assessments of pesticides that are known metabolites of one another (for instance, acephate and methamidophos) have been undertaken by the PMRA as the Agency continues to build its methods in this emerging area of science. The PMRA continuously monitors method development as well as specific cumulative assessments at the international level to determine their relevancy to the Canadian context.

This document sets out a framework to facilitate the assessment of cumulative risk of pesticides that share a common mechanism of toxicity. The framework is not intended to be prescriptive but rather is intended to function as a guide to those conducting cumulative assessments as well as a tool to communicate current practices to stakeholders. The document outlines general methods for cumulative risk assessment, considerations for identifying pesticides that belong to a common mechanism group, a tiered framework consisting of increasing levels of hazard and exposure refinement, elements of risk characterization and a discussion of uncertainties. The framework contained herein draws from efforts undertaken by other Health Canada programs, North American Free Trade Agreement (NAFTA) partners such as the United States Environmental Protection Agency (USEPA) and by international regulatory and scientific communities.

It is anticipated that by closely aligning the framework and methodology with that of other regulators, that PMRA can make use of cumulative assessments undertaken by those regulators, in whole or in part, provided that the assessments are relevant to the Canadian context.

3.0 Cumulative Risk Assessment Methods

In assessing the risk of chemicals with a common mechanism of toxicity, it is not necessary to have a full understanding of the entire molecular sequence of events required to produce a specific biological outcome. Rather, a more important aspect is having an understanding of the key cytological and biochemical events following chemical interaction. In this sense, the concept of mode of action, often used in cancer risk assessment, and generally considered to require less detail in the description of events than at the molecular level, is applicable. More recently, the term adverse outcome pathway has been employed to link the molecular initiating event(s) to

progressive levels of biological organization at the individual or population level. Mechanism of toxicity, mode of action and adverse outcome pathway are all conceptually similar constructs for establishing the key events that define a common mechanism group.

Fundamentally, exposure to more than one chemical at a time is required for there to be a cumulative effect. When combined, chemicals can act jointly, resulting in three distinct types of action: independent, as an interaction (that is synergistically or antagonistically) or in an additive manner. Chemicals that act independently typically do so through different modes of action and are referred to as complex mixtures. Independently-acting chemicals, by definition, are not addressed by cumulative assessment as mandated under current pesticide legislation.

Interactions refer to synergistic or antagonistic actions between or among chemicals. From a public health perspective, synergistic interactions are of concern as default assumptions of additivity could lead to an under-prediction of risk; however, synergistic interactions are quite rare. Data analysis suggests that when present, the magnitude of the under-prediction is relatively small (EC, 2009; EC 2012).

Chemicals that act via the same mode of action, referred to as simple mixtures when combined, can be characterized as behaving in an additive manner. The concept of dose or concentration addition assumes no chemical interactions, but acknowledges that the combination of effects will be greater than that of each individual chemical. For the purpose of cumulative assessment, as described herein, an additive action is the default assumption used by most regulatory authorities (USEPA, 2002; EFSA, 2008).

The most common dose/concentration addition approaches are the hazard index method, margin of exposure method or relative potency factor method. These methods are described herein in further detail. The choice of method used in a cumulative risk assessment will be influenced primarily by the context of the assessment, the available data and the level of refinement required in the assessment. The use of an alternate approach is not precluded but it is paramount that any alternate approach is scientifically defensible, well-documented and communicated in a transparent manner.

3.1 Hazard Index Method

The hazard index (HI) method is a simple and flexible approach that sums the individual hazard quotients (HQ) of individual chemicals in a cumulative assessment group. The HQ is the ratio of an individual chemical's exposure to its reference value. The reference value is the point of departure, (that is, the No Observed Adverse Effect level [NOAEL], Lowest Observed Adverse Effect level [LOAEL], or lower confidence limit on the benchmark dose [BMDL]), divided by the composite assessment factor (that is, the product of the uncertainty factors and the PCPA factor). The PCPA factor is a legally-mandated margin of safety intended to afford particular protection of infants and children (Health Canada, 2008). A HI index greater than 1 would indicate a potential health risk concern. It is worth emphasizing that the points of departure used in a cumulative risk assessment, using any method, may be different from those used in the risk assessment of an individual chemical given the focus on common effect.

$$HQ = \frac{\text{Exposure}}{\text{Reference Value}} \qquad \text{Reference Value} = \frac{\text{Point of Departure}}{\text{Composite Assessment Factor}}$$

$$HI = \frac{\text{Exposure}_1}{\text{Reference Value}_1} + \frac{\text{Exposure}_2}{\text{Reference Value}_2} \ldots + \ldots \frac{\text{Exposure}_n}{\text{Reference Value}_n}$$

The approach allows for the application of chemical-specific uncertainty factors regardless of whether they are applied for scientific reasons (such as the extrapolation of short-term data to a long-term scenario) or for policy considerations (such as the PCPA factor). It should be noted however, that the application of these uncertainty factors can mask the relative potency of the chemicals in a common mechanism group and thus, can inflate the overall uncertainty in the group.

3.2 Margin of Exposure (MOE) Method

The margin of exposure of a chemical is the ratio of its point of departure to its exposure. The adequacy of the MOE is determined by comparing it to a target MOE, the latter being an expression of the limitations (that is, the product of the uncertainty factors and the PCPA factor) associated with that chemical. The margin of exposure method (MOE_{Total}) calculates the reciprocal of the sum of the reciprocals of the MOEs of individual chemicals in a cumulative assessment group (see equation below). This method does not include consideration of the limitations associated with each individual assessment. Limitations associated with the common mechanism group at large are taken into account in determining the target MOE for the group. A potential health concern would be flagged if the MOE_{Total} is less than the target MOE or composite assessment factor (that is, the product of the uncertainty factors and the PCPA factor) for the group of chemicals.

$$MOE = \frac{\text{Point of Departure}}{\text{Exposure}}$$

$$MOE_{Total} = \frac{1}{\frac{1}{MOE_1} + \frac{1}{MOE_2} \ldots + \ldots \frac{1}{MOE_n}}$$

This method is currently used by the PMRA in conducting aggregate assessments of individual pesticides. The limitations of the database for each chemical in the assessment group are not quantified in this approach, but it remains a simple and flexible method to assess cumulative risk.

3.3 Relative Potency Factor Method

The relative potency method is a more complex approach that capitalizes on the occurrence of similar effects seen in chemicals with a common mechanism of action. This approach relies upon the selection of an index chemical within a cumulative assessment group, against which the other members of the group are compared. The index chemical should have a robust database and be

representative of the chemicals in the assessment group. The relative potency factor (RPF), or scaling factor, for each chemical is derived by dividing the point of departure for a common measure of effect for the index chemical, termed the effective dose (ED), by the point of departure for the same measure of effect for the individual chemical. For example, the effective dose of the index chemical that results in 10% response is compared to the effective dose of each test chemical in the assessment group that also results in a 10% response.

$$RPF_1 = \frac{ED_{index}}{ED_1}$$

In cases where the magnitude of the uncertainty factors is the same for each chemical of the assessment group, this magnitude would be reflected as the target MOE for the combined exposures (see Table 1, Example 1). In situations where the uncertainty factors vary among the chemicals, the relative potency factor for each chemical can be multiplied by the respective factor to yield an adjusted RPF (see Table 1, Example 2). Any factor used to adjust the RPF should not be double-counted in the target MOE for the combined exposures. For example, as illustrated in Table 1, Example 2, the uncertainty factor for interspecies extrapolation and the PCPA factor differs among the three chemicals. Therefore, the adjusted RPF for each chemical is calculated by multiplying the RPF by the chemical-specific uncertainty factor for interspecies extrapolation and PCPA factor. As the uncertainty factor for intraspecies variability for all three chemicals is the same (that is, 10-fold), and was not used to calculate the adjusted RPF, it forms the basis of the target MOE for the combined exposures.

Once the relative potency factor (adjusted or otherwise) for each individual chemical has been derived, exposures of these chemicals can be converted to an index chemical equivalent exposure (multiplying the chemical-specific exposure estimates by their respective RPF) and compared to the point of departure for the index chemical and the target MOE for the combined exposures.

Table 1 Examples of Uncertainty Factor Incorporation in RPF Methodology.

Chemical	RPF	UF_A	UF_H	PCPA	Adjusted RPF	Target MOE
Example 1						
Index Chemical A	1	10	10	1	-	100 ($UF_A \times UF_H \times$ PCPA)
Chemical B	2.5	10	10	1	-	
Chemical C	0.4	10	10	1	-	
Example 2						
Index Chemical X	1	10	10	1	10	10 (UF_H)
Chemical Y	3	3	10	1	9	
Chemical Z	0.01	10	10	3	0.3	

UF_A – uncertainty factor for interspecies extrapolation (that is, animal to human extrapolation)
UF_H – uncertainty factor for intraspecies variability (that is, within human variability)
PCPA – PCPA factor

The RPF approach provides a more refined method for standardizing the dose metrics for chemicals in an assessment group, but is heavily reliant on the quality and availability of appropriate toxicology data. Although it allows for the consideration of potency and uncertainties of individual chemicals, a limitation of the approach is the assumption of similarly shaped dose-response curves. This approach has been utilized by the USEPA in their cumulative assessment of various pesticide classes such as the organophosphates and N-methyl carbamates.

4.0 Selection Considerations for Common Mechanism Groups

A common mechanism of toxicity pertains to two or more chemicals that share a common toxic effect that results from the same, or essentially the same, sequence of major biochemical events. Care must be taken not to confuse mechanism of toxicity with site of toxic action. Likewise, for some chemicals, the site of toxic effect may be different than the site of toxic action. For instance, the anterior pituitary gland would be the site of toxic action for a chemical inhibiting the thyroid stimulating hormone (mechanism of toxicity) whereas the thyroid would be the site of toxic effect for the ensuing hypothyroidism. Another chemical could share the common toxic effect of hypothyroidism but have a different mechanism of toxicity such as the inhibition of thyroxine and triiodothyronine; in this case, the site of toxic effect and site of toxic action would be the same.

Many chemicals can cause more than one toxic effect, depending on the level of exposure, and do so by different mechanisms of toxicity at different sites of toxic action. However, a chemical may also cause multiple toxic effects at multiple sites from a single mechanism of toxicity taking place at a single site of toxic action. An example of the latter would be the downstream effects occurring from inhibiting the conversion of cholesterol to corticosteroid hormones in the adrenal cortex.

The PMRA follows a “weight-of-evidence” approach to support the development of hypotheses pertaining to mechanisms of toxicity. Generally, a single piece of information is insufficient on its own to support the characterization of a specific or common mechanism of toxicity; this finding will require support by the analysis and interrelationships of multiple pieces of information.

4.1 Preliminary Grouping

The process of cumulative assessment begins with identifying a preliminary grouping of chemicals that might cause a common toxic effect by a common mechanism of toxicity. This preliminary grouping of chemicals will be based upon at least one of the following criteria.

Structural similarity

> It is assumed that chemicals that are structurally analogous could contain a common toxophore and may interact analogously with cellular molecular sites to cause a common toxic effect. This would also include any chemicals that are biotransformed by mammals to yield a common toxophore upon metabolism. Data on structure-activity relationships, quantitative structure-activity relationship modelling and structural alerts can contribute to the identification of structural analogs.

Similarity of mechanism of action

(a) General mechanism of toxicity in pests: the mechanisms by which some pesticides are toxic to humans can be fundamentally similar or, in some cases, identical to their mechanisms of intended toxicity to pests.

(b) General mechanism of mammalian toxicity: this is based on the possibility that chemicals that share a known general mechanism of toxicity may cause a common toxic effect. A general mechanism of toxicity may include, for example, chemicals that uncouple oxidative phosphorylation.

Similarity of toxic effect

It is possible that a particular toxic effect known to occur in experimental animals or humans could be common (that is , concordant in both site and nature) to many chemicals, and that this commonality in toxicity could be due to a common mechanism. Since this type of grouping is functionally based, not structurally based, it enables the identification of structurally unrelated chemicals that cause a common toxic effect from a common mechanism that otherwise might not be identifiable from groupings based on structural similarity or mode of pesticidal action alone.

Not all toxic effects can be used as a preliminary basis for grouping chemicals. Toxic effects that have many possible unrelated causes, or that could be defined as nonspecific in origin, are not appropriate as the primary basis for the initial grouping of chemicals. These effects, such as body weight changes or death, can result from many unrelated factors and are usually of limited value in understanding the mechanism of toxicity. Such generalized effects, therefore, will not typically be used as a basis for an initial grouping. The PMRA will group chemicals that cause multiple toxic effects by a common mechanism from a common site of toxic action for purposes of the preliminary grouping, provided at least one of the toxic effects is common among the chemicals.

Following the initial grouping of chemicals, a detailed evaluation of available toxicology data for each chemical will be undertaken to identify and characterize the toxic effects caused by each chemical, and to determine which of the chemicals cause toxic effects that are common with other chemicals (that is, toxic effects that are concordant in both site and nature). Toxicity data generated in support of regulatory submissions will be the primary source of information used by the PMRA. The PMRA may also use toxicity data obtained from other studies, such as those described in regulatory reports, or the published scientific literature. Chemicals may be placed in more than one group in instances where chemicals cause more than one common toxic effect.

The PMRA does not regard the preliminary grouping alone to reliably conclude that such chemicals have a common mechanism of toxicity. Hence, only those chemicals that cause a common toxic effect by a common mechanism (through the in-depth review described below) will be considered by the PMRA for cumulative risk assessment.

4.2 Refined Grouping

The next phase of the review process is to determine the mechanisms by which the chemicals of the preliminary group cause the common toxic effect(s). Once the critical biochemical/molecular events pertaining to toxicity are understood for each chemical, they can be compared and the identification of those chemicals that are toxic from a common mechanism can be made. The PMRA will base this assessment on previous Agency reviews, scientific literature, toxicity databases, and information from registrants, the EPA, or other regulatory authorities, ensuring that the mechanism is consistent with current toxicological theory and knowledge and deemed scientifically plausible by the PMRA for these purposes.

For those chemicals whose toxic mechanisms are not known or not well understood, or for which there is an absence of direct mechanistic data, the PMRA will analyze available structural data, pharmacokinetic data, and toxicity data of the pesticide, its toxophore, and its analogs. A weight-of-evidence approach will be undertaken to determine the major biochemical events that are most critical in causing toxicity. Mechanistic similarities that would support a finding of a common toxic mechanism include, for example, analogous interactions of the pesticide with identical or similar biological targets, and the occurrence of similar metabolic transformations that yield common or structurally analogous metabolites that interact with similar biological targets, or that are otherwise involved in causing toxicity. Chemicals that cause a common toxic effect by different mechanisms will be excluded from the refined grouping.

5.0 Cumulative Risk Assessment Framework

Once a refined common mechanism group has been established, the assessment of the cumulative exposures to the chemicals of that group will be undertaken. The PMRA supports the use of the WHO/IPCS framework to maximize efficiency in performing this task (Meek et al, 2011). The framework involves a tiered approach to the assessment of exposure and hazard, with each tier being more refined (that is, less conservative and uncertain) than the previous tier. As the tiers of assessment increase, the effort to perform the assessment generally increases as does the data required to support the refinements. The WHO/IPCS framework has also been employed by regulators responsible for Canada's Chemical Management Plan (Health Canada, Environment Canada, 2015). This iterative process is also similar to the screening analysis framework put forth by the USEPA (USEPA, 2015).

A conceptual representation of the framework, as constructed by WHO/IPCS, is presented in Appendix 1 and forms the foundation of the approach that the PMRA will take. The elements of the framework are not fixed and will vary depending on the available data. It is not necessary for the hazard and exposure components to be assessed at similar tiers of refinement; rather, the available data will dictate the extent to which either component can be refined. The risk assessor needs only to progress through the tiers to the point where risk does not exceed the level of concern; if unacceptable risk is still present with the maximal level of refinement, then regulatory action is warranted.

As part of the approach to conserving resources in assessment and focussing on critical areas, the PMRA will leverage assessments (or parts of assessments) from other jurisdictions that have

undertaken a cumulative assessment. In these cases, the assessments must be applicable to the Canadian context and consistent with current policy.

A narrative is provided below to illustrate levels of refinement in both the hazard and exposure components of an assessment. The content of each tier is not meant to be prescriptive or fixed but is intended to show the progressive steps that could be undertaken in an analysis.

5.1 Hazard Assessment

At the least refined level (Tier 0), it is assumed that all chemicals in a common mechanism group have the same potency and the point of departure of the most potent member of the group is used in the assessment. This assumption, while conservative, can be used as an initial screening method to determine if further refinement is necessary and if so, to what degree. Similarly, selecting the lowest point of departure for a chemical, rather than the most relevant point of departure, can be used at an early screening stage.

At the next level of refinement (Tier 1), information on each of the chemicals in the common mechanism group can be integrated into the assessment to provide relative measures of potency. Points of departure such as the NOAELs or LOAELS for the apical effect of the individual chemicals can be used.

At a higher tier of refinement (Tier 2), additional refinements can be made incorporating information on mode of action where available. The use of benchmark dosing can allow for a more refined comparison of potencies in that it can determine the dose associated with defined response level (for example, a 10% change in the parameter of interest) for each chemical of the common mechanism group. This facilitates the comparison of potency of each chemical against an index chemical in the common mechanism group, which is then expressed as an equivalent of the index chemical or relative potency factor.

At the highest level of refinement (Tier 3), analyses can be quite sophisticated and include further consideration of mode of action data, toxicokinetics and toxicodynamics. Data modelling and probabilistic techniques can be employed although the extent of these advanced analyses will depend on the data availability, quality, strength and reliability.

5.2 Exposure Assessment

At the least refined level (Tier 0), it is assumed that exposure is based on simple semi-quantitative estimates of exposure. Semi-quantitative estimates are based on limited data and a few very simple assumptions to determine a worst-case scenario. Similarly, determining a best-case scenario can be used at an early screening stage.

At the next level of refinement (Tier 1), generic exposure scenarios are assessed using conservative point estimates. This assumption provides a conservative risk assessment in the absence of more specific, reliable exposure data, addressing a range of similar uses with limited numbers of parameters being included. However, if the risk estimates from these conservative assumptions are considered acceptable, no further evaluation is necessary.

At the next level of refinement (Tier 2), chemical-specific and more detailed and reliable data for key parameters in conjunction with risk mitigation factors are incorporated to refine the exposure risk assessment. Although still conservative, this results in more realistic exposure estimates.

At the highest level of refinement (Tier 3), data modelling and probabilistic techniques can be employed. This approach requires representative information on exposure for the scenarios of interest, and for the relevant populations and different uses across populations. The extent of these advanced analyses will depend on the data availability, quality, strength, and reliability.

6.0 Risk Characterization

In case studies undertaken by the WHO/IPCS, it has been demonstrated that refinements in the exposure assessment lead to the largest gains in characterizing risk (Meek, 2013). There is likely to be a greater difference between the lower and upper tiers of exposure assessment than there is for the tiers of hazard assessment, due to the higher reliance on assumptions in the exposure assessment. Hazard refinement, particularly at the uppermost tier, is more constrained by the absence of data on mode of action or toxicokinetics and toxicodynamics.

In assessing cumulative exposure, it is appropriate to integrate only those exposures that are likely to co-occur within the critical time window for the common toxicological effect. The challenges posed by complex exposure scenarios require approaches that allow the assessment of the effects of multiple chemicals via multiple routes and exposure pathways, and over multiple time frames. Risk assessments should consider all sources, pathways, and routes of exposure that could contribute materially to a person's total exposure.

Given the complexity of cumulative risk assessment, the characterization of risk is of utmost importance. Each assessment must clearly identify the pesticides and exposure scenarios addressed, the types and quality of data available, and the methods of estimation. It is critical that the strengths, and limitations associated with the data and analyses be discussed together with the uncertainties and assumptions. The overall level of risk can be expressed in different ways, depending on whether deterministic or probabilistic methods were used, and can reflect a series or range of estimates in light of the numerous input parameters in the assessment. These risk estimates can be specific to different age groups, durations of exposure and/or geographic regions where data permits. The target against which the cumulative risk estimates are compared should incorporate uncertainty factors that represent the cumulative assessment group as a whole (such as the factors for interspecies extrapolation and intraspecies variability) as well as the PCPA factor.

Acceptability of cumulative risk estimates must also take into account direction and magnitude of bias in the data and confidence in the data. Sensitivity analyses can assist in determining the impact of various parameters in the assessment and can contribute to the development of risk mitigation options by identifying drivers of risk.

In those cases where PMRA has leveraged a cumulative assessment from another jurisdiction, a narrative that characterizes the risk and its acceptability in the Canadian context is vital. Regardless of the approach utilized, cumulative assessments will be subject to consultation prior to final decisions as per established processes; accordingly, it is imperative that the assessments are transparent and clearly communicated.

7.0 Uncertainties and Challenges

Cumulative risk assessment represents a complex series of analyses; as such, varying degrees of uncertainty are unavoidable. These sources of uncertainty can be generic or chemical-specific.

In the case of the hazard assessment, generic sources of uncertainty can include the assumptions of dose-additivity or similar-shaped dose-response curves of chemicals within a common mechanism group and the lack of data on mode of action. Chemical-specific sources of uncertainty in hazard assessment can include the adequacy of the toxicological data to define appropriate points of departure (that is, points of departure that are temporally relevant, age relevant etc.) as well as lack of knowledge regarding human relevance.

Uncertainties in the cumulative exposure assessment include, but are not limited to, the following:

- the level of accuracy with which exposure to different chemicals can be characterised;
- the degree of understanding on the extent and profile of co-exposure to different chemicals. Different chemicals have different persistence in the environment and in the body, and therefore duration of exposure will vary; in other words, it may be episodic for one chemical and continuous for another; and
- the variability and uncertainty within the algorithms used to estimate exposure, which is compounded across substances in a cumulative context and may lead to overestimates of exposure.

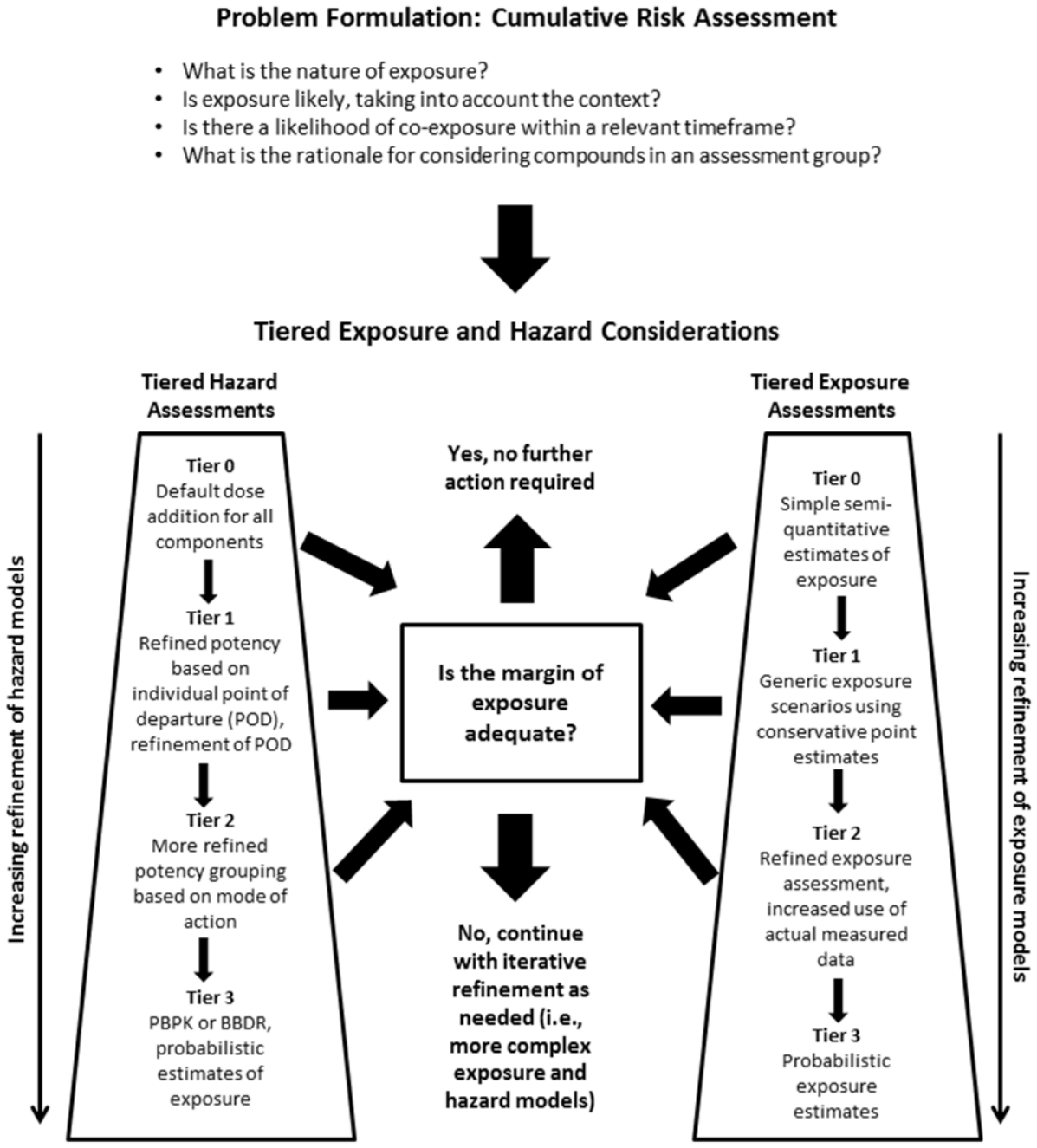
8.0 Conclusions

Cumulative risk assessment methodology is a rapidly developing field as more regulatory authorities incorporate cumulative assessment into their practices. It is expected that methodology will continue to evolve with increased experience in conducting cumulative risk assessment; hence, the current framework is considered as a starting point upon which the methodology will be further developed as approaches and scientific understanding progress.

9.0 Next Steps

Before making a final decision on the proposed framework, the PMRA will consider any comments received from the public in response to this document. The PMRA will then publish the assessment framework, a summary of comments received on the proposed framework and the PMRA response to these comments.

Appendix I WHO/IPCS Framework for Risk Assessment of Combined Exposure to Multiple Chemicals (modified from M.E. Meek et al., (2011) Regulatory Toxicology and Pharmacology, 60: S1-S14).



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Glossary

Adverse Outcome Pathway: A linear representation of key events between a molecular initiating event and an adverse outcome

Analog(s): A generic term used to describe chemicals that are chemically closely related. Structural analogs are chemicals that have similar or nearly identical molecular structures. Structural analogs may or may not have similar or identical biological properties.

Common Mechanism Group (CMG): Pertains to two or more chemicals that cause a common toxic effect to human health by the same, or essentially the same, sequence of major biochemical events. Hence, the underlying basis of the toxicity is the same, or essentially the same, for each chemical.

Common Toxic Effect: Two or more chemicals that are known to cause the same toxic effect (that is, concordant in the nature of the effect) in or at the same anatomical or physiological site or location (for example, same organ or tissue).

Cumulative Assessment Group (CAG): Two or more chemicals grouped together for evaluation.

Cumulative Toxic Effect: The net change in magnitude of a common toxic effect resulting from the exposure to two or more chemicals acting by a common mechanism, relative to the magnitude of the common toxic effect caused by exposure to any of the chemicals individually.

Lower Confidence Limit on a Benchmark Dose (BMDL): The lower confidence limit on a benchmark dose. The benchmark dose is the dose or concentration that corresponds with a specified level of response. Both the benchmark dose and its lower limit are derived through statistical modelling of dose-response data.

Lowest Observed Adverse Effect Level (LOAEL): The lowest level of exposure in an organism that causes an adverse alteration of morphology, function, capacity, growth, development or lifespan.

Mechanism of Toxicity or Action: The molecular sequence of events that produces a specific biological outcome.

Mode of Action (MOA): A plausible hypothesis about measurable key events by which a chemical exerts it biological effects. It does not imply full understanding of mechanism of action at the molecular level. In the context of this document, mode of action refers to the key cytological and biochemical events by which a pesticide is toxic to humans or experimental animals, and not the mode of action by which it is toxic to target or intended species (that is, its pesticidal action).

No Observed Adverse Effect Level (NOAEL): A level of exposure in an organism at which there is no biologically or statistically significant increase in the frequency or severity of an adverse effect.

Point of Departure (POD): A dosage or concentration of a single chemical used in regulatory toxicology for estimating tolerable exposures to humans. The point of departure is typically based on a NOAEL, NOAEC or benchmark dose.

Site of Toxic Action: The anatomical or physiological site(s) or location(s) at which the interaction of the chemical with its biological targets occurs that leads to a toxic effect.

Site of a Toxic Effect: The specific anatomical or physiological site or location (e.g., organ or tissue) at which the effect occurs.

Toxic Action: The interaction of a given chemical with biological targets that leads to a toxic effect.

Toxic Effect: An effect known (or can reasonably be expected) to occur from exposure to a chemical and that will or can reasonably be expected to endanger or adversely affect the quality of life. Some examples of toxic effects are acute lethality, loss of hearing, renal tubule necrosis, and cardiomyopathy.

Toxophore: A structural feature or moiety that bestows the toxic property through interaction with a molecular site (e.g., receptor) in cells of tissue or organs. The resulting biochemical changes or alterations lead to the disruption of physiological processes performed by the tissue or organs and, ultimately, to the toxic effect. The toxophoric portion of a chemical may interact reversibly or irreversibly with its molecular site, depending upon its reactivity and the molecular site. For some chemicals, toxicity results from the metabolism of a structural substituent to a toxophore. Metabolic pathways that lead to toxicity are often called bioactivation pathways.

Weight-of-Evidence (WOE): A qualitative evaluation that takes into account the nature and quality of scientific information regarding a chemical for a specific purpose. A weight-of-evidence evaluation can involve a detailed analysis of several data elements, such as data from different toxicity tests, pharmacokinetic data, and chemistry data, followed by a conclusion in which a hypothesis is developed or selected from previous hypotheses.

This is **Exhibit "C"** referred to in the affidavit of **Margaret Sears** affirmed remotely before me in accordance with O. Reg 431/20, Administering Oath or Declaration Remotely this 2nd day of November, 2021.

Commissioner for Taking Affidavits
(or as may be)

April 14, 2017

Pest Management Regulatory Agency
Health Canada
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Address Locator: 6607D

BY E-MAIL to PMRA.publications@hc-sc.gc.ca

Re: Proposed Cumulative Risk Assessment Framework, PRO2017-01

To Whom It May Concern:

In response to the Proposed Cumulative Risk Assessment Framework, PRO2017-01 (posted March 1, 2017), these are the comments of the Canadian Association of Physicians for the Environment, Canadian Environmental Law Association, the David Suzuki Foundation, Ecojustice, Environmental Defence, Équiterre and Prevent Cancer Now. Our organizations have a long-standing interest in the regulation of pesticides to protect human health and the environment. In general, while recognizing the limits of the risk assessment paradigm,[1] we welcome the proposed framework as progress toward implementing at last the legal requirement to consider cumulative effects when evaluating the health risks of pesticides. We offer several recommendations, detailed below, that would strengthen the framework and ensure its relevance within the regulatory system.

1. Assessment of cumulative pesticide risks is legally required and long overdue

The preamble to the *Pest Control Products Act* (PCPA) states:

> WHEREAS it is in the national interest that the primary objective of the federal regulatory system be to prevent unacceptable risks to individuals and the environment from the use of pest control products, [...]

[1] McClenaghan, T., K. Cooper, L. Vanderlinden, P. Muldoon, A. Abelsohn, K. Khatter, and K. Keenan. (2003) Environmental Standard Setting and Children's Health: Injecting Precaution into Risk Assessment, *J. Env'l Law and Practice* 12(2): 141-279.

> in assessing risks to individuals, consideration be given to aggregate exposure to pest control products, cumulative effects of pest control products and the different sensitivities to pest control products of major identifiable subgroups...

Sections 7, 11 and 19 of the Act require consideration of "cumulative effects of the pest control product and other pest control products that have a common mechanism of toxicity" in relation to evaluating health risks. This requirement applies to decisions with respect to applications for registration or amendment (section 7), maximum residue limits (section 11), special reviews and re-evaluations (section 19).

Despite these legal requirements (in place since 2006), the PMRA has not assessed the cumulative health effects of pesticides approved for use in Canada. In contrast, in other scientific and regulatory contexts, recognition of cumulative impacts/risk is not new; efforts have been made to assess cumulative impacts/risks for many years.

The proposed Cumulative Risk Assessment Framework for pesticides marks an important milestone, and we are encouraged by this progress. We recommend that the PMRA finalize the framework and operationalize it without further delay. We also recommend that the PMRA establish timelines for addressing the backlog of currently registered pesticides for which cumulative risks have not been assessed.

2. Embedding cumulative risk assessment within the regulatory process

The proposed framework does not clearly specify how cumulative risk assessments will relate to and inform decisions concerning individual pesticide registrations/registration amendments, maximum residue levels, re-evaluations and special reviews. The consultation document implies that individual pesticide re-evaluations will be completed prior to assessing — ergo, without considering — cumulative risks:

> Currently, the PMRA is completing individual assessments for pesticides within the same common mechanism group through its re-evaluation program. It is essential that toxicological and exposure assessments of individual chemicals are up-to-date prior to undertaking the complex task of cumulative assessment.

In our view, the re-evaluation of individual pesticides within the same common mechanism group should not be considered complete until cumulative risks have been assessed. Furthermore, consideration of cumulative risks, where applicable, should factor into decisions on individual pesticide registrations/registration amendments, maximum residue levels and special reviews, as well as re-evaluations. Sections 7, 11 and 19 of the PCPA require consideration of cumulative effects in evaluating the health risks of individual pesticides.

We recommend including a decision tree with the framework setting out the points in the decision-making process when cumulative risk assessments may be triggered and how conclusions about cumulative risk will influence regulatory action on individual pesticides.

In consideration of the uncertainties involved in assessing cumulative risks, we further recommend that the PMRA clearly set out in the framework how the legislative requirement for precaution (in conducting special reviews and re-evaluations) applies.

3. Identifying common mechanism groups

The framework sets out a step-wise approach to identify pesticides that belong to a common mechanism group as the precondition for assessing cumulative risks. The consultation document states that PMRA follows a "weight-of-evidence" approach to support the development of hypotheses pertaining to mechanisms of toxicity. However, when the Commissioner of the Environment and Sustainable Development audited the PMRA in 2015, the audit identified inconsistencies:

> The Agency concluded that a cumulative risk assessment was not warranted in 6 of the 10 re-evaluations we examined. However, in some of the 6 cases, we found no evidence to support the Agency's conclusion that there was no common mechanism of toxicity. For 2 of the other 4 re-evaluations, we found that the Agency had yet to determine whether a cumulative risk assessment was warranted. For the 2 remaining re-evaluations, the Agency had determined that the assessment was warranted, but it had not completed the work.[2]

According to the Commissioner's 2015 report, the PMRA told the auditors "that information was typically not available to determine which chemicals act in the same manner."[3]

We are concerned that failure to identify common mechanism groups will thwart assessment of cumulative risks. In keeping with the PCPA requirement for application of the precautionary principle, we recommend the PMRA adopt a precautionary approach to grouping pesticides for cumulative risk assessment. If there is uncertainty about mechanisms of toxicity, the PMRA should proceed with a cumulative risk assessment. The onus should be on the registrant to disprove hypotheses about common mechanisms of toxicity.

Furthermore, we question whether the proposed framework will be applicable to certain types of adverse health outcomes, including endocrine disruption, neurodevelopmental effects and cancer. For example, several pesticides and pesticide groups/classes are identified in the peer-reviewed literature as being causally linked to specific cancer outcomes, yet the relevant mechanism of toxicity remain only partially elucidated. For this reason, we recommend applying a weight-of-evidence approach that considers epidemiological data, in addition to in vivo cancer studies in model animals, in vitro genotoxic assays, and mechanistic studies. To ensure transparency, rigour and confidence in "weight of evidence" approaches, it is necessary to use systematic review methods and reporting,[4] particularly to advance from simplistic biochemical groupings to more meaningful but complex outcomes. To support the data requirements of cumulative risk assessment, external surveillance programs that calculate lifetime cancer risk and average daily lifetime exposures of selected pesticides may be useful (see CAREX

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[2] *Fall 2015 Reports of the Commissioner of the Environment and Sustainable Development. Report 1 – Pesticide Safety*, paragraph 1.41. < http://www.oag-bvg.gc.ca/internet/English/parl_cesd_201601_01_e_41015.html>

[3] *Ibid,* paragraph 1.42.

[4] e.g., Rooney, A. A., A. L. Boyles, M. S. Wolfe, J. R. Bucher, and K. A. Thayer. "Systematic Review and Evidence Integration for Literature-Based Environmental Health Science Assessments." *Environ Health Perspect* 122, no. 7 (July 2014): 711–18. doi:10.1289/ehp.1307972.

Canada's indicators of environmental exposure to carcinogens: http://www.carexcanada.ca/en/profiles_and_estimates/).

Toxic mechanisms and effects are defined differently among various jurisdictions, and are quickly evolving with advancing science. The North American grouping method as conducted by the U.S. Environmental Protection Agency has to date been very narrowly defined at the level of a particular biochemical reaction, and these assessments have resulted in no action taken against any pesticide as a result of cumulative assessments conducted to date. The European Union approach to examine effects such as neurotoxicity is more complex, but more relevant. We recommend that the PMRA initiate cumulative assessments with a view to rapid development of expertise to be applied within broader frameworks on a tissue rather than a biochemical basis. We further recommend that the PMRA consult regarding proposed groupings of pesticides for cumulative assessments.

When a pesticide has more than one mechanism of toxicity identified (for example, an acute response and a chronic carcinogenicity), this raises an important question of how the chemical groupings will be prioritized and regulated. Quantitative assessment of cancer risk is a different approach compared to the margin-of-safety approach used for non-cancerous endpoints. If a pesticide grouping is being assessed in a cumulative risk assessment for a non-cancer mechanism of toxicity, it may not capture an appropriate level of safety without a separate cumulative risk assessment for its cancerous mechanism of toxicity. We recommend that the PMRA clarify in the framework how such situations will be addressed.

To improve transparency, we further recommend the PMRA maintain a publicly accessible database of pesticide toxic effects and associated hypotheses about mechanisms of toxicity, including groupings of pesticides for cumulative risk assessments.

4. Assessing cumulative exposure

The consultation document states, "In assessing cumulative exposure, it is appropriate to integrate only those exposures that are likely to co-occur within the critical time window for the common toxicological effect." In our view, sequential exposures over time to different pesticides within a common mechanism group should be considered in assessing cumulative chronic risks. We recommend that the PMRA define "critical time window" and clarify its approach to assessing cumulative chronic exposure to multiple pesticides within a common mechanism group.

5. Characterization of the "PCPA factor"

In reference to the Hazard Index Method for assessing cumulative risk (and elsewhere), the consultation document states, "The approach allows for the application of chemical-specific uncertainty factors regardless of whether they are applied for scientific reasons (such as the extrapolation of short-term data to a long-term scenario) or for policy considerations (such as the PCPA factor)." We strongly disagree with this distinction between "scientific" and "policy" uncertainty factors. The so-called PCPA factor is required by the Act "to take into account potential pre- and post-natal toxicity and completeness of the data with respect to the exposure of, and toxicity to, infants and children"; in other words, to address uncertainties in assessing risks to infants and children, with life-long implications. The PCPA factor is based on the scientific understanding of infants and children's increased vulnerability to

toxic exposures. We recommend the PMRA revise references to uncertainty factors in the framework to avoid stating or implying that application of the PCPA factor lacks scientific basis.

6. Assessing cumulative environmental risks

Although the PCPA explicitly mandates consideration of cumulative effects only in relation to evaluation of health effects, in general the act requires parallel consideration of risks to health and the environment. In our view, consideration of cumulative effects is equally relevant in determining whether risks to the environment are acceptable. The proposed framework applies only to the assessment of cumulative human health risks, although the same methodologies could be applied to assess cumulative risks to the environment. For example, the PMRA is currently re-evaluating risks to pollinators from a group of neonicotinoid insecticides, which might support a cumulative assessment of environmental risks. We recommend expanding the framework to enable assessment of cumulative environmental risks.

7. Complementary measures to monitor exposure

We note that the strength of cumulative risk assessment depends on the availability and quality of cumulative exposure data. Operationalization of the proposed framework would benefit from improved and expanded monitoring of human and environmental exposures to pesticides, including pesticide residues in foods and drinking water — and public access to the data. Although beyond the scope of the proposed Cumulative Risk Assessment Framework, we recommend the Government of Canada increase funding and strengthen reporting requirements for monitoring programs, including the Canadian Food Inspection Agency sampling programs, the Canadian Health Measures Survey, the House Dust Survey, and environmental monitoring conducted by Environment and Climate Change Canada, and ensure co-ordination between these programs and the data needs of the PMRA pesticide evaluation program.

8. Future directions

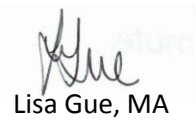
The consultation document presents the proposed framework as "a starting point upon which the methodology will be further developed as approaches and scientific understanding progress." Recognizing that cumulative risk assessment methodologies are rapidly developing, we encourage the PMRA to build on the proposed framework to develop complementary approaches in the following related areas:

- Consideration of cumulative risks associated with mixtures of pesticides with disparate mechanisms of toxicity but the same toxic effect;
- Consideration of synergistic effects associated with mixtures of pesticides, regardless of mechanisms of toxicity and individual toxic effects;
- Consideration of cumulative risks associated with pesticide formulations (beyond active ingredients); and,
- Mixture risk assessments to consider cumulative risks associated with pesticides in combination with other chemicals with common toxic effects and/or mechanisms of toxicity.[5]

[5] Evans, R. M., O. V. Martin, et al. (2016). "Should the scope of human mixture risk assessment span legislative/regulatory silos for chemicals?" Science of The Total Environment 543, Part A: 757-764. http://www.sciencedirect.com/science/article/pii/S0048969715309785

We appreciate the opportunity to comment on the proposed Cumulative Risk Assessment Framework. Do not hesitate to contact us should you require clarification or to discuss these matters further.

Sincerely,



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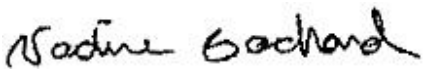

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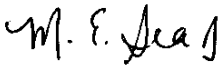

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About our organizations:

*The **Canadian Association of Physicians for the Environment (CAPE)** is a non-profit organization run by physicians that seeks to better human health by protecting the planet.*

*The **Canadian Environmental Law Association** works to protect human health and our environment by seeking justice for those harmed by pollution and by working to change policies to prevent such problems in the first place.*

*The **David Suzuki Foundation** collaborates with Canadians from all walks of life to conserve our environment and find solutions that will create a sustainable Canada through science-based research, education and policy work.*

*Leading the legal effort for a brighter future, **Ecojustice** is Canada's only national environmental law charity. Ecojustice has a staff of lawyers and scientists who use the power of the law to defend nature, slow climate change, and stand up for the health of our communities.*

***Environmental Defence** is a national charity that challenges and inspires change in government, businesses and people to ensure a greener, healthier and prosperous life for all.*

***Équiterre** helps build a social movement by encouraging individuals, organizations and governments to make ecological and equitable choices, in a spirit of solidarity.*

***Prevent Cancer Now** works to stop cancer before it starts by eliminating preventable contributors to cancer, with research, public education and advocacy.*

This is **Exhibit "D"** referred to in the affidavit of **Margaret Sears** affirmed remotely before me in accordance with O. Reg 431/20, Administering Oath or Declaration Remotely this 2nd day of November, 2021.

Commissioner for Taking Affidavits
(or as may be)

PREVENT CANCER NOW

PreventCancerNow.ca

Submission Regarding:
Chlorpyrifos and Its Associated End-use Products:
Updated Environmental Risk Assessment
Proposed Re-evaluation Decision PRVD2019-05

August 29, 2019

Submitted via email:
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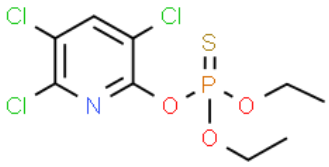


Summary

Canada's Pest Management Regulatory Agency proposes largely to discontinue registrations of chlorpyrifos products, but to maintain registration for:

1. Standing water - temporary pools for larval mosquito control;
2. Outdoor adult mosquito control;
3. Structural indoor and outdoor (non-residential);
4. Outdoor ornamentals (container stock only) for control of Japanese beetle larvae; and
5. Greenhouse ornamentals.

Prevent Cancer Now maintains that chlorpyrifos is excessively persistent and toxic for these uses, that there are preferable alternatives, and that it should be taken off the market forthwith.

Background on chlorpyrifos

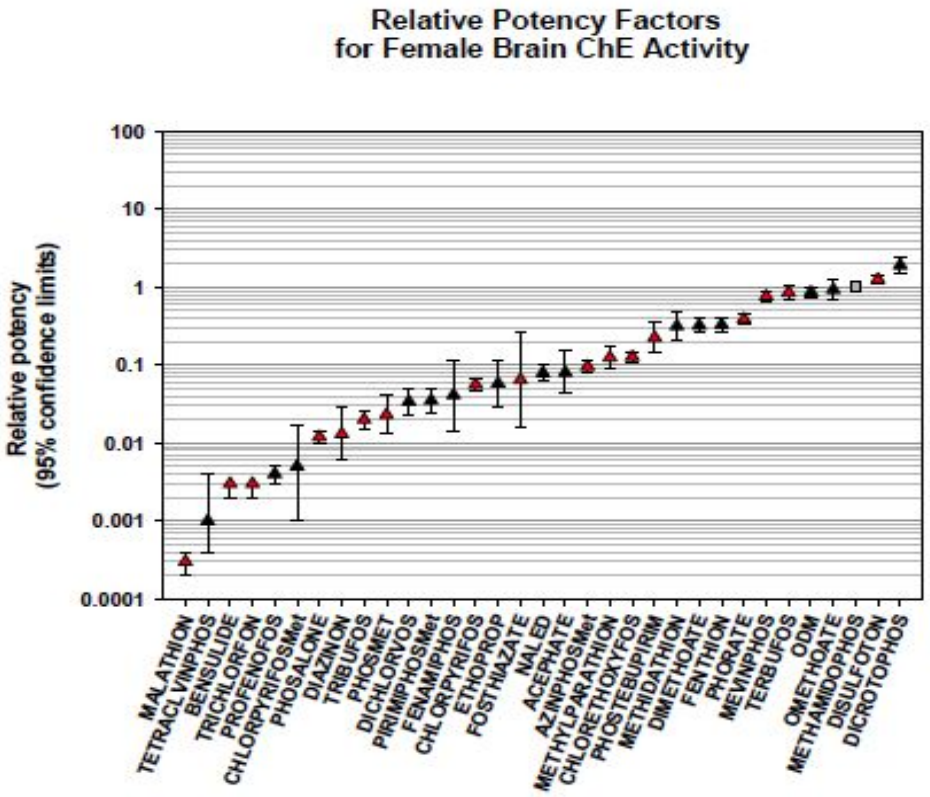
Chlorpyrifos is a potent, persistent, mobile insecticide that has been in production longer than the majority of Canadians have been alive. It has become a global pollutant, being found even in Arctic ice.[1]

Chlorpyrifos kills insects by interfering with nerve transmissions; acute exposures also affect humans' brain and nervous system, as well as respiration. In the developing child it causes permanent brain damage. Although chlorpyrifos was not itself assessed, it is an organophosphate – a member of a family of chemicals that the International Agency for Research on Cancer indicated in 2015 (monograph published in 2017) probably causes cancer.[2]

Chlorpyrifos is commonly implicated in the intitiation of the condition known as multiple chemical sensitivity (MCS).[3] Previous versions of the "Dursban" label (a commercial name for chlorpyrifos insecticide) noted that exposure to this organophosphate could cause sensitization such that an individual would in the future become symptomatic upon exposure to even low levels of *any* organophosphate pesticide. Use of Dursban or Pyrate, particularly in structures where it

results in long-term ongoing exposure, has been noted by affected individuals as being the initiator. Canadian Community Health Survey data indicate higher incidence of cancers and other chronic diseases among individuals with MCS (Margaret Parlor, unpublished). Canada requires greater accountability, and recording of exposures to pesticides and other toxicants, so that eventually it will be possible to research and understand the increases in chronic diseases, particularly in the young.

There is a large number of insecticides that inhibit Acetylcholine esterase (AChE), and chlorpyrifos is a much stronger inhibitor than some commonly used alternatives such as malathion (an approximately 700-fold less potent inhibitor, see Figure). *Prevent Cancer Now* does not advocate use of malathion because it is among the potential carcinogens assessed by IARC.



U.S. Environmental Protection Agency. Organophosphorus Cumulative Risk Assessment – 2006 Update. Available at: http://www.epa.gov/pesticides/cumulative/2006-op/op_cra_main.pdf http://www.epa.gov/pesticides/cumulative/2006-op/op_cra_appendices_part1.pdf

The European Food Safety Authority reported in August 2019 that chlorpyrifos and chlorpyrifos-methyl test data and public scientific literature demonstrated adverse neurological and developmental effects at such low levels that it was not possible to establish a "reference dose" (no-effect dose), and therefor risk assessments could not be conducted and thus the necessary approval criteria were not met.[4] It is expected that the insecticides will be discontinued completely.

Proposed continuing uses of chlorpyrifos are not justifiable

As long as chlorpyrifos is on the market, and in sheds and trucks of pesticide applicators, it will be used. Neither the federal government nor provincial governments have the wherewithal to educate and police the small specialized of proposed continuing uses. If insecticide is being applied to lilies, it may well be applied to other plants in the greenhouse. This represents an unnecessary toxic exposure, and for a mother-to-be working in a greenhouse, it may even represent a lifetime of impairment for her offspring. Therefore, the prudent, logical step is to discontinue registration of this toxic, unnecessary chemical.

Mosquito control: Safer alternatives for both larval and adult mosquito control include bacterial products (e.g., Bt_k), repellants (including garlic spray for landscapes), and physical protective measures (e.g., nets).
Structural pest control: This is an application noted frequently as initiating MCS. Safer alternatives include addressing structural issues that create habitat for pests (e.g., moisture), using pest-proof materials such as concrete, and as an adjunct, alternative safer products may be helpful.
Ornamental plants: No parent of a child harmed for life by a neurotoxin would agree that potent, persistent toxic chemicals should be used on ornamental plants. There are alternative means to control pests, and there are alternative, hardier ornamental plants.

We look forward to a strong restriction, so that this toxicant will not pose temptation to be used inappropriately. Please do not hesitate to contact us, if we can assist in this matter.

Respectfully submitted,

Meg Sears PhD
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References

1. Hoferkamp L, Hermanson MH, Muir DCG. Current use pesticides in Arctic media; 2000–2007. Science of The Total Environment. 2010 Jul 1;408(15):2985–94.

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This is **Exhibit "E"** referred to in the affidavit of **Margaret Sears** affirmed remotely before me in accordance with O. Reg 431/20, Administering Oath or Declaration Remotely this 2nd day of November, 2021.

Commissioner for Taking Affidavits
(or as may be)

PLOS MEDICINE

POLICY FORUM

Organophosphate exposures during pregnancy and child neurodevelopment: Recommendations for essential policy reforms

Irva Hertz-Picciotto[1]*, Jennifer B. Sass[2,3], Stephanie Engel[4], Deborah H. Bennett[1], Asa Bradman[5], Brenda Eskenazi[5], Bruce Lanphear[6], Robin Whyatt[7]

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Citation: Hertz-Picciotto I, Sass JB, Engel S, Bennett DH, Bradman A, Eskenazi B, et al. (2018) Organophosphate exposures during pregnancy and child neurodevelopment: Recommendations for essential policy reforms. PLoS Med 15(10): e1002671. https://doi.org/10.1371/journal.pmed.1002671

Published: October 24, 2018

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Summary points

- Widespread use of organophosphate (OP) pesticides to control insects has resulted in ubiquitous human exposures.
- High exposures to OP pesticides are responsible for poisonings and deaths, particularly in developing countries.
- Compelling evidence indicates that prenatal exposure at low levels is putting children at risk for cognitive and behavioral deficits and for neurodevelopmental disorders.

To protect children worldwide, we recommend the following:

- Governments phase out chlorpyrifos and other OP pesticides, monitor watersheds and other sources of human exposures, promote use of integrated pest management (IPM) through incentives and training in agroecology, and implement mandatory surveillance of pesticide-related illness.
- Health professions implement curricula on the hazards from OP pesticides in nursing and medical schools and in continuing medical education courses and educate their patients and the public about these hazards.
- Agricultural entities accelerate the development of nontoxic approaches to pest control through IPM and ensure the safety of workers through training and provision of protective equipment when toxic chemicals are to be used.

design, data collection and analysis, decision to publish, or preparation of the manuscript.

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Introduction

Organophosphate (OP) compounds were originally developed as human nerve gas agents during the 1930s–1940s, and some were later adapted as insecticides at lower doses [1]. High exposure to OP compounds leads to acute poisoning from the irreversible inhibition of the enzyme acetylcholinesterase (AChE), resulting in cholinergic syndrome (including narrowed pupils, excessive salivation, bronchoconstriction, mental confusion, convulsions or tremors, and in some cases, death). Additionally, delayed polyneuropathy has been described in association with high exposures [1].

In the United States, many OP pesticides—including malathion, dichlorvos, azinphos-methyl, and chlorpyrifos—were licensed for insecticidal use before requirements to evaluate human toxicity or ecologic effects were established [2]. Because OP pesticides rapidly degrade in the environment, they were considered safer than persistent organochlorine insecticides like DDT, aldrin, and dieldrin, but over 40 OP pesticides, including the most commonly used ones, are now considered by the US Environmental Protection Agency (EPA) [3] and/or the WHO Food and Agriculture Organization [4] to be moderately or highly hazardous to human health.

The most comprehensive global database on recent pesticide use includes information reported by 71 countries in five regions [5]. Annual use during 2010–2015 of OP pesticides in agriculture averages 1,145 tonnes (i.e., metric tons) for 13 African countries, 4,342 tonnes for 11 Caribbean and Central American countries, 10,013 tonnes for 24 European countries, 13,404 tonnes for 6 South American countries, and 29,554 tonnes for 17 Asian countries, with India dominating use. We additionally obtained data from the US [6] and have mapped total annual agricultural OP use by country (Fig 1) and total annual agricultural use by country per 1,000 square km (S1 Fig). Widespread use of OP pesticides in agriculture—as well as in homes, parks, schools, and hospitals and on golf courses, right-of-ways, and other public spaces—has led to ubiquitous human exposure.

OP pesticides present a range of health hazards. Here we review the scientific evidence of OP impacts on child neurodevelopment. In addition, we discuss inadequacies in current OP pesticide regulations and present recommendations for urgently needed policy change.

Neurodevelopmental effects of OP pesticides

Systematic reviews and multiple epidemiologic studies in the US and other countries, spanning diverse populations in both urban and agricultural settings, have linked OP exposures during fetal development with poorer cognitive, behavioral, and social development in children [7–11]. Generally, levels of exposure in these studies are too low to induce measurable depression of cholinesterase in adults. In one review, adverse effects of OP pesticide exposure on neurodevelopment were seen in all but one of the 27 studies evaluated; the strongest associations occurred following prenatal exposures [9]. Outcomes associated with OP pesticide exposure to the fetus include abnormal primitive reflexes in newborns; mental and motor delays among preschoolers; and decreases in working and visual memory, processing speed, verbal comprehension, perceptual reasoning, and IQ among elementary school–age children. Prenatal exposures also elevated risks for symptoms or diagnoses of attention-deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD).

Consistent with the wide range of outcomes reported in human studies, the toxicity of early-life OP pesticides on neurodevelopmental end points has been confirmed in experimental animal studies. Parallel with epidemiologic findings, effects on cognition, motor activity, and social behaviors were repeatedly demonstrated in rodents dosed in early life with concentrations of OPs eliciting little to no inhibition of AChE in the brain [10,12]. The timing of

IHP is Co-Director of Project TENDR (unpaid), an organization seeking to reduce the incidence of child neurodevelopment disorders by eliminating or lowering exposures that increase risks. IHP serves on the Science Advisory Board to the California Breast Cancer Prevention Program (unpaid). BE served as a member, National Research Council of the National Academies, Committee to Review California's Risk Assessment for Pesticides (unpaid); and serves currently as a member of the National Advisory Environmental Health Sciences Council (unpaid). RW submitted information to the US EPA regarding regulation of chlorpyrifos (unpaid). RW is a founding member/advisor to International Society for Children's Health and the Environment (unpaid) and serves on the science advisory board for Women's Voices for the Earth (unpaid). BL has no competing interests to report.

Abbreviations: AChE, acetylcholinesterase; ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; EPA, Environmental Protection Agency; FFDCA, Federal Food, Drug, and Cosmetic Act; FIFRA, Federal Insecticide, Fungicide, and Rodenticide Act; FQPA, Food Quality Protection Act; IPM, integrated pest management; JMPM, Joint FAO/WHO Meeting on Pesticide Management; lbs/yr, pounds per year; OP, organophosphate; PAN, Pesticide Action Network; PON1, paraoxonase 1.

exposure played a critical role in the biochemical and anatomic targets affected, as well as in the specific behavioral and developmental alterations evoked [12].

Since publication of the epidemiologic reviews, a higher likelihood of an ASD diagnosis was observed for children born to women residing within (versus beyond) 1.5 km of OP pesticide applications on agricultural fields; the strongest associations were for chlorpyrifos [13]. Another recent study showed that higher OP pesticide metabolite concentrations in maternal urine during pregnancy were associated with ASD traits identified in adolescence [14]. Other research teams reported residential proximity to agricultural OP use during fetal development to be associated with reduction in child's IQ at age 7 years [15] and higher umbilical cord blood concentrations of chlorpyrifos with mild to moderate arm tremors in children at approximately age 11 years [16]. Risks for impaired neurodevelopment were greater among children of farmworkers, who experience higher exposures [17], and children with genetic susceptibility factors that reduce capacity to detoxify OP pesticides [7]. In the same study that examined ASD, moderate to severe developmental delay was associated with nearby applications of carbamates, similar to OP pesticides, but not with OP pesticides [13]. Two other studies, both conducted in urban cohorts of higher social and economic status, found no associations of OP pesticide metabolites with scores on intelligence tests [18,19]. Still, the weight of evidence clearly indicates that OP exposures during prenatal development are likely detrimental to brain function.

Accurate measurement of exposure is critical in environmental health studies. The OP pesticide studies determined exposure in various ways, ranging from quantification of OP metabolites in maternal urine collected during pregnancy and direct measurement of chlorpyrifos in umbilical cord blood to quantifying nearby pesticide use by geographically linking residential addresses with California's database of commercial pesticide applications [20,21]. The California Pesticide Use Report Database, which contains specific pesticide quantity and the date and location of each application, has been validated by two exposure assessment studies, which showed that the amount applied within a few days to a week correlates highly with measured ambient air concentrations in nearby locations [22,23]. In the vast majority of studies reviewed, objective measures (both biologic markers and validated application data) were generated according to scientifically established protocols and obtained independently of the child's outcome.

Concerns at both high and low OP exposures

Critical to understanding the influences on early child neurodevelopment is the distinction between acute effects after high-level exposures versus sequelae from chronic lower exposures. As noted above, by inhibiting the enzyme AChE, high-level OPs cause acute, in some cases fatal, effects in humans [2]. Indeed, internationally, pesticide poisonings take a heavy toll, estimated at 200,000 deaths per year [24], with approximately 99% occurring in developing countries [25]. About 110,000 pesticide self-poisoning deaths occur each year globally, which represents an average across the reporting countries of 13.7% of all suicides [26], with a wide range from 0.9% in low- and middle-income European countries to 48.3% for low- and middle-income countries of the Western Pacific region.

Large quantities of highly hazardous OP pesticides are imported into developing countries. For example, OP pesticides ranked fourth among 24 chemical groups of pesticides imported into Central American countries [27], for which the two OP pesticides imported in the greatest quantity (terbufos and methamidophos) have been targeted for phaseout by the Rotterdam Convention, an international trade agreement on hazardous chemicals aimed at protecting human health and the environment [4,28]. Pesticide poisoning affects agricultural workers

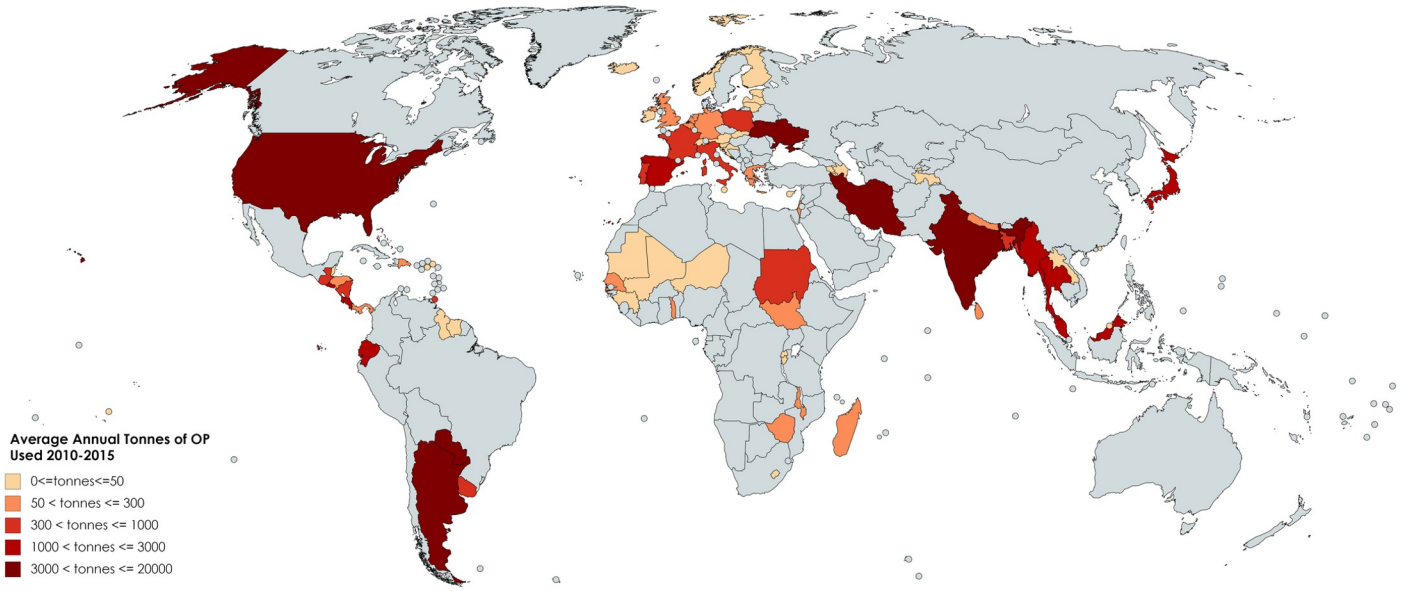

Fig 1. Average annual tonnes of OP pesticides used in agriculture, by country, 2010–2015. Darker shading indicates greater usage. Gray shading indicates that no data were available during that time period. For countries with data available for some but not all years during 2010–2015, the available data within that period were used. Source for US data was [6]; and for all other countries, [5]. *Map created with mapchart.net*. OP, organophosphate.

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who often receive little or no instruction on the use of hazardous substances, are not provided with personal protective equipment, and/or operate application equipment that is not properly maintained. Additionally, overuse, misuse, and accidents have led to deaths of schoolchildren, e.g., in India in 2013, China in 2014, and Bangladesh in 2015, from consumption of meals with high levels of OP pesticides [4,24,29,30].

As tragic as these acute poisonings are, an OP pesticide exposure in the absence of overt poisoning does not imply that neurologic damage has not occurred—for both children and adults [31]). The US EPA concluded in 2016 that the existing epidemiologic literature provided "sufficient evidence that there are neurodevelopmental effects occurring at chlorpyrifos exposure levels below that required to cause acetylcholinesterase inhibition" [11]. Such chronic, low-level exposures are often overlooked or dismissed as benign because neither the pregnant woman nor the fetus shows clinically visible signs or symptoms. Furthermore, the developmental deficits do not manifest until months or years later. Indeed, the scientific consensus is that AChE inhibition is uninformative with regard to neurodevelopmental effects in children and that the toxic effects from chronic, low-level exposure occur at concentrations too low to inhibit cholinesterase [1,9]. The evidence thus indicates that OP pesticides can interfere with brain development at levels previously thought to be safe or inconsequential.

Hence, AChE inhibition cannot be used as a biomarker to identify neurodevelopmentally harmful OP pesticide exposures. Reliance on AChE inhibition for regulatory purposes obscures the serious threat that OP pesticides pose to early brain development and represents an unscientific and inadequate approach to health risk assessment. In fact, other effects appear likely to mediate the OP toxicity to neuronal systems that is foundational for childhood behavioral and cognitive deficits. Toxicologic evidence implicates OP pesticides in neuroinflammation, protein-kinase C receptor signaling, insulin resistance, dopaminergic and glutamatergic neurotransmission, and interference with DNA synthesis and nuclear transcription factor functioning, mechanisms highly relevant for brain development [12,32–34].

Indeed, as-yet-undiscovered harm may emerge from further follow-up of those exposed in early life. Outcomes from fetal exposures appear to be persistent, with associations observed into mid- and late childhood. One cohort repeatedly showed deficits in memory, IQ, and attention deficits or ADHD at ages 2, 3, 5, and 7 years, whereas another exhibited deficits in mental development and reasoning in infancy and at ages 6–9 years (reviewed in [8]). Children with high versus low chlorpyrifos concentrations in their umbilical cord blood had differences in brain volume in regions responsible for attention, receptive language processing, social cognition, and regulation of inhibition [35]. These neuroanatomic alterations, which potentially constitute a pathway from pesticide exposure to the associated behavioral and cognitive deficits, may be permanent.

Pesticide regulation

Pesticide regulations vary widely across the globe. As with pesticide usage, no database has consolidated this information for all countries. Table 1 shows available data on 47 OP insecticides [36] banned by one or more countries, as well as the level of health hazard and the number of countries that have banned each OP pesticide. The most comprehensive database available on current governmental regulation of pesticides provides data covering 39 of these 47 OP insecticides, obtained from 106 countries outside the US [37]. Included in this database are total bans, along with denials of approval, but not restrictions. Of the 106 countries, 81% have regulated one or more of the 39 OP insecticides [37]. The 28 countries of the European Union have taken action on the most OP pesticides (33). Additional countries that have banned more than 10 include the US (26), Cambodia (15), China (15), Saudi Arabia (15), Guinea (12), Korea (12), Mauritania (12), and Thailand (12). Notably, having regulations in place does not necessarily mean that they are enforced. Furthermore, some of the most toxic OP pesticides that are banned across dozens of countries are exported elsewhere, often to developing countries and sometimes in large quantities, for example, to Costa Rica and Guatemala [27]. In Mexico, at least a dozen OP pesticides that are classified as highly hazardous by the WHO Food and Agriculture Organization are used [38].

Within the US, the EPA regulates pesticides under two overlapping statutes—the Federal Food, Drug, and Cosmetic Act (FFDCA) and the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). Many of the insecticides banned in the US were initially licensed prior to 1970, when required health and safety assessment was minimal and before the US EPA was formed. As a result of legislation in the 1970s requiring increased health and safety studies, voluntary agreements were reached between manufacturers and the EPA to cancel or phase out registrations for some pesticides, including 18 OP insecticides.

In 1996, the Food Quality Protection Act (FQPA) amended FIFRA and FFDCA by requiring the EPA to include additional safety factors to protect children because of their greater exposures and heightened susceptibility [39]. Children have larger body burdens of pesticides because of greater intake of food, water, and air than adults, per unit of their body weight; they explore the world through mouthing behaviors; and they frequently crawl or play on floors where pesticides and other toxic chemicals settle. Heightened susceptibility during early years arises in part from immature detoxifying enzyme systems, including paraoxonase 1 (PON1) [7,40,41]. Under the FQPA, the EPA must show that there is reasonable certainty that no harm will result from aggregate exposure to the pesticide, including all anticipated dietary exposures and all other exposures for which there is reliable information.

After passage of the FQPA, OP pesticide use across all market sectors declined by over 70%, from 70 million pounds per year (lbs/yr) in 2000 to about 20 million lbs/yr in 2012 (the most

Table 1. OP insecticides, hazard levels, and number of countries banning them.

	Compound[1]	Hazard level			Number of countries (outside US) that have banned it[2]	Banned OPs in US designated by X. All other OPs on list are currently registered for use in the US[3]
		US EPA[4]	FAO-WHO[5]	PAN[2]		
1	Acephate	M	M	H	31	
2	Azinphos-methyl	H	H	H	39	X
3	Cadusafos	**	H	H	31	
4	Chlorethoxyphos	**	E	H	29	
5	Chlorfenvinphos	H	H	H	35	X
6	Chlorpyrifos	M	M	H	2	
7	Chlorpyrifos-methyl	**	S	H	1	
8	Chlorthiophos[6,7]	H	**	**	**	X
9	Coumaphos	H	H	H	30	
10	Dichlorfos (dichlorvos)	M	H	H	32	
11	Dialifor/dialifos[6,7]	H	**	**	**	X
12	Diazinon	M	M	H	30	
13	Dicrotophos	H	H	H	34	
14	Dimethoate	**	M	H	4	
15	Dioxathion[6,7]	H	**	**	**	X
16	Disulfoton	H	E	H	38	X
17	Ethion	M	M	—	30	X
18	Ethoprop (ethoprophos)	M	E	H	8	
19	Ethyl parathion[7]	H	**	**	**	X
20	Fenamiphos	H	H	H	6	X
21	Fenitrothion	M	M	H	28	
22	Fenthion	M	M	H	30	X
23	Fonofos (fenophos)[6]	H	**	—	33	X
24	Isazophos[6,7]	**	**	**	**	X
25	Isofenphos[6]	H	**	—	29	X
26	Malathion	M	S	H	2	
27	Methamidophos	H	H	H	49	X
28	Methidathion	H	H	H	34	X
29	Methyl parathion	H	E	H	59	X
30	Mevinphos	H	E	H	37	X
31	Monocrotophos	H	H	H	60	X
32	Naled	M	M	H	28	
33	Oxydemeton-methyl	M	H	H	30	X
34	Phorate	H	E	H	37	
35	Phosalone	M	M	—	29	X
36	Phosmet[7]	M	M	**	**	
37	Phosphamidon	H	E	H	49	X
38	Phostebupirim[7]	**	**	**	**	
39	Pirimiphos-methyl[7]	M	M	**	**	
40	Profenofos	M	M	H	29	X
41	Propetamphos	M	H	H	28	X
42	Sulfotepp	H	E	H	32	X
43	Sulprofos[6,7]	M	**	**	**	X

(*Continued*)

Table 1. (Continued)

	Compound[1]	Hazard level			Number of countries (outside US) that have banned it[2]	Banned OPs in US designated by X. All other OPs on list are currently registered for use in the US[3]
		US EPA[4]	FAO-WHO[5]	PAN[2]		
44	Temephos	M	S	H	28	X
45	Terbufos	H	E	H	34	
46	Tetrachlorvinphos	M	**	H	28	
47	Trichlorfon	M	M	H	32	

Level of hazard: E, extreme; H, high; M, moderate; S, slight

**, not classified;—, not H (PAN[6] ranking); X, banned in the US.

[1] This list of OP insecticides is taken from the US EPA Office of Pesticide Programs "Organophosphorus Cumulative Risk Assessment, 2006 Update" [36] (Table ES-1, p. 16 "OP Pesticides Considered in the 2006 Update of the Cumulative Risk Assessment"), from which we have excluded those pesticides that are not insecticides.

[2] Hazard Ranking and number of countries that banned: from PAN International Consolidated List of Banned Pesticides [37] (http://pan-international.org/pan-international-consolidated-list-of-banned-pesticides/). Methods and sources for collection of these data are described in the Explanatory Notes: (http://pan-international.org/wp-content/uploads/Consolidated-List-of-Bans-Explanatory-2017April.pdf). This list does not include restrictions, only bans or decisions to not approve.

[3] A "banned" pesticide in the US is defined as a pesticide for which all registered uses have been prohibited by final EPA action and includes pesticides that have been withdrawn through voluntary agreements between industry and the US EPA. Status of OPs that are either banned or registered for use in the US provided in personal communication from Yu-Ting Guilaran (Director, Pesticide Re-evaluation Division, Office of Pesticide Programs, US EPA) to JBS, July 12, 13, and 23, 2018.

[4] Hazard ranking [3].

[5] Hazard ranking [4]: The concept of and criteria for "Highly Hazardous Pesticides" was initially described in the JMPM second report in 2008,"Report of the 2nd FAO/WHO Joint Meeting on Pesticide Management" (last accessed July 2018) (http://www.fao.org/fileadmin/templates/agphome/documents/Pests_Pesticides/Code/Report.pdf). As scientific understanding of mechanisms for pesticide toxicity has advanced, these have been included, as described in the 2016 publication of "International Code of Conduct on Pesticide Management Guidelines on Highly Hazardous Pesticides" (http://apps.who.int/iris/bitstream/handle/10665/205561/9789241510417_eng.pdf;jsessionid=D3B3CCA5B28692A5F3D437B2CF7F0AA0?sequence=1). The FAO-WHO JMPM defined banned pesticides thus: "Banned pesticide means a pesticide all uses of which have been prohibited by final regulatory action, in order to protect human health or the environment. It includes a pesticide that has been refused approval for first-time use, or has been withdrawn by industry either from the domestic market or from further consideration in the domestic approval process, and where there is clear evidence that such action has been taken in order to protect human health or the environment."

[6] Considered to be obsolete or no longer used as a pesticide, according to the WHO Recommended Classification of Pesticide Hazards, 2010.

[7] Not included in the PAN database.

Abbreviations: EPA, Environmental Protection Agency; FAO-WHO, WHO Food and Agriculture Organization; JMPM, Joint FAO/WHO Meeting on Pesticide Management; OP, organophosphate; PAN, Pesticide Action Network.

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recent available data) [6]. By 2002, most nonagricultural uses were phased out by agreements between the EPA and the pesticide manufacturers, based on results of EPA risk assessments for chlorpyrifos and diazinon showing unacceptably high risks to residents, particularly children, from residential pest control [42,43]. The volume of OP pesticides used on foods commonly consumed by children, such as fruits, decreased by 57% between 1994 and 2004, from 28 to 12 million pounds (12,701 to 5,443 metric tonnes) of active ingredient applied annually [44]. This action resulted in dramatic reductions in blood and urine concentrations of OPs among the US population [45]. However, agricultural OP pesticide use continues to contribute to exposures for farmworkers, their families [15], and residents in homes, children in schools, and other bystanders near farmlands [23], as well as to food and drinking water contamination that affects a broader population.

In 2016, the EPA concluded that exposure to chlorpyrifos—the most commonly used OP insecticide in the US—from either food or drinking water alone could lead to unacceptably high population exposures and determined that some reproductive-aged women, infants, and children consumed levels of chlorpyrifos substantially above the acceptable level for these

vulnerable life stages [11]. The EPA also identified numerous scenarios that could result in unsafe exposures for agricultural workers and bystanders. For these reasons, as required by law, the EPA proposed to revoke all standards (called tolerances) that permit residues of chlorpyrifos on food. Revocation of these tolerances would essentially ban this OP on food crops [11]. However, in March 2017, despite overwhelming evidence of harm and contrary to the EPA's own risk assessments, the Trump administration EPA announced that "the science addressing neurodevelopmental effects remains unresolved, and that further evaluation of the science . . . [therefore] is warranted to achieve greater certainty as to whether the potential exists for adverse neurodevelopmental effects to occur from current human exposures to chlorpyrifos," concluding that the EPA would not cancel any uses of chlorpyrifos [46]. This action would delay potential regulatory action until October 2022. However, on August 9, 2018, the US Court of Appeals for the Ninth Circuit ordered the EPA to finalize the ban on chlorpyrifos within 60 days, including a ban on all US sales and a prohibition of food contaminated by the insecticide from reaching the US market. The court based its decision on the EPA's 2016 findings that the pesticide fails to meet federal safety standards and is particularly harmful to infants and children. In September 2018, the EPA filed a petition for a rehearing of the chlorpyrifos case.

Recommendations

In 2014, the American Academy of Pediatrics called for pediatricians and governments to recognize and reduce pesticide exposures through education, pesticide labeling, public health surveillance, and regulatory action [47]. In 2016, an independent group of scientists and health professionals published the Project TENDR Consensus Statement as a national call to action to significantly reduce exposures to chemicals—including OP pesticides—that have been identified as putting children in the US, and likely throughout the world, at increased risk of neurodevelopmental disorders [48]. Project TENDR concluded that the evidence of significant risks to children's neurodevelopment from OP pesticide exposure warrants strong regulatory action. In 2017, a United Nations report on the Right to Food called for changes to agricultural practices to ensure food that is safe, free from pesticides, and qualitatively adequate [24]. To achieve the goal of reducing exposures to OP insecticides, we therefore propose an action plan for governments, public health and medical institutions or organizations, and agricultural entities. Our recommendations are detailed in Box 1. These steps would markedly reduce prenatal and childhood exposures to OP pesticides.

Exemplary actions at various governmental levels have been taken. At the multinational level the EU chose to not approve close to 200 pesticides, of which over 20 are OPs, and multiple individual countries have instituted bans on OPs such as dichlorvos, methamidophos, and methyl parathion [37]. In the US, California has taken steps to limit agricultural use of pesticides near schools and childcare facilities when children are present [50], and Hawaii recently banned the distribution, sale, transport, and use of any pesticide containing chlorpyrifos as an active ingredient [51].

In reducing OP pesticide usage, toxic effects from substitute or replacement chemicals require scrutiny. Pyrethroid pesticides have replaced OPs as the main class of insecticides in residential pest control products, but recent rodent laboratory studies and epidemiologic studies suggest that prenatal pyrethroid pesticide exposures may also increase the risk of adverse neurodevelopment and behaviors and negative emotions [13,52–54]. Neonicotinoid pesticides are now the fastest-growing class of insecticides used on crops in the US [55]; they are persistent in plants, soil, and water and highly toxic to invertebrates, including endangered aquatic species, bees, and other beneficial insects [56]. Moreover, the impacts of broad and systemic

Box 1. Recommendations to move towards elimination of human exposures to OP pesticides

We recommend the following actions by governments:

- National and state or provincial governments, globally: phase out use of all OPs in agriculture;
- National and state or provincial governments, globally: ban nonagricultural use of all OPs, including household products;
- US EPA: revoke all food tolerances for chlorpyrifos, as the agency previously proposed;
- US EPA and state governments: phase out the use of all other OPs in agriculture;
- US EPA: ban nonagricultural pest control uses of the few remaining OPs;
- In the interim, national, state, and local agencies: take steps to reduce human exposure (e.g., require advance notification to nearby residents and schools before applications of OP pesticides; implement restrictions on application methods such as aerial spraying and air blast to reduce drift exposures and to protect water and sensitive sites such as homes and schools);
- National, state, and local agencies: conduct regular monitoring of watersheds to ensure OPs do not continue to pollute lakes, rivers, and streams, including those that are sources of drinking water, and implement targeted monitoring of drinking water;
- National and state agencies: establish an effective comprehensive pesticide use and illness reporting program either nationally or through coordinated statewide programs.

We recommend that medical schools, public health programs, and healthcare associations:

- organize continuing medical education courses to educate healthcare providers on both acute and chronic effects of exposures to toxic chemicals, including how to recognize and treat children who received high OP exposures; how to advise pregnant women and parents of young children on steps they can take to avoid pesticide exposures from lice, flea, and tick treatments [49], lawn and garden products, and applications in nearby agricultural land, golf courses, schools, and shopping malls; and how properly to clean potential pesticide residues from fruits and vegetables and to identify which produce contain the highest levels;
- educate health providers on the necessary reporting of pesticide poisonings to state surveillance;
- encourage schools of nursing and medicine to incorporate curricula on environmental hazards that include pesticides and medical boards to include environmental health in their examinations.

We recommend that agricultural entities:

- provide enhanced training for workers, in the most appropriate languages and at relevant educational levels, on the handling and application of pesticides and on the worker protection standards. In the US, this means EPA Worker Protection Standards training at the required frequency;

- educate workers on how to avoid take-home exposures to their families;
- institute environmentally friendly approaches to control pests—integrated pest management (IPM)—with a goal to eliminate or minimize toxic chemicals in our food sources.

pesticide use are well documented to have had significant negative ecological consequences affecting terrestrial, aquatic, wetland, marine, and benthic habitats and posing risks to ecosystem functioning and resilience.

What are the alternatives, if synthetic pesticides other than OPs are also neurotoxic?

Agriculture represents the vast majority of OP pesticide use, which includes both crop and livestock production. Widespread implementation of IPM is needed to reduce this use. IPM is a reduced-risk pest management strategy that emphasizes inspection, monitoring, prevention, and pest control using the least toxic methods including (agri)cultural practices such as intercropping (growing two or more crops in close proximity, which can reduce susceptibility to disease and pests), crop rotation, and cover crops (to reduce soil erosion and improve soil health); physical controls such as traps or bug vacuums; habitat management that encourages beneficial insects; and biological control, such as the release of parasitic wasps to control aphids, with pesticides used only as a last resort. When used, least-toxic pesticides are chosen first, such as materials approved for organic farming (e.g., *Bacillus thuringiensis* to control Lepidoptera) [57].

While IPM strategies do not, in principle, forbid the use of OP and other neurotoxic pesticides, these higher-risk materials serve as a last resort and should be applied in a way that protects human and environmental health. That most crops produced with OP pesticides are also produced organically provides compelling evidence that OP pesticides are not essential [58]. Some recalcitrant pests may be difficult to manage with less toxic pesticides, which in some instances may result in lower yields or higher production costs, reducing competitiveness. Recent research, however, indicates that crop yields from organic and other alternative production systems are increasing and in some cases match conventional yields [59]; these approaches additionally would likely reduce external costs to public health and the environment [60]. To ensure that farmers are not threatened with rising costs and thinner profit margins, many agricultural trade and policy organizations recommend increased government support for extension research and outreach needed to support transitions to less toxic materials [61].

Public health, a second use of OP pesticides, represents a small fraction of their applications. For example, OP pesticides are used for mosquito and other vector control to prevent vector-borne diseases such as Zika virus or West Nile virus. We do not recommend abrupt changes in pest management that would increase the risk of exposure to these viruses. We do advocate increased funding for better understanding of the ecology and biology of these and other vectors and the diseases they spread and alternative methods to control them without the use of OP or other neurotoxic pesticides. The historical example of the Mediterranean fruit fly in California, a serious invasive agricultural pest, provides a model for application to disease vectors. In the early 1990s, state officials used helicopters to spray malathion over residential areas where over 2 million people resided [62]. Subsequent concerns [63] resulted in development of a comprehensive sterile fruit fly release program that, combined with spot treatments often

using organically approved pesticides, has successfully controlled infestations without the need for OP pesticide applications over wide swaths of residential areas [64,65]. Similar strategies should also be considered for new invasive species, such as the spotted lanternfly, currently threatening eastern US ecosystems and agriculture. Integrated vector management would favor using least-toxic options.

Structural, indoor, and landscape pesticide applications, the third category of OP uses, can result in high exposures. Dichlorvos, an OP already banned in many countries, is still permitted indoors by the US government for flying insects. Similarly, malathion is still sold for landscape and garden use. Given risks of adverse health effects due to chronic, low-level exposures and reported acute poisoning of consumers in the US [66], we recommend that all remaining structural, indoor, and landscape use of OPs be phased out immediately, especially in environments where children are present. Basic IPM principles should be applied in these environments, including pest exclusion (i.e., screens) and traps.

To preserve health and sustainability, both indoor and outdoor pest management must ultimately rely on nontoxic or less toxic alternatives; simultaneously, agriculture needs stronger support to move towards a systems approach that minimizes use of neurotoxic pesticides while providing healthy food and economic sustainability for farmers. The Report on the Right to Food by the Special Rapporteur to the UN General Assembly articulates a similar philosophy: in order to successfully reduce or eliminate use of hazardous pesticides, the international community's efforts will need to address the ecologic, social, and economic factors currently embedded in agricultural policies. At the national level, this will require challenging agrochemical-dependent farming to restructure and seek the safest feasible alternatives [24]. We join the American Academy of Pediatrics and the UN in recommending close surveillance of pesticide poisonings, incentives for nonchemical approaches to pest control, monitoring of water and food sources of pesticides, and enforcement of the public's right to know through full disclosure, labeling, and further communications for pesticide formulations and for residues in food, water, and elsewhere. Finally, we believe it is an ethical and social responsibility for civil society, for the medical profession, and for the agricultural industry to disseminate widely to the general public what is known about the sources of pesticide exposures and their adverse impacts on health and to develop training programs in agroecology in order to achieve a paradigm shift in food production.

Supporting information

S1 Fig. Average annual tonnes of OP pesticides used in agriculture per 1,000 square km, by country, 2010–2015. Darker shading indicates greater usage per 1,000 square km. Gray shading indicates that no data were available during that time period. For countries with data available for some but not all years during 2010–2015, the available data within that period were used. Source for US data was [6]; and for all other countries, [5]. *Map created with mapchart.net*. OP, organophosphate.
(TIF)

S1 Text. Spanish translation of full article.
(DOCX)

S2 Text. Chinese translation of full article.
(DOCX)

S3 Text. French translation of summary bullet points.
(DOCX)

S4 Text. Italian translation of summary bullet points.
(DOCX)

Acknowledgments

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This is **Exhibit "F"** referred to in the affidavit of **Margaret Sears** affirmed remotely before me in accordance with O. Reg 431/20, Administering Oath or Declaration Remotely this 2nd day of November, 2021.

Commissioner for Taking Affidavits
(or as may be)

July 31, 2019

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To Whom It May Concern:

Re: Proposed Re-evaluation Decision PRVD2019-05, Chlorpyrifos and Its Associated End-use Products: Updated Environmental Risk Assessment

These are the comments of the David Suzuki Foundation, the Canadian Association of Physicians for the Environment, Canadian Environmental Law Association, Équiterre and Environmental Defence on the proposed re-evaluation decision for chlorpyrifos (PRVD2019-05). Our organizations have a long history of advocacy for effective pesticide regulation to protect the environment and human health. Over all, we strongly support the proposed decision to cancel most uses of chlorpyrifos on the basis of the updated environmental risk assessment. Risks to pollinators, birds, mammals, aquatic invertebrates and fish are not acceptable. We urge PMRA to confirm immediate cancellation of these uses without further delay, especially considering that this evaluation has already been underway for more than 15 years. Further, and as detailed below, we believe a complete ban on chlorpyrifos is justified.

As a preface to our detailed comments on PRVD2019-05, we note with concern that lack of surface water monitoring data was identified as a limitation in the original environmental risk assessment published for consultation in 2003 (PACR2003-03) and that this critical data gap persisted for more than a decade. In regions for which robust monitoring data is now available, chlorpyrifos is being detected in surface waters at concentrations that frequently exceed levels of concern for invertebrates and fish. Recent assessments of aquatic risks from neonicotinoid insecticides, after decades of their extensive use, also concluded on the basis of newly available water monitoring data that risks are not acceptable, and the similarities suggest a troubling pattern: risk assessments underestimate environmental exposure in the absence of appropriate environmental monitoring data, obscuring environmental risks. Canada urgently needs a systematic and co-ordinated approach to ensure availability of robust environmental monitoring data, as well as pesticide use data, to support PMRA's exposure assessment calculations.

Also, we urge PMRA to proceed swiftly with the update to the health risk assessment of uses proposed for continued registration in PRVD2019-05, in particular mosquito control. Recent studies confirm risks to child neurodevelopment posed by exposure to organophosphates including chlorpyrifos.[1] A review of animal studies and epidemiological evidence by the State of California's Department of Pesticide Regulation in July 2018[2] prompted a recommendation by a scientific review panel to add chlorpyrifos to the list of toxic air contaminants in the state. Several U.S. states, including Hawaii and California, are now moving to ban all uses of chlorpyrifos due to health concerns. Canada should too.

International context

Although chlorpyrifos is currently authorized at the EU-level, it should be noted that eight of the 28 EU-member states (all OECD members) have not approved its use within their national boundaries and a ninth, the U.K., banned all but one use in 2016. As mentioned above, several U.S. states are moving to ban chlorpyrifos.

Pollinator risk assessment

PRVD2019-05 identifies potential risks to bees from foliar applications of chlorpyrifos but only considers exposures to bees foraging on the target crop/field. Ignoring the risk of exposure from spray drift, PMRA concludes risks to pollinators are minimal for applications on crops harvested before bloom, not attractive to pollinators or deflowered as a standard practice. For other crop applications with the potential for high pollinator exposure, PMRA concludes risks to pollinators are acceptable if chlorpyrifos is not applied during bloom. However, PMRA acknowledges, "Non-target plants may be exposed to chlorpyrifos by direct overspray and spray drift" (page 13) and estimates that 11 to 74 per cent of spray will drift one metre downwind from the application site during spraying, depending on the application method. A British study concluded that ground spraying of chlorpyrifos at typical application rates would result in exposures of honeybees at the LD_{50} within 36–46 m of the application site at a wind speed of 4 m sec−1 (14.4 km h−1).[3] Pollinators may therefore be exposed to spray drift, especially if bee-attractive plants (e.g., wildflowers) are growing in adjacent areas. As non-target plants often have different bloom cycles than the crops considered in the assessment, application timing restrictions are unlikely to reduce risks from this exposure pathway.

Furthermore, soil and soil-water exposures from both foliar and granular applications have not been assessed and may present risks to ground-nesting native bees.[4] The timing restrictions contemplated in the assessment are unlikely to reduce risks from soil and soil-water exposure.

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While the proposed use cancellations will protect insect pollinators, the assessment should acknowledge risks from spray drift, and from soil and soil-water exposures. Application timing restrictions are inadequate to reduce these risks.

We also strongly disagree with the suggestion on page 12 that risks deemed unacceptable to managed bees could be acceptable for wild pollinators for certain crop applications. While risks to honeybees are better documented, native bees in some cases may be more vulnerable. A precautionary approach should apply.

Canadian water-monitoring data

In areas of the country for which robust surface water monitoring data are available, the measured levels of chlorpyrifos are alarming, more so considering that monitoring data typically underestimate peak exposure. We agree there is no reason to believe that detection patterns would be different in other areas where monitoring data are lacking. The available monitoring data reveal widespread environmental contamination, which adds to the toxic burden for species and ecosystems affected by multiple stressors (including exposure to other insecticides). Risks to the environment are not acceptable and have not been for many years; PMRA must immediately cancel agricultural uses of chlorpyrifos, and other uses that may contribute to surface water contamination, as required by the *Pest Control Products Act*.

Mosquito control

The assessment concludes that environmental risks from mosquito larvae control applications are acceptable because "the presence of aquatic biota in temporary standing pools is expected to be limited." This assumption is not supported by research. A March 2009 study identified 86 insect species in temporary pools of water in an urban area.[5] Field studies in North Carolina between 1974 and 1990 identified over 150 species of insects in temporary pools.[6] A comparison of biota in temporary pools in the United Kingdom, Australia and northeastern North America found a wide diversity of insect species.[7] This potential exposure pathway for non-target insects, as well as birds, requires further examination.

Also, risks from spray drift and leaching associated with mosquito control uses do not appear to have been assessed.

For adult mosquito control applications, the assessment concludes that risks to non-target terrestrial and aquatic biota are acceptable if chlorpyrifos is applied by ultra-low volume (ULV) applicators for adult mosquito control because spray droplets are very small and are likely to dissipate or evaporate while suspended in air. Risks to other insects (including pollinators) and birds in flight do not appear to have been assessed. Moreover, while ULV applicators *may* be used in mosquito control, they are not required. Environmental risks from mosquito control applications should be examined more closely –

[5] Fontanarrosa, M. Soledad; Marta B. Collantes; and Axel O. Bachmann (2009). "Seasonal Patterns of the Insect Community Structure in Urban Rain Pools in Temperate Argentina." Journal of Insect Science, 9(1).
[6] HM Wilbur (1997). "Experimental Ecology of Food Webs: Complex Systems in Temporary Ponds." Ecology Journal, 78(8): 2279–2302.
[7] DD Williams (1998). "Temporary pools and their invertebrate communities." Marine Conservation, 7(2).

without delaying cancellation of other uses/products. The latter should be confirmed immediately as an interim measure.

Greenhouse use

PMRA proposes to continue registration of greenhouse applications with an additional label restriction: "DO NOT allow effluent or runoff from greenhouses containing this product to enter lakes, streams, ponds or other waters." We question whether this label restriction will be effective in reducing risks. Neonicotinoid pesticides used in greenhouses have been measured in nearby surface water, despite label warnings/restrictions intended to reduce risks to aquatic ecosystems. It is not clear whether monitoring data were available for surface water near greenhouse operations where chlorpyrifos is used to confirm actual environmental concentrations. We are also concerned that Health Canada and the PMRA lack capacity to properly monitor compliance and enforce label requirements. Given these uncertainties, cancelling greenhouse uses would be an appropriate precautionary approach.

Thank you for your consideration.

Sincerely,

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This is **Exhibit "G"** referred to in the affidavit of **Margaret Sears** affirmed remotely before me in accordance with O. Reg 431/20, Administering Oath or Declaration Remotely this 2nd day of November, 2021.

Commissioner for Taking Affidavits
(or as may be)

Canadian Chlorpyrifos sales data reported by the Pest Management Regulatory Agency (PMRA), according to sales reports received from the PMRA

Year	Rank among Insecticides (based on kg sales)	Total sales (kg)	Only Organophosphate Insecticide (OP) Listed?	Other OP in top 10, if reported
2007-2008	2	>500,000	No	diazinon
2009	6	>100,000	Yes	
2010	4	>100,000	Yes	
2012	3	>100,000	No	dimethoate
2013	2	>500,000	Yes	
2014	4	>100,000	Yes	
2015	9	>100,000	No	malathion
2016	4	>500,000	NR; Table 3.7 reports decreasing OP sales and % all pesticides, 2000-2012*	
2018	5	>100,000	Yes	

* # 1 on Table 3.8 Most Commonly Used Organophosphate Insecticide Active Ingredients, All Market Sectors, 2005, 2007, 2009, and 2012 Estimates (Ranked by Range in Millions of Pounds of Active Ingredient)

This is **Exhibit "H"** referred to in the affidavit of **Margaret Sears** affirmed remotely before me in accordance with O. Reg 431/20, Administering Oath or Declaration Remotely this 2nd day of November, 2021.

Commissioner for Taking Affidavits
(or as may be)

Health Canada Santé Canada

Paragraph 19(1)a Announcement of Data Call-In

Active Ingredient: Chlorpyrifos

Reference Number: 2019-3275

Date Sent: 10 February 2021

Health Canada's Pest Management Regulatory Agency (PMRA) has sent a notice to registrants as per paragraph 19(1)(a) of the *Pest Control Products Act* (PCPA). The following is a summary of the notice.

Information Required for Re-evaluation

I. Toxicology Data

DACO	Reference
Chlorpyrifos – Parent compound studies	
4.2.1	Acute oral toxicity study in rats. 2008-06-20
4.2.1	Acute Oral Toxicity Study of Chlorpyrifos TGAI in Rats, 141233, 401-01-10383; 2015.
4.2.1	Chlorpyrifos: Acute One Day Dietary Toxicity Study in Crl:CD1(ICR) Mice, 2007
4.2.1	Acute Oral Toxicity Study of Chlorpyrifos TGAI in Mice, 2013
4.2.2	Acute dermal toxicity study in rats. 2008-05-29
4.2.3	Acute inhalation toxicity study in rats. 2008-07-16
4.2.3	Acute inhalation exposure of adult Crl:CD(SD) rats to particulate chlorpyrifos aerosols: kinetics of concentration-dependent cholinesterase (ChE) inhibition in red blood cells, plasma, brain and lung. 2010-06-28
4.2.4	Acute eye irritation study in rabbits. 2008-06-20
4.2.4	Chlorpyrifos technical: Acute eye irritation test in the rabbit. November 1994.
4.2.5	Acute dermal irritation study in rabbits. 2008-05-29
4.2.6	Skin sensitization in Guinea pigs. 2008-08-28
4.3.2	Results of two-year dietary feeding studies on Dowco 179 in beagle dogs. December 10, 1971.
4.3.2	Supplement to original report entitled "Results of two-year dietary feeding studies on Dowco 179 in beagle dogs." March 26, 1985
4.3.2	Oral administration - dogs. Dursban. November 13, 1968
4.3.3	Chlorpyrifos: A Four Week Dietary Study in CD-1 Mice. 1985
4.3.8	Chlorpyrifos: 2-week Nose-Only Vapor Inhalation Exposure Study in Fischer 344 Rats. 1986
4.3.8	Chlorpyrifos: 2-week Whole-Body Vapor Inhalation Toxicity Study in Fischer 344 Rats. 1987
4.3.8	Chlorpyrifos: Pubertal Development and Thyroid Function in Intact Juvenile/Peripubertal Female Crl:CD(SD) Rats. 2011-10-31
4.3.8	Chlorpyrifos: Uterotrophic Assay in the Immature Female Crl:CD(SD) Rat. 2011-10-10
4.3.8	Chlorpyrifos technical: 6-week dietary study with histopathologic evaluation of the adrenal glands in beagle dogs. 2001
4.3.8	Chlorpyrifos: Two Week Dietary Probe Study in Sprague-Dawley Rats. 1990
4.3.8	Communication: Preliminary evaluation of acetylcholinesterase (AChE) in brain, peripheral tissues, and RBC in beagle dogs. 2001

4.5.1	Two-generation Dietary Reproduction Study in Sprague- Dawley Rats. 1991
4.5.1	Effects of Chlorpyrifos Administered via Gavage to CD Rats During Gestation and Lactation on Plasma, Erythrocyte, Heart and Brain Cholinesterase and Analytical Determination of Chlorpyrifos and Metabolites. 1998
4.5.1	Three generation reproduction and teratology study in the rat following prolonged dietary exposure to Dursban 0,0-diethyl 0-3,5,6-trichloro-2-pyridyl phosphorothioate. 20 August, 1971
4.5.2	Pyrinex. Preliminary teratology study in rats. 11 February 1987.
4.5.2	Dose range-finding study for developmental toxicity study (Fischer rats). 1983
4.5.4	Bacterial reverse mutation test using Salmonella typhimurium. 2008-08-26
4.5.7	Micronucleus test in Mice. 2008-07-01
4.5.7	Micronucleus Test of Chlorpyrifos TGAI in Mice, 2015.
4.5.9	Nose-Only Inhalation of Chlorpyrifos Vapor: Limited Toxicokinetics and Determination of Time-Dependent Effects on Plasma, Red Blood Cell, Brain and Lung Cholinesterase Activity in Female CD(SD):Crl Rats. 2013-05-01
4.5.9	Physiologically Based Pharmacokinetic-Pharmacodynamic (PBPK/PD) Modeling of Dermal Exposure to Chlorpyrifos: Validation and Application to Mixed Oral and Dermal Exposures. 2013-03-04
4.5.9	Chlorpyrifos: Tissue Distribution and Metabolism of Orally Administered 14C-labelled Chlorpyrifos in Fischer 344 Rats, K-044793-76 (Ref H015). 1987
4.5.9	Chlorpyrifos: Part A - Concentration-Time Course of Chlorpyrifos and Chlorpyrifos-oxon in Blood. 1998
4.5.9	Chlorpyrifos: Absorption by Female Fischer 344 Rats Exposed to Vapours of Chlorpyrifos in a Nose only OR a Whole Body Inhalation Chamber. 1986.
4.5.12	Acute neurotoxicity study in Fischer 344 rats. 11 September 1992.
4.5.13	Chlorpyrifos: 13-Week Neurotoxicity Study in Fischer Rats; 1993
4.5.14	Developmental Neurotoxicity of Chlorpyrifos Administered Orally via Gavage to Crl;CDBRVAF / Plus Presumed Pregnant Rats - Appendix M : Neuropathology report on adult (Day 66 Postpartum) rats, 304-001 (Supplement 1), 1988
4.5.14	Developmental Neurotoxicity of Chlorpyrifos Administered Orally via Gavage to Crl;CDBRVAF/Plus Presumed Pregnant Rats – Reanalysis of morphometric data, 304-001 (Supplement 2), 1988
4.5.14	Developmental Neurotoxicity of Chlorpyrifos Administered Orally via Gavage to Crl;CDBRVAF/Plus Presumed Pregnant Rats – Historical control morphometric data (Supplement 3), 1988
4.5.15	Chlorpyrifos: Assessment of Immunotoxic Potential using the Sheep Red Blood Cell Assay after 28-day Dietary Exposure to Rats. 2010-06-27
4.8	Comparison of cholinesterase (ChE) inhibition in young adult and preweanling CD rats after acute and repeated chlorpyrifos and chlorpyrifos-oxon exposure. 2010-06-28
4.8	Evaluation of the Dermal Delivery Compartment of the Chlorpyrifos PBPK Model. 2016-01-24
4.8	Development of Chemical Specific Adjustment Factors for Chlorpyrifos and Chlorpyrifos Oxon Using Target Red Blood Cell Acetyl Cholinesterase Inhibition Levels of 10%, 5%, and 1%. 2014-10-28
4.8	Derivation of human biomonitoring guidance values for chlorpyrifos using a physiologically based pharmacokinetic and pharmacodynamic model of cholinesterase inhibition. 2014-08-17
4.8	Epidemiology Studies Pertaining to Chlorpyrifos Exposure: Consideration of Reliability and Utility. 2013-11-11
4.8	Dow AgroSciences LLC's Response to EPA's Revised Human Health Risk Assessment for Chlorpyrifos Registration Review - EPA-HQ-OPP-0850-0224. 2015-04-28
4.8	Chlorpyrifos: Evaluation of Chlorpyrifos in the Human Recombinant Aromatase Assay. 2011-10-20
4.8	Benchmark Dose Modeling for Cholinesterase Inhibition from Exposure to Chlorpyrifos and Chlorpyrifos-Oxon. 2010-06-29
4.8	Chlorpyrifos: Pubertal Development and Thyroid Function in Intact Juvenile/Peripubertal Male Crl: CD(SD) Rat. 2011-10-27
4.8	Chlorpyrifos: Evaluation of Chlorpyrifos in an In Vitro Estrogen Receptor Binding Assay. 2011-

	10-30
4.8	Chlorpyrifos: evaluation of single oral doses on cholinesterase and neurotoxic esterase inhibition in F344 rats. 1997
4.8	Dietary Exposure to Chlorpyrifos: Effects on Butyrylcholinesterase. 2004
4.8	Critical analysis of the allegations of neuropathy due to chlorpyrifos. 1994
4.8	Memo from Paul Price dated October 1, 2014. Additional PBPK modeling to estimate 1% RBC AChE inhibition levels from simulated exposures to chlorpyrifos. 2014
4.8	Memo from Paul Price dated October 29, 2014. Development of Chemical Specific Adjustment Factors for Chlorpyrifos and Chlorpyrifos Oxon Using Target Red Blood Cell Acetyl Cholinesterase Inhibition Levels of 10%, 5%, and 1%. 2014
4.8	Memo from Paul Price dated November 19, 2014. Additional information on PBPK modeling for Chlorpyrifos and Chlorpyrifos – Oxon. 2014
4.8	Chlorpyrifos Correspondence with Columbia Researchers: (1) Responses to Scientific Advisory Panel (SAP) comments (Whyatt and Rauh 2010), and (2) Responses to Dow AgroSciences inquiries (Whyatt 2010). 2011
4.8	Clarification of Relation between Blood Lead and Cord Blood Levels of Chlorpyrifos in the Columbia Center for Children's Environmental Health (CCCEH) Studies (Electronic mail communication). 2013
12.5.4	US EPA DER: Review of Nose-Only Inhalation of Chlorpyrifos Vapor: Limited Toxicokinetics and Determination of Time-Dependent Effects on Plasma, Red Blood Cell, Brain and Lung Cholinesterase Activity in Female CD(SD): Crl Rats. 2014.
Chlorpyrifos – Metabolite studies	
4.2.1	3,5,6-trichloro-2-pyridinol (TCP): Acute Oral Toxicity Up and Down Procedure in Rat; 2005
4.2.1	Chlorpyrifos oxon: Acute Oral Toxicity in Fischer 344 Rats. 1999
4.3.1	Sodium 3,5,6-trichloro-2-pyridinol: 3-Month Rat Dietary Toxicity Study. 1985
4.3.2	3,5,6-trichloro-2-pyridinol: Results of a One-Year Dietary Study in Male and Female Beagle Dogs. 1987
4.5.2	3,5,6-Trichloro-2-pyridinol: Oral Teratology Study in Fischer 344 Rats. 1987
4.5.2	3,5,6-trichloro-2-pyridinol: Oral teratology probe study in Fischer 344 rats. 1986
4.5.3	3,5,6-Trichloro-2-pyridinol: oral teratology study in New Zealand White rabbits. 1987
4.5.3	3,5,6-trichloro-2-pyridinol: Oral teratology probe study in New Zealand White rabbits. 1986
4.5.7	Evaluation of 3,5,6-trichloro-2-pyridinol in the Mouse Bone marrow Micronucleus Test. 1989
4.5.7	Evaluation of 3,5,6-Trichloro-2-pyridinol in the Mouse Bone Marrow Micronucleus Test. 1985
4.5.8	3,5,6-trichloro-2-pyridinol: Evaluation in the Ames' Salmonella/Mammalian Microsome Mutagenicity Assay. 1986
4.5.8	Evaluation of 3,5,6-trichloro-2-pyridinol (TCP) in the Rat Hepatocyte Unscheduled DNA Synthesis (UDS) Assay. 1987
4.5.8	Evaluation of 3,5,6-trichloro-2-pyridinol (TCP) in the Chinese Hamster Ovary Cell/Hypoxanthine-Guanine-Phosphoribosyl Transferase (CHO/HGPRT) Forward Mutation Assay. 1986
4.5.9	Physiologically Based Pharmacokinetic-Pharmacodynamic (PBPK/PD) Modeling of Oral Exposure to Chlorpyrifos-oxon: Impact on Toxicity Adjustment Factors. 2013
4.8	Desethyl Chlorpyrifos: Acute Oral Toxicity and Red Blood Cell Cholinesterase Inhibition Study in F344/DUCRL Rats. 2008
4.8	In vitro Sensitivity of Cholinesterase to Inhibition by Chlorpyrifos-oxon in Several Tissues of the Rat (Revision). 2013
4.8	Nose-Only Inhalation Of Chlorpyrifos-Oxon Vapor: Limited Toxicokinetics And Determination Of Time-Dependent Effects On Plasma, Red Blood Cell, Brain And Lung Cholinesterase Activity In Female CD(Sd):Crl Rats. 2013

II. Occupational and Non-Occupational Exposure

DACO	Reference
5.2	Use Description/Scenario (Application and Post Application)
5.8	2001. Chlorpyrifos: Comparative in vitro Dermal Penetration Study using Human Skin for Two Formulations.
5.8	1982. Chlorpyrifos: Pharmacokinetics in Human Volunteers following Oral and Dermal Doses
5.8	2015. In vivo Dermal Absorption of Chlorpyrifos, Formulated In EF-1551 and Two Spray Dilutions In Rats.
5.8	2015. In vivo Dermal Absorption of Chlorpyrifos, Formulated In EF-1551 And Two Spray Dilutions Through Human and Rat Split- Thickness Skin using Flow Through Diffusion Cells.
5.9	Deposited and/or transferable surface residue data of chlorpyrifos and chlorpyrifos oxon
5.10	Outdoor air monitoring data of chlorpyrifos and chlorpyrifos oxon
5.9, 5.10	1994. Mass Recovery of Malathion in Simulated Open Field Mosquito Adulticide Tests.
5.10	1993. Downwind Drift and Deposition of Malathion on Human Targets From Ground Ultra-Low Volume Mosquito Sprays. Journal of the American Mosquito Control Association. Vol. 9, No. 2.
5.9	1997. Persistence, Penetration, and Surface Availability of Chlorpyrifos, Its Oxon, and 3,5,6-Trichloro-2-pyridinol in Elm Bark.
5.10	Indoor air monitoring data of chlorpyrifos and chlorpyrifos oxon, including dissipation for indoor structural uses in non-residential areas.
5.9	USEPA's data evaluation records for the fraction of chlorpyrifos residue deposited following aerial mosquitocide application was determined with use of the AgDISP (v8.2.6) model. 2014-2020
5.9	USEPA's data evaluation records for ground fraction of mosquitocide application rate deposited on turf as determined using eight published studies on ground ULV application in which deposition was measured. 2014-2020
5.9, 5.10	2020. Residential Mosquito ULV Spreadsheets that was included in the USEPA's 2020 human health risk assessment. Appendix 7. • Appendix 7_1_Adult Worst Case Aerial Mosquito ULV applications.xlsx • Appendix 7_2_Adult Best Case Aerial Mosquito ULV applications.xlsx • Appendix 7_3_Child Worst Case Aerial Mosquito ULV applications.xlsx • Appendix 7_4_Child Best Case Aerial Mosquito ULV applications.xlsx • Appendix 7_5_Adult Ground Mosquito ULV applications.xlsx • Appendix 7_6_Child Ground Mosquito ULV applications.xlsx
5.10	USEPA's data evaluation records for air concentration estimate modeled using the well mixed box model. 2014-2020
5.10	Chlorpyrifos: Reevaluation of the Potential Risks from Volatilization in Consideration of Chlorpyrifos Parent and Oxon Vapor Inhalation Toxicity Studies. 6/25/2014.
5.10	Chlorpyrifos: Evaluation of the Potential Risks from Spray Drift and the Impact of Potential Risk Reduction Measures. 7/13/12.

DACO	Reference
5.10	Spray Drift Mitigation Decision for Chlorpyrifos (059101). 2012
5.10	The 2012 agreement between EPA and the technical registrants: buffer distances of 80 feet are required for coarse or very coarse droplets and buffer distances of 100 feet are required for medium droplets for aerial applications for application rates > 2.3 lb ai/A. In addition, the 2012 agreement requires buffer distances of > 25 feet and medium to coarse drops for airblast applications at rates >3.76 lb ai/A. 2012
5.10	Chlorpyrifos: Preliminary Evaluation of the Potential Risks from Volatilization. 1/31/13. U.S. EPA Office of Chemical Safety and Pollution Prevention. D399484, D400781. 2013
5.14	2013. Estimation of Chlorpyrifos Population Exposure from NHANES Biomonitoring Data. MRID 49234901.
5.14	USEPA's assessment for TCP (derived from triclopyr, chlorpyrifos, and chlorpyrifos-methyl). 6/6/2002.
5.14	USEPA's data evaluation records for human health risk assessment of chlorpyrifos used as tree trunk application
5.14	USEPA's data evaluation records for human health risk assessment of chlorpyrifos used as container stock root immersion application

Form and Time Frame for Submission of Required Information

- Items I and II are required within 30 calendar days.
- All required information must be submitted in correct format organized by data code (DACO).
- Each of the above items must be included in an electronic index. Any confidential business information (CBI, as defined in subsection 2(1) of the PCPA) should be designated and segregated according to PMRA guidance.

Registrants to whom Notice Was Sent

Adama Agricultural Solutions Canada Ltd.
Sharda Cropchem Limited