Stockholm Convention on Persistent Organic Pollutants

Persistent Organic Pollutants Review Committee
Nineteenth meeting
Rome, 9–13 October 2023

Report of the Persistent Organic Pollutants Review Committee on the work of its nineteenth meeting

Addendum

Risk profile for chlorpyrifos

At its nineteenth meeting, by decision POPRC-19/3, the Persistent Organic Pollutants Review Committee adopted a risk profile for chlorpyrifos on the basis of the draft contained in the note by the Secretariat (UNEP/POPS/POPRC.19/4), as revised during the meeting. The text of the risk profile as adopted is set out in the annex to the present addendum. It has not been formally edited.

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Annex*

Chlorpyrifos

Risk profile

October 2023

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Executive summary

1.	The Persistent Organic Pollutants Review Committee (POPRC) at its seventeenth meeting concluded that chlorpyrifos fulfilled the screening criteria in Annex D (decision POPRC-17/4) and decided to prepare a risk profile in accordance with Annex E to the Convention, which was revised at its eighteenth meeting (decision POPRC-18/3).

2.	Chlorpyrifos, which belongs to the group of organophosphate pesticides, is widely applied as an insecticide in agriculture and as a biocide to control non-agricultural pests. At its peak, in 2008 chlorpyrifos products were authorised for use in more than 88 countries. While its production and use declined in some regions such as Europe and North America following regulatory measures such as bans or restrictions, chlorpyrifos still has a wide application range in many countries worldwide, including for termite control in buildings.

3.	Chlorpyrifos was first produced commercially in 1965 by Dow Chemical Company. While data are not available on total global production volumes, data from the China Crop Protection Industry Association (CCPIA) indicated that prior to 2007, global use was about 10,000 tonnes/year. Based on increasing demands in some regions the global production and use have substantially increased to approximately 50,000 tonnes/year. China and India are assumed to be currently the biggest producers of chlorpyrifos globally.

4.	Environmental degradation half-lives of chlorpyrifos range from a few days to several years (in the case of termite control), depending on application rate, ecosystem type, soil or sediment characteristics, and other environmental factors, including temperature. Monitoring data from the Arctic and Antarctica demonstrate that chlorpyrifos is transported over long distances to remote regions. Since degradation of chlorpyrifos is temperature dependent, it is expected to persist in relatively colder regions for a considerable length of time. Frequent findings of chlorpyrifos in all media in the Arctic support this. In addition, chlorpyrifos is found in dated sediment cores in Arctic and sub-Arctic lakes. Thus, chlorpyrifos is considered persistent in some environments.

5.	For chlorpyrifos, experimental and estimated octanol/water partition coefficient (log K_{ow} values) around 5 indicate potential bioaccumulation in aquatic organisms. Fish studies generally show moderate bioaccumulation with a bioconcentration factor (BCF) in the range of 1,000 to 2,000 at concentrations showing toxic effects. Certain fish BCF values above 5000 are observed in early life stages.

6.	While modelling results do not predict long-range environmental transport, chlorpyrifos is widely detected in abiotic compartments of remote regions such as sea-ice meltwater and air of Antarctica, as well as in lake sediments on the Tibetan plateau as well as in biotic compartments of remote regions, such as in caribou, seals and polar bears in the Arctic, far away from point sources with agricultural use, indicating that long-range environmental transport has occurred. Potential routes of transport include atmosphere (gas and particulate) and water (ocean currents and rivers).

7.	In the EU the GHS system is implemented via the CLP Regulation (EC No 1272/2008). Under this regulation, chlorpyrifos has a harmonized classification as "H301: Toxic if swallowed, H400: Very toxic to aquatic life and H410: Very toxic to aquatic life with long lasting effects". Due to the building block approach of the GHS and different databases used for classification, the classification results may vary in different legislations.[1]

8.	Chlorpyrifos is highly toxic to aquatic organisms, especially for aquatic invertebrates and early life stages of fish. Chlorpyrifos also shows high acute toxicity to terrestrial vertebrates, especially to birds, and mammals. In combination with high toxicity, even moderate bioaccumulation may lead to body burdens that elicit adverse effects, thus may be a serious concern.

9.	 Chlorpyrifos induces irreversible inhibition of acetylcholinesterase in the central and peripheral nervous system. *In vivo* animal studies provide evidence of developmental neurotoxicity, with effects on the developing nervous system including altered cognition, motor control, and behavior in rats and mice. These studies, along with epidemiological evidence, suggest that chlorpyrifos has the potential to affect the developing nervous system at doses below those causing cholinesterase inhibition. Additionally, chlorpyrifos exhibits acute and chronic toxic effects at very low concentrations.

10.	The European Food Safety Authority (EFSA) could not conclude on the absence of risk for human health from exposure to chlorpyrifos in its latest evaluation. Both EFSA and the United States Environmental Protection Agency (US EPA) have identified risks of concern for human health from exposure to chlorpyrifos. The EU funded human biomonitoring project HBM4EU recently concluded that exposure levels to chlorpyrifos of 7.3% of children tested exceeded the provisional guidance level 0.01 mg/L derived for the project. Similarly, the US EPA revoked food tolerances based on human health risks of concern.

11.	A comparison of concentrations of chlorpyrifos measured in biota in remote regions with quality standard (QS) recently proposed in the framework of the EQS Directive (Directive 2008/105/EC) shows exceedance for the higher concentrations measured and, in some cases, for the average concentrations, indicating potential concerns.

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[1] Some classifications from different regulations are collected here: https://comptox.epa.gov/dashboard/chemical/safety-ghs-data/DTXSID4020458.

While concentrations of chlorpyrifos measured in lakes and marine water in remote regions are generally below the environmental quality standard (EQS) proposed for water, some data measured in sea water samples and fresh water exceed the limit that was set to protect aquatic organisms.

12.   Based on the persistence, potential for bioaccumulation, toxicity to aquatic organisms and terrestrial animals (including humans) and the widespread occurrence in environmental compartments including remote regions at levels of concern, it is concluded that chlorpyrifos is likely, as a result of its long-range environmental transport, to lead to significant adverse human health and/or environmental effects such that global action is warranted.

1.   Introduction

1.1   Chemical identity

13.   Chlorpyrifos is an organophosphate pesticide. Figure 1 and Table 1 provide details of the chemical structure and identity for chlorpyrifos.
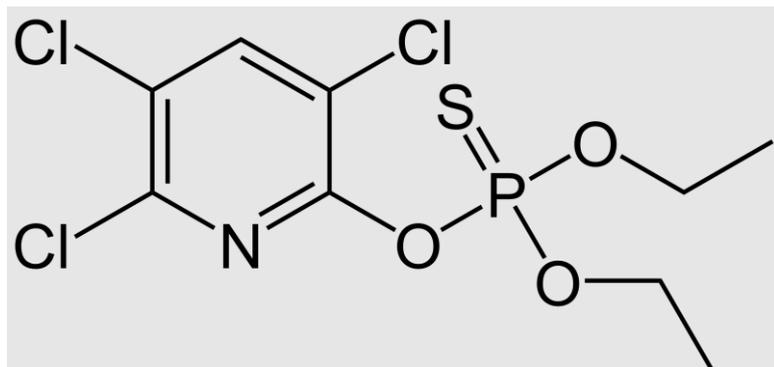
Figure 1. Structural formula of chlorpyrifos (Credit: Andreas Buser, Switzerland).

Table 1. Chemical identity of chlorpyrifos.

CAS number:		2921-88-2
CAS chemical name:		O,O-diethyl O-(3,5,6-trichloro-2-pyridyl) phosphorothioate
IUPAC name:		O,O-Diethyl O-3,5,6-trichloro-2-pyridinyl phosphorothioate
EC number:		220-864-4
Smiles code		CCOP(=S)(OCC)Oc1nc(Cl)c(Cl)cc1Cl
Molecular formula:		$C_9H_{11}Cl_3NO_3PS$
Molecular weight:		350.59 g/mol
Synonyms:		chlorpyriphos; chlorpyrifos-ethyl; O,O-diethyl O-3,5,6-trichloro-2-pyridinyl phosphorothioate; phosphorothioic acid, O,O-diethyl O-(3,5,6 trichlor-2-pyridinyl) ester
Trade names:		Dursban, OMS 0971, Lorsban, Brodan, Killmaster, Pyrinex, Suscon, Coroban, Terial, Danusban, Durmet, Eradex

Physical and chemical properties

14.   Table 2 reports the main physicochemical properties of chlorpyrifos, additional information can be found in Table 1 of document UNEP/POPS/POPRC.19/INF/11. The vapour pressure value and Henry's law constant indicates that it is semi-volatile. It has a low water solubility. The log K_{OW} value shows that it can partition into lipophilic material and the organic carbon/water partition co-efficient log K_{OC} shows that it can adsorb to the organic fraction in soil and sediment.

Table 2. Overview of selected physicochemical properties of chlorpyrifos.

Property	Value	Source
Physical state at 20°C and at 101.3 kPa	Tan, crystalline solid (94% purity) Colourless to white crystalline solid	European Commission (2005) (WHO 2009)
Vapour pressure (Pa)	3.35×10^{-3} 25°C (purity 99.8%) 1.43×10^{-3} 20°C (purity 99.8%) 1.0×10^{-3} Experimental, 25°C (purity 98%) 2.3×10^{-3}	European Commission (2005) European Commission (2005) (WHO 2009) Compiled by Mackay et al. (2014)
Water solubility (mg/L)	1.05 at 20°C, in unbuffered solution, no pH dependency reported 0.39 at 19.5°C, pH not cited (98% purity) 0.73 0.941 (20°C, pH unknown, guideline EEC Method A6/OECD 105) Dow 0.588 (20°C, pH not stated, guideline OECD 105 flask method) Makhteshim	European Commission (2005) WHO (2009) Mackay et al. (2014) WHO (2009) WHO (2009)
n-Octanol/water partition coefficient, K_{OW} (log value)	4.7 at 20°C, neutral pH 5.0 at 24.5°C (purity 98%) 4.96–5.11 at 20°C 5.2–5.27 at 25°C	European Commission (2005) WHO (2009) Gebremariam et al. (2012) Gebremariam et al. (2012)
n-Octanol-air partition coefficient K_{OA} (log value)	8.88 (estimated) 8.34	US EPA (2012) Mackay et al. (2014)
Air/water partition coefficient (log K_{AW})	-3.92 Experimental database	US EPA (2012)
Soil organic carbon/water partition coefficient (log K_{OC})	3.4–4.5 (mean: 3.9) 3.7 Experimental database 3.93 (mean value)	EC (2005) US EPA (2012) Mackay et al. (2014)
Organic carbon normalized adsorption coefficient (K_{OC}, mL/g)	Commerce loam 7300 Tracy sandy loam 5860 Catlin silt loam 4960	US EPA (2022b)

Transformation products

15.   The main transformation products of chlorpyrifos are 3,5,6-trichloro-2-pyridinol (TCP), chlorpyrifos-oxon, des-ethyl chlorpyrifos, 3,6-dichloro-2-pyridinol (3,6-DCP) and 2,3,5-trichloro-6-methoxypyridine (TMP). TCP is not exclusive to chlorpyrifos but is also formed from chlorpyrifos-methyl and triclopyr (Health Canada 2017). Information on chemical identity, physico-chemical properties and environmental hazard information can be found in paragraphs 1-3 of document UNEP/POPS/POPRC.19/INF/11.

1.2   Conclusion of the POPRC regarding Annex D information

16.   In June 2021, the European Union and its Member States submitted a proposal to list chlorpyrifos in Annex A, B and/or C of the Stockholm Convention (UNEP/POPs/POPRC.17/5). The POPRC evaluated the proposal regarding chlorpyrifos (UNEP/POPS/POPRC.17/5) according to the requirements in Annex D of the Stockholm Convention at its seventeenth meeting. In Decision POPRC.17/4 the Committee reached the conclusion that the screening criteria set out in Annex D to the Stockholm Convention had been fulfilled for chlorpyrifos. The Committee decided to review the proposal further and to prepare a draft risk profile in accordance with Annex E to the Convention.

17.   The POPRC considered the draft risk profile at its eighteenth meeting and adopted decision POPRC-18/3, by which it decided to defer its decision on the draft risk profile (UNEP/POPS/POPRC.18/INF/27) to its nineteenth meeting. In its decision, the Committee noted that, while the Committee agrees that the screening criteria set out in Annex D to the Stockholm Convention have been met, the Committee has been unable to agree that chlorpyrifos is likely, as a result of its long-range environmental transport, to lead to significant adverse human health and/or environmental effects such that global action is warranted. The Committee also decided to establish an intersessional working group to review and update the draft risk profile; and invited Parties and observers to submit to the Secretariat additional information relating to adverse effects resulting from long-range transport of chlorpyrifos before 5 December 2022.

1.3   Data sources

18.   The draft risk profile is based on the following data sources:

(a)   The proposal submitted by the European Union (UNEP/POPS/POPRC.17/5);

(b)   Information and comments by Parties and Observers received in response to the invitation to submit the information specified in Annex E. Annex E information was provided by: Argentina, Australia, Austria, Belarus, Canada, Colombia, Dominican Republic, Egypt, Guatemala, India, Indonesia, Kenya, Monaco, the Netherlands, Norway, Oman, Republic of Korea, Saudi Arabia, Sweden, Thailand, Trinidad and Tobago, United Kingdom of Great Britain and Northern Ireland (UK), Uzbekistan, the United States of America (USA), China Crop Protection Industry Association (CCPIA), International Pollutants Elimination Network, Alaska Community Action on Toxics (IPEN/ACAT), la Grande Puissance de Dieu, Pesticide Action Network (PAN) and Pesticides Manufacturers & Formulators Association of India (PMFAI);

(c)   Reports and other grey literature, as well as peer-reviewed scientific journals.

1.4   Status of the chemical under national regulations and international forums

19.   Chlorpyrifos is not listed under an international agreement. However, several countries have evaluated the substances and initiated regulatory processes. Chlorpyrifos is banned in Argentina, Morocco (ONSSA, 2020), Sri Lanka (PIC Database, 2021), Indonesia (Indonesia, 2019), Switzerland (Switzerland, 2019), Saudi Arabia (Ministry of Environment, Water & Agriculture, 2023), Palestine, Thailand (Thailand, 2022), Trinidad and Tobago (Ministry of Health's Pesticides and Toxic Chemicals Control Board, 2023) and Türkiye (PIC Database, 2022). In the US, residential uses (except for ant and roach baits in child resistant packaging and fire ant mound drenches for public health purposes), all indoor non-residential non-agricultural uses, and most outdoor non-residential uses were eliminated in 2000 (US EPA 2006). All chlorpyrifos tolerances expired on 28 February 2022 pursuant to the final rule. The non-food uses will remain registered as chlorpyrifos undergoes registration review, a program that re-evaluates all pesticides on a 15-year cycle. Use of chlorpyrifos on exported food crops can still take place as long as it is not in conflict with the laws of the country to which it is intended for export ((21 USC 381 (e)(1) (US EPA 2021, US EPA 2022a). In the European Union and Norway chlorpyrifos has been prohibited to be placed on the market and use as an active substance in plant protection products since 2020 and in biocidal products since 2008 (Regulation (EC) No 1107/2009, Regulation (EU) No 528/2012). Also, chlorpyrifos is subject to the Prior Informed Consent Regulation including an export notification procedure within the EU. In India chlorpyrifos has been registered under the Insecticides Act of 1968 since 1977. The use of chlorpyrifos on vegetables is banned since 31 December 2016 in China. All identified information on national-level regulations can be found in Table 2 of document UNEP/POPS/POPRC.19/INF/11.

2.   Summary information relevant to the risk profile

2.1   Sources

2.1.1   Production, trade, stockpiles

20.   Chlorpyrifos was first produced commercially in 1965 by Dow Chemical Company in the USA. While a number of methods for the commercial preparation of chlorpyrifos have been reported, a common method is by reaction of 3,5,6-trichloro-2-pyridinol with diethyl phosphorochloridothioate under basic conditions e.g., in the presence of sodium carbonate (ATSDR 1997b).

21.   While data are not available on total global production volumes, data from the CCPIA (2022) indicated that, prior to 2007, global use was about 10,000 tonnes/year, which has since grown to an estimated global production and use of around 50,000 tonnes/year. It was indicated that, following the prohibition of five highly toxic organophosphate pesticides in China, chlorpyrifos has become one of the most dominant insecticides used in the country (Chen et al. 2012).

22.   While production previously mainly occurred in North America and Europe, China and India are currently two of the biggest producers of chlorpyrifos globally. Total production of chlorpyrifos in India in 2021 was reported to be 24,000 tonnes, of which 11,000 tonnes were used domestically, 12,000 tonnes were exported, and 1,000 tonnes were in stockpiles (PMFAI, 2022). Data on total volumes of production and use of chlorpyrifos in China have not been provided. However, it has been estimated that in 2019, a total of 32,500 tonnes of chlorpyrifos were exported from China[2]. The main destinations were Brazil, Vietnam, Indonesia and Thailand. Note, however, that subsequently use in Vietnam, Indonesia, and Thailand has been or is in the process of being phased out. The products with highest

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[2] https://news.agropages.com/News/NewsDetail---36034.htm.

export value were chlorpyrifos 97% TC (technical concentration), chlorpyrifos 40% EC (Emulsifiable Concentrate) and chlorpyrifos 95% TC.[3]

23.   While volumes of chlorpyrifos production in the USA have not been provided, it is likely to have declined significantly in the past 25 years. It was reported that annual use of chlorpyrifos in the USA for the period 1987-1998 was ~9,500 tonnes, while annual use between 2014 and 2018 was ~2,300 tonnes (US EPA 2020a). The majority of chlorpyrifos products registered for residential treatments were voluntarily cancelled or phased out by the registrants between 1997 and 2001 (US EPA 2006). Furthermore, applications for use have reportedly declined due to State-level restrictions (e.g., in California), reduced production and the development of alternative products. It is also noted that several manufacturers have voluntarily halted production in the USA in recent years.

24.   In Canada, no production is reported. Chlorpyrifos active ingredient and most chlorpyrifos end-use products were imported into Canada prior to its cancellation in 2021. Annual sales of chlorpyrifos in Canada, expressed as volume of active ingredient sold were 133 tonnes in 2020. Australia (2022) reported importing 2,131 tonnes of chlorpyrifos (including 1,426 tonnes as active ingredient and 705 tonnes in products) in 2020–2021.

25.   The non-renewal of chlorpyrifos authorization in the European Union in 2020 is expected to have resulted in the cessation of use and imports of chlorpyrifos in European countries. It is noted that volume of use in the UK has displayed a notable decrease in recent years, with use of >17 t reported in 2016 declining to ~0.1 t in 2020. This is as a consequence of the authorization for the use of the substance being withdrawn in 2020. However, export of chlorpyrifos from the EU to various countries is still happening (more than 380,000 L of both product and active ingredients exported in 2022).[4]

26.   As presented in European Commission et al. (2017), according to the Food and Agriculture Organization of the United Nations (FAO), chlorpyrifos has been imported during the period 2008–2015 by 12 developing countries and economies in transition in Europe (Serbia and Türkiye), Near East (Lebanon), Africa (Burundi, Malawi, Madagascar and Senegal), Latin America and the Caribbean (Ecuador) and Asia (Thailand, Bangladesh, Myanmar and Malaysia). The total amount of import into these markets in 2015 was estimated to be ~7,000 tonnes (European Commission et al. 2017). Overall, the general trend for the total import into these countries over the period 2008–2015 was an increase in import volume. For example, Türkiye import quantities followed a clear increasing trend over the period 2008–2015. Malaysia and Myanmar import quantities displayed an increasing trend over this time-period, despite some slight decreases for some years. In Brazil, annual national quantity of chlorpyrifos used in pesticide formulations production showed an increase from 2009 (1,467 tonnes) to 2014, when it reached a peak of 12,989 tonnes. As of 2014, production decreased and started to rise again. It reached 9,679 tonnes in 2019 and decreased again to 5,491 tonnes in 2020. Imports and domestic use followed the same trend and varied from 8 to 6,441 tonnes of imported pesticide formulations with chlorpyrifos, and from 2,449 to 16,452 tonnes used domestically over the considered period, 2009-2020 (Agrochemical Marketing Reports available at ibama.gov.br).

2.1.2   Uses

27.   Chlorpyrifos is a broad-spectrum chlorinated organophosphate insecticide and has been used as an active substance in large number of products for pest control on various crops as well as lawns and ornamental plants (John and Shaike 2015). Pesticide products containing chlorpyrifos are registered for use on many agricultural crops, including corn, soybeans, alfalfa, oranges, apples, bananas, wheat, and walnuts (Foong et al. 2020, US EPA 2020a). Additionally, chlorpyrifos products are registered for use on non-food sites such as ornamental plants in nurseries, golf course turf, as a wood treatment, and as an ear tag for cattle. There are also public health uses including aerial and ground-based mosquito adulticide fogger treatments, use as fire ant control and for some tick species that may transmit diseases such as Lyme disease (US EPA 2020a).

28.   In the USA, for the period 1987–1998, it was estimated that, of the ~9,500 tonnes of chlorpyrifos used annually, approximately 25% was used on corn, 25% for termite control and 12.5% on turf (US EPA 2006). Based on estimates from the US EPA pesticide program, as of 2007 it was still the highest volume insecticide in use within the USA (US EPA 2011). As a result of the elimination of residential uses and phase out of the termite uses for chlorpyrifos in the USA, it was estimated that these led to a reduction in sales of 4,500 tonnes of chlorpyrifos on the US market (US EPA 2006). Between 2014–2018 use had fallen to 2,300 t of chlorpyrifos, with primary use on soybeans, alfalfa (lucerne) and corn, which made up nearly 50% of the total volume used. Within these estimates, soybeans accounted for nearly 25% of total volume applied (US EPA 2020a). In August 2021 the US EPA ended the use of chlorpyrifos products on all food products nationwide. US EPA will next proceed with registration review for the remaining non-food uses(US EPA 2022a). The use of chlorpyrifos as a termiticide was phased-out in the USA in 2000.

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[3] Plant Production and Protection Division: Manual on Development and Use of FAO and WHO Specifications for Pesticides.

[4] Chlorpyrifos is subject to the Prior Informed Consent regulation including an export notification procedure within the EU. The aggregated data reported is derived from the export notifications.

29.   In Belarus chlorpyrifos is still used in agriculture to treat cereals, corn, rapeseed, fruit and vegetables, with a total volume used of 64.6 t used in 2018 (Belarus, 2022). In Sweden and Norway, chlorpyrifos was never authorized as a plant protection product (Sweden, 2022; Norway 2022). In January 2020, the European Commission adopted implementing Regulation EU 2020/18,[5] meaning that the European Union (EU) Member States must withdraw all authorizations for plant protection products containing chlorpyrifos as an active substance. Individually, some European countries had restricted or banned chlorpyrifos prior to this. Austria ceased all pesticidal uses in 2020 (Austria, 2022). In the Netherlands, it was widely used from 1971, however, following the EU level ban use has ceased and alternative insecticides are being developed.

30.   PMFAI (2022) reported that, of the 24,000 tonnes of chlorpyrifos produced in India in 2021, 11,000 tonnes were used domestically. In 2021, it was reported that chlorpyrifos is approved for a number of specific agricultural uses in India. An overview of the specific products, crops and target pests approved for use in India is provided in Table 3 of document UNEP/POPS/POPRC.19/INF/11.[6] Other chlorpyrifos products are used in India for non-agricultural purposes, namely, to protect buildings (both indoors and outdoors) from termite attack at pre and post construction stages and to control adult mosquitoes and vector-borne diseases .[7] Although several other countries also have phased out the use of chlorpyrifos in termite control, it is still used as a termiticide in India (Rother, India 2020).

31.   In Australia, the remaining product registrations and label approvals of products that included a combination of home garden and agricultural uses in 2020 were cancelled (APVMA 2020). The reconsideration of agricultural uses of chlorpyrifos is ongoing.

32.   Chlorpyrifos, among other pesticides, has been reported to be sold as "street pesticide" on the informal market in developing countries, often in unlabeled and unsafe containers, and used as a pesticide for domestic applications in several African countries irrespective of the registration status (Rother 2010 and Rother, 2016).

2.1.3   Releases and emissions to the environment

33.   Upon its application as a pesticide, chlorpyrifos is directly released to the environment and can be further distributed by several potential pathways. It either sorbs to the soil particles or sediment, may leach through the soil into groundwater, reaches the aquatic environment through runoff irrigation water, or travels through the air as a result of spray drift and/or volatilization (Das et al. 2020, Nandhini et al. 2021), where it can be taken up by biota (see chapter 4.2).

34.   Only limited data exists to capture potential emissions to environment during production. ATSDR (1997b) reported data from 1980 production facilities in the USA quoting releases to air of 0.5 kg per 1,000 kg (1 metric tonne) of chlorpyrifos produced. Given global production rates of 50,000 tonnes per annum, up to 25 tonnes of releases to air during production are estimated.

35.   Between 2007 and 2017, in Europe, emissions of chlorpyrifos to water were recorded 24 times in 5 countries with a total annual emission ranging from 8.2 kg to 28 kg as reported under the Regulation on the European Pollutant Release and Transfer Register (E-PRTR[8]). The emissions year on year fluctuate, but suggest an overall declining trend, with the primary source of the emissions being urban wastewater treatment works. In 2016, according to a Water Framework Directive (Directive 2013/39/EC) dataset review, chlorpyrifos emissions values above zero were reported in nine countries;[9] however, only one country reported the pollutant's release from agricultural activities, while three countries reported the pollutant's release from riverine load.

36.   As described above, chlorpyrifos can contaminate surface water via spray drift at the time of application or associated with soil, as runoff up to several months after application. Available data indicate that most chlorpyrifos runoff is generally via adsorption to eroding soil rather than by dissolution in runoff water.

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[5] https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32020R0018&rid=7.

[6] Government of India Ministry of Agriculture & Farmers Welfare Department of Agriculture, Cooperation & Farmers Welfare Directorate of Plant Protection, Quarantine & Storage Central Insecticide Board & Registration Committee N.H.-IV, Faridabad-121 001 (Haryana) MAJOR USES OF PESTICIDES (Registered under the Insecticides Act, 1968) (UPTO - 31/01/2020) (Based on certificate issued).

[7] Ibid.

[8] https://industry.eea.europa.eu/#/home.

[9] Belgium, Cyprus, Czechia, France, Germany, Italy, Netherlands, Spain, and Slovakia.

3. Environmental fate

3.1 Persistence

37. The environmental degradation half-lives of chlorpyrifos range from a few days to several years and are dependent on a wide range of factors, including application rate, ecosystem type, soil or sediment characteristics, and other environmental factors, including temperature. All half-lives mentioned in the following chapters are listed in Tables 4–9 of document UNEP/POPS/POPRC.19/INF/11, together with more detailed information.

38. Various studies examining the route of degradation have been assessed in the European Union Renewal Assessment Report (EU RAR) for chlorpyrifos (Spain 2017). A total of five metabolites were identified: the major transformation product detected was 3,5,6-trichloro-2-pyridinol (TCP), with maximum mean concentrations of 14.8–59.7% and a half-life of 8.6–61 d in soil. Other minor metabolites, 2-methoxy-3,5,6-trichloropyridine (TMP, max 2.9%AR, half-life of 12–17 d in soil), MTCP (max 3.9% AR), 3,5 DCMP (max 2% AR) and 5,6 DMCP (max 0.7% AR) were identified. In summary, chlorpyrifos will degrade mainly to TCP and to various other minor metabolites in soil. TCP is considered moderately persistent in soil and highly mobile and is eventually degraded to CO_2 and to non-extractable residues.

3.1.1 Environmental distribution and abiotic degradation

39. Vapor pressure and Henry's Law constant (see UNEP/POPS/POPRC.19/INF/11, Table 1 for values) indicate that chlorpyrifos is semi-volatile. Volatilization plays a role in the overall dissipation process in the field. In the USA, chlorpyrifos has been detected in the air regularly at various sites by the California Department of Pesticide Regulation's Air Monitoring Network, which has conducted both seasonal air monitoring in certain counties and weekly random ambient air sampling throughout the year at sites located in major California agricultural regions, starting in 2011 (California Department of Pesticide Regulation 2018).

40. Chlorpyrifos photolysis is a minor degradation pathway. Hydrolysis is dependent on pH at alkaline pH, but independent of pH below a pH of 7. Reported half-lives for hydrolysis at pH < 5 were generally longer (16–210 d) and at pH >9 shorter (0.1–10 d) (Mackay et al. 2014). High losses due to volatilization as reported by some studies (e.g. Schimmel et al. (1983) can reduce the half-lives attributed to hydrolysis. Detailed information on abiotic degradation can be found in chapter 5.1 of document UNEP/POPS/POPRC.19/INF/11.

41. The European Union Risk Assessment Report – EU RAR (Spain 2017) lists seven studies on soil leaching behavior (column leaching studies): (Pike and Getzin 1981, Somasundaram et al. 1991, Racke 1993, Reeves and O'Connor 1994a, Reeves and O'Connor 1994b, Fenoll et al. 2011, Rani et al. 2014). In no study more than 1% of the applied radioactivity was recovered in the soil layers below 2.5 cm or in the leachate. These results all show that chlorpyrifos is strongly bound to soil. Chlorpyrifos is expected to be immobile to slightly mobile in soils as indicated by KOC values ranging from 2,785–31,000 (PMRA 2019).

3.1.2 Biotic degradation

42. Degradation half-lives in water may be underpredicted and cannot be regarded as "true degradation", since in all of the studies that were reviewed, significant dissipation occurred. In aquatic systems, the primary routes of dissipation of chlorpyrifos from the water phase are partitioning to the sediment (10–52%) and volatilization especially after spray application or in aerated surface waters (NRA 2000, Australia 2022), not biological degradation. In a marine water test system, with no sediment, the estimation of a mass balance based dissipation half-life (DT50) of 75 d at 8 °C was possible, showing that chlorpyrifos can be considered persistent in open sea water, at 8 °C (Swales 2003). All available studies are described in more detail in UNEP/POPS/POPRC.19/INF/11, chapter 5.2.1.

43. Numerous studies are available for the assessment of route and rate of degradation of chlorpyrifos in **soil**, both published papers and proprietary studies conducted for registration purposes. Summaries for the proprietary studies, with details on mass balances, recovery rates and losses as well as other information on validity criteria, are provided in the EU RAR (Spain 2017) and PMFAI, 2022.

44. According to the EU RAR (Spain 2017) and US-EPA (2006), chlorpyrifos can degrade slowly in soil under both aerobic and anaerobic conditions, however, half-lives vary depending on laboratory and environmental field conditions.

45. As mentioned in table 6 of UNEP/POPS/POPRC.19/INF/11, in laboratory studies, degradation half-lives cover a wide range from 6 to 224 days in soils from temperate to tropical regions, tested at a variety of temperatures. The major transformation product of chlorpyrifos in soil is TCP (maximum mean concentrations of 14.8–59.7%). TCP is weakly bound to soil and highly mobile (K_{OC} 27–389), with increasing mobility as the pH increases. Degradation half-lives of chlorpyrifos are longer in soils with low water contents, and in experiments at lower temperatures.

46. At application rates of 1000 mg/kg, replicating those used for control of termites, which is still an approved use in a number of countries, half-lives of chlorpyrifos for degradation in soils ranged from 175 to 1576 d for five

U.S. soils at 25 °C (Racke et al. 1994). The application rates are given as 392 kg/ha in soil trench applications for termite applications, as opposed to 0.28–2.24 kg/ha for agricultural broadcast applications. The reduced degradation of chlorpyrifos at high application rates may be a result of toxicity to microorganisms that might otherwise degrade it. Detailed information on degradation in soil can be found in chapter 5.4 of document UNEP/POPS/POPRC.19/INF/11.

47.   Following application in the field, volatilization is expected to contribute significantly to early losses of chlorpyrifos from soil surfaces (up to 25% within 24–48 h) and plant surfaces (80% within 24–48 h) (NRA 2000, Australia 2022). Leistra et al. (2006) investigated the volatilization of chlorpyrifos in a field experiment on a potato crop with the characterization of meteorological conditions. Cumulative volatilization of chlorpyrifos was estimated to be about 65% of the applied substance.

48.   Half-lives reported for chlorpyrifos in aerobic water-sediment degradation studies in the laboratory range from 22 to 58 days for the total water-sediment system. In most cases, an estimation of half-lives for the sediment alone cannot be done. Under anaerobic conditions, the half-life values reported were longer with up to 171 d (Bidlack, 1979).

49.   Chlorpyrifos is found in sediment cores dating back several decades, both in use and remote areas (Landers et al. 2008, Sun et al. 2018). Chlorpyrifos adsorbs fairly strongly to sediment and suspended solids (Readman et al. 1992, Dabrowski et al. 2002, Gebremariam et al. 2012). Depending on sediment characteristics, the extent of adsorption and desorption can vary. Adsorption processes can have a profound influence on degradation processes, apparently from reduced availability of sorbed substance to microorganisms. Adsorption of chlorpyrifos strongly correlates with organic carbon content of soils and sediments. Mean and median values for chlorpyrifos partition coefficients normalized to organic carbon, K_{OC}, were 8,163 and 7,227 L/kg for soils and 13,439 and 15,500 L/kg for sediments (Gebremariam et al. 2012). (Mackay et al. 2014) lists a mean K_{OC} of 8,500, and the Health Canada Pest Management Regulatory Agency Proposed Re-Evaluation Decision (PRVD2019-05 (PMRA 2019)) describes a range of 2,785–31,000. "The amount of chlorpyrifos available to be volatilized from surface water is reduced by sediment adsorption. Chlorpyrifos has a strong affinity for soil colloids, as evidenced by its measured range of organic carbon-adjusted soil sorption coefficient (K_{OC})" (ATSDR (1997a). This process can contribute to persistency and may transport considerable amounts of chlorpyrifos from water to particulate matter such as suspended soil.

50.   Environmental degradation half-lives of chlorpyrifos range from a few days to over 200 days, depending on ecosystem type, soil or sediment characteristics, and other environmental factors, including temperature (Gebremariam et al. 2012). Monitoring data from the Arctic demonstrate that chlorpyrifos can be transported over long distances to remote regions (see section 3.3). Similar to most organic chemicals, the degradation of chlorpyrifos is temperature dependent, so it is expected to persist in these regions for a considerable length of time. Frequent findings of chlorpyrifos in all media in the Arctic support this, as well as measurements of total chlorpyrifos (including chlorpyrifos oxon) in dated sediment cores from three west coast parks in the USA (Washington and California), three Alaska parks north of the 60th parallel, and two parks in the Rocky Mountains of the USA (Colorado and Montana) (Landers et al. 2008). In conclusion, chlorpyrifos is considered sufficiently persistent in some environments to justify its consideration within the scope of the Convention.

3.2   Bioaccumulation

51.   For chlorpyrifos, experimental and estimated log K_{OW} values between 4.7 and 5.2 have been reported, indicating potential bioaccumulation in aquatic organisms. Bioaccumulation of chlorpyrifos in fish has been studied for many species, developmental stages and exposure scenarios. The available BCF values cover a broad range, but in many studies, toxicity occurred at low doses. An overview of all bioconcentration studies assessed for this dossier can be found in document UNEP/POPS/POPRC.19/INF/11, Table 10.

52.   Regulatory assessments conducted by the USA, Canada, Australia and the EU have determined a moderate BCF of < 5,000 for chlorpyrifos in fish. The EU RAR (Spain 2017) lists several fish bioconcentration studies, yet only one was conducted according to an accepted guideline. This study was conducted according to EPA Guideline No. 72-6 and 165-4, and a BCF of 1,374 ± 321 in rainbow trout (*Onchorhynchus mykiss*) was estimated. Values were not normalized for lipid content or growth dilution. In a published study with guppy (*Poecilia reticulata*) by Deneer (1993), a BCF of 1580 was estimated, but toxic effects occurred during these experiments at very low doses, thereby compromising the acceptability of the study results. BCF above 5000 are observed for zebrafish (*Danio rerio*) in early life stages, which are considered especially sensitive, (El-Amrani et al. (2012) Alharbi et al. (2017): BCF of 6918 in eleuthero embryos of zebrafish at 10 µg/L.

53.   An extensive review on bioaccumulation was conducted by Giesy et al. (2014) with BCFs ranging from 0.6 to 5100 in fish, with the highest value estimated in embryos and fry (Hansen et al. (1986) as cited by Giesy et al. 2014).

54.   The BCF values in the invertebrates ranged from 3.4 to 691. The value for the only amphibian (*Ambystoma mexicanum*) in the data set was 3,632 (Robles-Mendoza et al., 2011, as cited by Giesy at al., 2014). Tsuda et al., 1997, exposed four fish species to chlorpyrifos at 1.7 – 2.3 µg/L. The BCF measured after 7 days was 745 for white cloud mountain fish (*Tanichtys albonubes*), 763 for goldfish (*Carassius auratus*), 1464 for female guppy, 1561 for killifish

(*cyprinodontiform spp.*) and 2406 for male guppy. Steady state was not reached, and a kinetic BCF could not be calculated as water and fish concentrations were not reported separately. Although this was no guideline study, this is in the range of the other fish data.

55.   The biomagnification of chlorpyrifos was investigated in the vegetation-caribou-wolf food chain in the Bathurst region (Nunavut) in Canada by Morris et al. (2014). The lichen-caribou-wolf food chain leads to a trophic magnification factor (TMF) of < 1 for muscle, liver and total body burden (see UNEP/POPS/POPRC.19/INF/11, Table 10). Morris et al. (2016) further described the trophic dilution of chlorpyrifos in the polar bear-ringed seal food web based on data from three food chains sampled across the Canadian Arctic.

56.   Chlorpyrifos shows moderate bioaccumulation in aquatic and air-breathing organisms. In combination with high toxicity (see chapter 4), even moderate bioaccumulation can lead to body concentrations that elicit adverse effects.

3.3   Potential for long-range transport

57.   Chlorpyrifos has been detected in many different environmental matrices and biota in remote regions including in locations far away from point sources and without known use. Detections in the Arctic include: air, snow, lake sediment, fresh water, sea water, marine fog and ice, as well as in ice-cores (Chernyak et al. 1996, Garbarino et al. 2002, Hermanson et al. 2005, Jantunen et al. 2007, Hung 2013, Bigot et al. 2017, Balmer et al. 2019, Hermanson et al. 2020, Hermanson et al. 2021), as cited in Hoferkamp et al. (2010), Jantunen et al. (2015), Muir et al. (2004), Pućko et al. (2015), Pućko et al. (2017), Rice and Chernyak (1997); Ruggirello et al. (2010a) Landers et al. (2008), Zhong et al. (2012)), as well as various biotic compartments such as in fish, caribou, seals and polar bears. Detections in Antarctica include air, ice and sea-ice meltwater (Bigot et al. (2017), Hermanson et al. (2021)).

58.   It was also found in ice from the Lys Glacier and meltwater from six glaciers in the European Alps (Rizzi et al. 2019), as well as in air and precipitation in Sweden (Boström 2020). The results of these monitoring studies, which have been published in scientific literature, are summarized in chapter 3.4 Exposure.

59.   von Waldow et al. (2010) proposed an index to characterize the remoteness of regions. The resulting remoteness index is based on calculations with a global atmospheric transport model, with two different emission scenarios for industrial chemicals and plant protection products, respectively. For the crop emission scenario, regions with farmland were used as source regions. It should be noted that this remoteness index was derived based on atmospheric transport modelling and does not consider transport through water. A map generated by von Waldow et al. (2010) showing the resulting remoteness indices together with findings of chlorpyrifos in remote sections manually plotted by the dossier drafters, illustrates that chlorpyrifos is widely detected in remote areas (see UNEP/POPS/POPRC.19/INF/11, Figure 2).

60.   Based on physico-chemical properties and modelling results, transport in the water phase is expected to be relevant for chlorpyrifos. In the water compartment, (Macalady and Wolfe 1985) chlorpyrifos will sorb preferentially to suspended solids (see chapter 3.1.3). Chlorpyrifos bound to particles in the Arctic Ocean has been measured by Bigot et al. (2017). The numerous detections of chlorpyrifos in water samples from remote areas indicate that transport either occurs via water or chlorpyrifos is deposited from air transport.

61.   Modelled atmospheric half-life depends on the atmospheric OH radical concentration used for calculation. Annual average OH radical concentration of 0.5×10^6 molecules/cm^3 ,1.5×10^6 molecules/cm^3 and 1.5×10^5 molecules/cm^3 have been used, resulting in atmospheric half-lives ranging from 1.4 h and 4.1 h (AOPWIN; ver.1.89 (US EPA 2002)), to 14 h (Muir et al. 2004). Atmospheric half-life is impacted by seasonal variations of OH radical concentration. Calculations indicate that a reduced OH radical concentration would result in longer half-lives in the atmosphere.

62.   As described in the section on persistence, chlorpyrifos binds strongly to soil and sediment. Coscollà et al. (2014) hypothesize that chlorpyrifos adsorbed to the coarse fraction (e.g., 2.5 – 10 μm) of soil particles could be transported by wind erosion as has been shown for other pesticides (Larney et al. 1999). Socorro and co-workers showed that pesticides adsorbed to particulates may show an overall atmospheric half-life that exceeds values relevant for long range transport (Socorro et al. 2016). Although these experiments were not conducted with chlorpyrifos, but with 8 other pesticides, the results explain the general mechanisms.

63.   In air monitoring studies the percentage of particulate chlorpyrifos generally ranges from < 0.001% to 27% of the total chlorpyrifos (Rice and Chernyak 1997, Watts 2012, Li et al. 2014) with a recent case even reaching more than 80% (Degrendele et al. 2022). The partitioning between gaseous and particulate phases has been shown to be more variable in air than in soil as a result of environmental conditions (Degrendele et al. 2022). AEROWIN has three models and the predicted fraction of chlorpyrifos sorbed to particulates in air was 6.9% (Junge-Pankow model), 14.1% (Mackay model) and 0.24% (Octanol/air (K_{OA}) model). (US EPA 2012).

64.   Long-range transport is not predicted by modelling results using the OECD Pov and LRTP Screening Tool, which give a half-live of 1.4 h (AOPWIN; ver.1.89;(US EPA 2002)) to 14 h (Muir et al. 2004), with a characteristic travel

distance of 106 to 276 km, respectively, for chlorpyrifos in the vapor phase, but chlorpyrifos sorbed to airborne particles is far more recalcitrant to degradation by OH-radicals. The compound has been found far away from point sources in various abiotic and biotic compartments, which indicates that long-range environmental transport occurs.

4. Exposure

65.   Chlorpyrifos has been detected globally, in all continents and in all compartments, including soil, sediment, air, fresh water, salt water, rain, snow, sea ice and biota, both in regions close to application areas and in remote locations. The key data, focusing on monitoring data from remote regions and human biomonitoring (breast milk) is compiled below. Additional information, including monitoring from source regions and results from pesticide residue monitoring related to food and exposure in humans can be found in sections 8.1 and 8.2 of document UNEP/POPS/POPRC.19/INF/11.

4.1   Abiotic matrices

66.   In the Arctic, chlorpyrifos has been measured in air, snow, lake sediment, fresh water, sea water, marine fog and ice ((Chernyak et al. 1996, Garbarino et al. 2002, Hermanson et al. 2005, Jantunen et al. 2007, Hung 2013, Bigot et al. 2017, Balmer et al. 2019, Hermanson et al. 2020, Hermanson et al. 2021) as cited in Hoferkamp et al., 2010; (Rice and Chernyak 1997, Muir et al. 2004, Landers et al. 2008, Ruggirello et al. 2010b, Zhong et al. 2012, Jantunen et al. 2015, Pućko et al. 2015, Pućko et al. 2017), as well as in Antarctic air, ice and sea-ice meltwater (Bigot et al. 2017, Hermanson et al. 2021). In several of the studies, chlorpyrifos has been among the most abundant organochlorine pesticide detected. Chernyak et al. 1996 investigated current-use pesticides in the Bering and Chukchi marine ecosystems in the summer of 1993. Chlorpyrifos was measured in 4 of 7 fog condensates; the highest concentration was 0.005 µg/L. Chlorpyrifos was the third most abundant chemical identified at most sampling points. Among the five pesticides analyzed, chlorpyrifos was the most frequently identified contaminant in sub-surface sea water with levels ranging from 0.018 to 0.067 µg/L in 6 of 9 samples. Chlorpyrifos was measured at 0.17 µg/L in the single melted ice sample, where only atrazine was found in higher concentrations. Chlorpyrifos was also detected in lake sediment on the Tibetian plateau (Sun et al. 2018), in ice and meltwater from glaciers in the European Alps (Rizzi et al. 2019), as well as in air and precipitation in Sweden (Boström 2020). The results of these monitoring studies, which have been published in scientific literature, are summarized in Table 12 of document UNEP/POPS/POPRC.19/INF/11.

67.   Comparative analyses of chlorpyrifos and other pesticides (including pesticides listed as POPs such as endosulfan, chlordane and DDT) in ice-cores in the Arctic and Antarctica have shown that chlorpyrifos was among the most abundantly detected pesticides (Ruggirello et al. 2010b). Winter snow from four glacial sites on Svalbard was analyzed for atmospheric deposition of 36 organochlorine pesticides. At the time, chlorpyrifos dominated pesticides flux at three of the sites and was the second highest at the fourth site (Hermanson et al. 2020). From the samples taken in sea water in the Canadian Arctic Archipelago from 1999 to 2013, chlorpyrifos concentrations were among the highest when compared to other organochlorine pesticides being used at the time, including endosulfan which is now listed as a POP (Jantunen et al. 2015). The studies cited above are discussed in more detail in chapter 7.2 of document UNEP/POPS/POPRC.19/INF/11.

68.   A trend in chlorpyrifos occurrence in a 125 m deep ice core drilled at Holtedahlfonna in 2005 on Svalbard was observed by Ruggirello et al. (2010b). Chlorpyrifos was first detected in 1971–1980 with a comparatively low input (64.8 pg/cm²/year) and decreasing trend until the mid-1990s. Then it increased rapidly reaching maximum concentrations in the time period of 1995–2005. During this period the flux peaked at 808 pg/cm²/year. In the Holtedahlfonna ice core, chlorpyrifos was the only organophosphate current-use pesticide that was detected continuously, making up about 34% of the total pesticide burden in the core. It was noted that evidence of chlorpyrifos at Holtedahlfonna is contrary to the short atmospheric half-life of the substance predicted for mid-latitude environments. The authors also speculated that peak ice core concentrations of chlorpyrifos (and other pesticides) after 1979 may have been associated with pesticide use in Russian farmlands north of 60 °N. Landers et al. (2008) investigated contaminations of lake sediment cores corresponding the last 150 years in eight national parks in the USA as part of the Western Airborne Contaminants Assessment Program (WACAP). Results from two of the remote Alaskan national parks showed increasing contamination of lake sediments with total chlorpyrifos until 2000 (sum of chlorpyrifos and chlorpyrifos oxon), the most recent year represented by the sediment cores. On the Tibetan plateau, chlorpyrifos was found in 2 sediment cores of lake Yamzho Yumco with a detection frequency of 76% and 94%, with mean concentrations of 0.0059 and 0.0096 ng/g, in a range of <MDL (Minimum Detection Limit) to 0.0256 ng/g (Sun et al. 2018). The studies cited above are discussed in more detail in chapter 7.2 of document UNEP/POPS/POPRC.19/INF/11.

69.   Sources of chlorpyrifos for its long-range transport to the Arctic has been discussed by (Zhong et al. 2012) to be from Asian countries as demonstrated by monitoring along a transect of the East China Sea - Bering and Chukchi Sea and from populated and agricultural regions in northern Eurasia (Ruggirello et al. 2010b). The studies cited above are discussed in more detail in chapter 7.2 of document UNEP/POPS/POPRC.19/INF/11, as are studies that discuss

various mechanism of long-range environmental transport of chlorpyrifos (Chernyak et al. 1996, Zhong et al. 2012, Pućko et al. 2015, Bigot et al. 2017).

70.   Detections of chlorpyrifos in soil, sediment, air, fresh water, salt water, rain, snow and biota that reflect local sources and use, from a number of countries and regions (Australia, Austria, Brazil, Canada the European Union, New Zealand, Norway, Spain, Sweden and the USA) are presented in chapter 8.1 of document UNEP/POPS/POPRC.19/INF/11. Some of the monitoring results presented in document UNEP/POPS/POPRC.19/INF/11 come from regional and national monitoring programmes.

4.2   Biota data

4.2.1   Remote regions

71.   Chlorpyrifos has been detected in biota samples from around the world, including the Arctic. Muir et al. (2023) compiled, in a preprint paper to inform this risk profile, the monitoring data for chlorpyrifos in fish and marine mammal samples from the Canadian Arctic/sub-Arctic generated by ongoing projects of the Northern Contaminants Program (NCP). Details on these projects are also available on the NCP database at the Arctic Institute of North America.[10] The majority of the chlorpyrifos data was from samples collected from 2011 to 2021. In addition, ringed seal blubber and Arctic cod (whole body) samples from 2007 to 2008 reported in (Morris et al. 2016) were included. Detection frequencies of chlorpyrifos ranged from zero in Arctic grayling (4 samples) to 52% in Arctic cod (n =29; results from Morris et al. (2016)) (Table 3). To enable statistical analysis the non-detects were substituted with ½ the detection limit (½ DL) based on the assumption that the non-detects were not zero. Largest geometric mean chlorpyrifos concentrations were found in Arctic grayling (*Thymallus arcticus*) muscle (1.04 ng/g ww) and lake whitefish (*Coregonus clupeaformis)* muscle, (0.56 ng/g ww) while burbot (*Lota lota*) liver had the highest maximum concentration (8.2 ng/g ww). As generally applicable, certain limitations to the monitoring data include: a lack of defined or rigorous sampling protocols; small sample sizes. Overall, the study authors concluded that the results indicate widespread but very low-level contamination of Arctic fish and seals by chlorpyrifos. This was a monitoring study that did not assess the hazard of the concentrations detected.

Table 3. Concentrations of chlorpyrifos (CPY) in Arctic biota samples (ng/g ww), detection frequency (DF), and % lipid results for fish (Muir et al. (2023), adapted). The majority of samples were collected from 2011 to 2021; ringed seal blubber and Arctic cod samples from 2007 to 2008 reported in Morris et al. 2016 are included.

Species/tissue	Num. of samples	DF (%)	Median CPY ng/g ww	Geo mean CPY ng/g ww	Median detected* CPY ng/g ww	Range CPY ng/g ww	Arith mean % lipid	Range % lipid
Arctic char muscle	123	16%	0.012	0.010	0.140	<0.001–0.58	3.9	0.5–10.9
Arctic cod (WB)**	29	52%	0.031	0.027	0.107	<0.01–0.62	7.1	2.3–14.8
Arctic grayling muscle	2	0%	1.10	1.04	<1.45	0.75–1.45	3.0	2.5–3.6
Burbot liver	82	23%	0.060	0.048	0.558	<0.003–8.23	36.1	0.1–59.1
Lake Trout muscle	186	14%	0.026	0.030	0.096	<0.001–2.57	7.4	0.5–21.6
Lake Whitefish muscle	4	50%	0.657	0.564	2.17	<0.16–4.03	2.5	2.1–3.1
Ringed seal blubber	200	18%	0.135	0.116	0.561	<0.008–4.50		

*Median based on detected results only

** WB = whole body

72.   Temporal trends in concentrations of chlorpyrifos in ringed seals were evaluated by plotting the results versus year of collection (Figure 2, supporting data in Table 3). In Figure 2, non-detect values were calculated using the peak area within the chlorpyrifos retention time window during the chromatographic analysis, where peaks in sample blanks were less than 3-fold higher than the baseline. This resulted in having unique non-detect values for each sample. Replacement of non-detect values with ½ detection limit permitted analysis of the data with parametric statistics. Detected concentrations in the samples from 2011 to 2016 for all locations (Muir et al. (2023)) were generally higher than reported by Morris et al. (2016) for samples from Resolute and Gjoa Haven, Nunavut. Comparing only Resolute results from 2012–2016 also suggests higher levels compared to 2007-08, however, detection frequency was low (6 of 34 samples). Overall, lack of data prior to 2007, in 2009-2010, and after 2016 precludes any firm conclusions about temporal trends in seals.

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[10] https://www.aina.ucalgary.ca/ncp/.
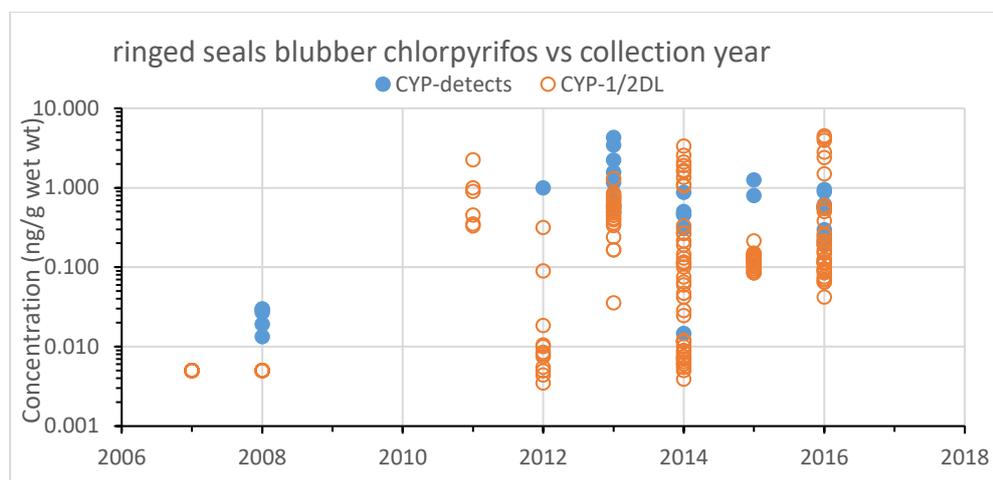
Figure 2. Chlorpyrifos results, including non-detects substituted with ½ detection limit (DL), in ringed seal blubber plotted by sampling year (Muir et al. 2023). Results from 2007 and 2008 are from Morris et al. 2016.

73.   During the Western Airborne Contaminant Assessment Project (WACAP), the contamination of the vegetation was investigated during 2003 and 2005 (Landers et al. 2008). Levels of total chlorpyrifos (including chlorpyrifos-oxon) in lichen were below the limit of detection in all Alaskan core and secondary parks except the Stikine-LeConte Wilderness, Tomgass National Forest, the most southern park located at the southern end of Southeast Alaska. In this park, the mean concentration in lichen was 0.60 ng/g lipid. The mean level of total chlorpyrifos in two-year-old conifer needles from Sitka spruce in the Denali National Park was 0.86 ng/g lipid while the mean concentrations in the four Alaskan secondary parks ranged from 0.61 to 2.35 ng/g lipid (Landers et al. 2008, Hoferkamp et al. 2010).

74.   WACAP also undertook fish monitoring which included *inter alia* the investigation of lake trouts (*Salvelinus namaycush*) from three lakes situated in the three Alaskan core parks and of whitefish (*Prosopium cylindraceum*) and burbot (*Lota lota*) from a second lake in the Denali National Park (Hoferkamp et al. (2010) and Landers et al. (2008)). Pesticide deposition in the Alaska parks is attributed to long-range trans-Pacific transport, because there are no significant regional pesticide sources nearby. Fish of similar age and sex distributions were collected. Since levels of current-use pesticides in fish were not available in tabular form, Hoferkamp et al. (2010) reported levels approximated from graphical illustrations. Total chlorpyrifos levels ranged from 0.041 to 0.1 ng/g ww in fish among the four lakes. The concentrations of chlorpyrifos reported in Landers et al. (2008) were similar to those for lake trout in the Muir et al. (2023) report as was detection frequency. Landers et al. (2008) reported 19% detection frequency in lake trout from remote lakes in National Parks in Alaska. Muir et al. (2023) reported 14% and 16% detection frequency for salmonid species lake trout (n = 186) and arctic char (n = 123), respectively, based on a compilation of freshwater fish data for samples collected from 2011 to 2021 under the Canadian Northern Contaminants Program (see table 3 above).

75.   Chlorpyrifos was detected in all muscle and liver samples (n=41) of polar cod sampled in and outside Bessel Fjord (NE Greenland) (Spataro et al. 2021), with 3.8 ± 2.4 ng/g ww in muscle and 5.9 ± 2.9 ng/g ww in liver of fjord fish (n=19), as opposed to only 0.9 ± 0.7 ng/g ww in muscle and 3.4 ± 1.8 ng/g ww in liver of ocean fish (n=22). The maximum concentrations for the fjord polar cod were 23.1 ng/g ww in muscle and 21.2 ng/g ww in liver.

76.   A study from Norway included analyses of chlorpyrifos in several Arctic species like fish, seabirds, seabird eggs and seals (Langford et al. 2012). The samples were collected in Svalbard during the autumn of 2011. The substance was detected in one of five seal blubber samples with a concentration of 1.4 ng/g ww in ringed seal. All other results were below the limit of detection in a total of 59 samples of fish, seabirds, seabird eggs, and seals. In another study chlorpyrifos was found in the blubber (n=8) of killer whales, collected in the northern Norway, in a concentration ranging from 1,800 to 21,000 ng/g lw (1.4–7.4 µg/g ww) while for the muscle samples (n=5) the range was between 2,600 and 21,000 ng/g lw (52–8000 ng/g ww) (Andvik et al. 2021).

77.   Measured concentrations in biotic samples are relatively low compared to legacy POPs such as PCBs (Cabrerizo et al. 2018, Houde et al. 2019) or PBDEs (Houde et al. 2017). However, chlorpyrifos concentrations were similar, although somewhat lower, to those reported for endosulfan in landlocked arctic char (α-endosulfan 0.12 ng/g ww and β- endosulfan 0.46 ng/g ww) and ringed seals in the Canadian Arctic (α- endosulfan 2.0 ng/g ww and β-endosulfan 0.88 ng/g ww) (Weber et al. 2010).

78.   Feathers of blackbrowed albatross (*Thalassarche melanophris*) and Cape petrels (*Daption capense*) were sampled on the Patagonian Shelf of Argentina during the winter of 2011 (Adrogué et al. 2019). Chlorpyrifos showed the highest concentrations of all substances analysed with 58.64 ± 27.31 ng/g feather in male and 49.56 ± 18.45 ng/g in female Albatross and 84.88 ± 50.57 ng/g for male petrels and 75.98 ± 47.97 ng/g for female petrels.

79.   Landers et al. (2008) reported total chlorpyrifos (including chlorpyrifos oxon) in lichen ranging from 1.57 to 19.83 ng/g lipid weight (lw) at sampling sites in national and secondary parks situated in the Western USA. First- and second year lodgepole pine (*Pinus contorta*) and white fir (*Abies concolor*) needles from Emerald Lake basin in Sequoia National Park showed a time-dependent increase of total chlorpyrifos concentration. In the one-year white fir needles chlorpyrifos was not detected, while the mean concentration in the older needles amounted to 19.7 ng/g lw. The mean concentration in the pine needles was 11.6 ng/g lw in the first year and 20.5 ng/g lw in the second year.

80.   In 1997 and 1998 blood samples from sea otters (*Enhydra lutris* ssp.) in California and Alaska, USA were analyzed for POPs and other chemicals of concern (Jessup et al. 2010). No chlorpyrifos contamination was reported for the 71 Alaskan sea otters sampled (the LOD was 4 ng/g lw). For 40 Californian sea otters sampled, a range from below LOD to 342.6 ng/g lw chlorpyrifos was reported, with a mean of 53.6 ng/g (range: 26.1–98.6 ng/g, sample size 5) for pups, 39.2 ng/g (range: 19.9–342.6 ng/g, sample size 6) for sub-adults, 43.8 ng/g (range: 0.3–201.7 ng/g, sample size 18) for adult females, 26.7 ng/g (range: 5.7–88.4 ng/g, sample size 11) for adult males Significant differences were found at the three sampling locations in California.

4.2.2   Use regions

81.   In 2005 the liver of river otters (*Lontra canadensis*) from New Jersey, USA were sampled for POPs and other contaminants (Stansley et al. 2010). The sample size was 32, of which 20 samples showed contamination with chlorpyrifos. This data showed a geometric mean concentration of 0.78 ng/g wet weight with a 95% confidence interval of 0.62–1.50 and values ranging from not detected to a maximum of 6.91 ng/g.

82.   Chlorpyrifos was detected in songbird spp. feet collected in Toronto, Canada in the springs of 2007 and 2011. The birds sampled were most likely to have overwintered in Mexican or Central American crops (cacao, citrus, and coffee). The overall recovery was 80% for chlorpyrifos, with an LOD of 0.1 ng/g feet weight. In the collection year 2011, chlorpyrifos ranged in feet samples from below LOD to 1.2 ng/g feet weight (Alharbi et al. 2016). Owl carcasses were sampled for tissues (heart, liver, and kidney). Chlorpyrifos was detected in the livers of two of the screech owl (*Megascops* spp.) (n=5), collected in 2018-2019 in Brazil, in an area with mixed agriculture and forests (Dal Pizzol et al. 2021).

83.   Sixty wild boars (*Sus scrofa*) from north-western Spain were sampled for POPs, such as HCB, α-HCH and chlordane, as well as the organophosphate pesticide chlorpyrifos. Hair and liver samples were taken, and chlorpyrifos was detected in 98% of hair samples and 90% of liver samples. Hair sample concentrations ranged from below LOD to 1.7 ng/g, and in liver, concentrations ranged from below LOD to 29 ng/g l.w. or below LOD to 3.2 ng/g w.w. (González-Gómez et al. 2021).

84.   In the Norwegian screening programme from 2017, chlorpyrifos was measured in 2 of 11 rat liver samples, both from Oslo city, at concentrations of 3.5 and 12.0 ng/g dry weight (dw) (Konieczny 2018). Another report from the Norwegian screening programme from 2017 shows that chlorpyrifos was detected with an average concentration of 0.30 ng/L and detection frequency of 83% in the effluent samples from one of the wastewater treatment plants in Tromsø, which is an urban area in Northern Norway (Schlabach and Rostkowski 2018). Chlorpyrifos was not detected in common gulls sampled in the urban area. In the Norwegian screening programme from 2016, chlorpyrifos was found in 4 of 5 liver samples of large perch from Lake Mjøsa at the levels ranging from 1 to 2.3 ng/g dw (Konieczny et al. 2016). Chlorpyrifos was also measured in one of 11 rat liver samples (2.4 ng/g dw) and was otherwise below the limit of detection in all samples of cod liver (n=15), fish fillets (n=16), shore crab (n=3), and winkie (n=2) that were analyzed.

85.   Chlorpyrifos and its transformation product chlorpyrifos oxon were detected in needles of potted ponderosa pines at three sites in California in 1994 (Aston and Seiber 1997). Needle compartments were analyzed separately and included a wash for polar and non-polar adsorbed substances, the waxy cuticle and the remainder needle. Values for chlorpyrifos residue in each compartment were combined to calculate total burden per sample. Two sites were sampled, one was located at the edge of the Central Valley (114 m altitude), while the others were situated at higher altitudes in the Sequoia National Park (533 and 1920 m, resp.). The detection frequency was significantly higher at the site in the Central Valley than those at the other two locations. The maximum level of chlorpyrifos in pine needles, which was found at the site in the Central Valley, amounted to ca. 129 ng/g dry weight, while the maximum level of chlorpyrifos oxon was about 110 ng/g dry weight at the same location.[11] Assuming that the needles of the potted pines, located at the site in the Central Valley, were in equilibrium with the compound in the surrounding air after 10 weeks of exposure, the vegetation: air BCF_m[12] was estimated as 9800.

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[11] The concentration values were estimated from a diagram of the cited publication.

[12] In this study the BCFm was defined as the mass: mass ratio of the concentration of a chemical in vegetation tissues to its concentration in air.

4.3   Human exposure

86.   Chlorpyrifos has been found in breast milk sampled from women in various parts of the world, both in agricultural and non-agricultural areas in countries where chlorpyrifos is or was used. Data from these biomonitoring studies are summarized in Table 4 and further details of the studies are presented in chapter 8.2 of document UNEP/POPS/POPRC.19/INF/11. Breast milk is considered an important source of exposure to chlorpyrifos for infants, particularly when considering neurodevelopmental effects of the pesticide.

Table 4. Human biomonitoring data.

Chlorpyrifos residues were measured in milk samples, and TCP residues were measured in urine and used as a biomarker to estimate chlorpyrifos levels.					
Weldon et al. (2011)	California breast milk	2002–2004	Median (range) 0.0245 (0.0129 – 0.23) ng/g milk (urban) 0.028 (0.0128 – 0.107) ng/g milk (rural)	LOD 0.151–0.256 pg/g milk DF 100%	Breastfeeding mothers from urban (n=21) and rural communities (n=13) in California
Hartle et al. (2018)	USA breast milk	2018	Range 0.0042 to 0.0546 ng/g median 0.0205 ng/g		n=21
Bedi et al. (2013)	Punjab, India breast milk	2011	Mean 84.1 ± 355.4 ng/g lw median 1664.2 ng/g lw (positive samples only)	MDL 0.01 mg/L DF 5.7%	n=53
Sanghi et al. (2003)	Bhopal, India breast milk	2001–2002	Mean 230 ± /24 µg/L range 85–355 µg/L	MDL 0.01 mg/kg	n=12, mean chlorpyrifos concentrations were second highest after endosulfan
Brahmand et al. (2019)	Iran, breast milk and urine	2017	Milk: mean cpy 1.3 ± 0.6 µg/L urine: mean TCP mothers 2.1 ± 1.4 µg/L; infants 1.4 ± 0.7 µg/L		n=61
Naksen et al. (2016)	Chiang Mai Province, Thailand, breast milk	2013	Median 0.1 µg/L Range < LOD–0.46 µg/L[13]	LOD 0.22 µg/L milk	Breastfeeding mothers from agricultural area (n=33)
(Rovira et al. 2022)	Catalonia, Spain	2016–2019	Mean 0.018±0.025 µg/L milk Median < 0.013 µg/L milk Range < LOD–0.149 µg/L	LOD 0.013 µg/L DF 39%	Spanish cohort of nursing mothers Breast milk during different lactation periods n=57

TBB: total body burden, DF: detection frequency, lw: lipid weight, ww: wet weight, MDL: minimum detection limit,

87.   An Acceptable Daily Intake (ADI)/ Provisional tolerable daily intake (PTDI) was set by FAO/WHO at 0–0.001 mg/kg body weight (bw) (FAO 2020). APVMA also proposed a new ADI of 0.001 mg/kg bw/day, noting that the reliability of the proposed new acceptable daily intake is regarded as being substantially lower than usual APVMA standards (APVMA 2019). The proposed new acute reference dose is 30 µg/kg bw (APVMA 2019). A more recent review by EFSA did not establish a reference value as there were considerable uncertainties for dose-response relationship concerning neurodevelopmental effects , as well as due to remaining uncertainties regarding a genotoxicity potential (EFSA 2019).

88.   Concentrations of chlorpyrifos in the placentas of pregnant women from Argentina were reported. Thus, 85 placentas were collected at birth, from an area of intensive fruit production for the international market, in Patagonia Argentina. Total mean pesticide concentration of chlorpyrifos was 188.4 ± 365.4 ng/g lw. Pesticide levels found exceeded those reported in Europe, Asia and Africa. When the results were analyzed by residence place, significantly higher concentrations of chlorpyrifos were observed in placentas collected from mothers living in rural settings compared to urban areas. (Rodriguez et al 2023).

89.   Human biomonitoring has also detected chlorpyrifos and/or its metabolites in urine (including from pregnant women), blood (including maternal blood), human plasma and saliva. In urine, usually TCP is measured and used as a biomarker of exposure to both chlorpyrifos and chlorpyrifos-methyl. Studies have shown that the majority of urinary TCP in the general population likely arises from direct exposure to TCP from food and the environment, which is less

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[13] Detected in 73% of samples, of which it was detected but not quantified in 63%, and quantified in 10% of the samples.

toxic than chlorpyrifos, rather than from human exposure to chlorpyrifos. Thus, urinary TCP levels are not necessarily meaningful as markers of chlorpyrifos exposure (Health Canada 2016). Results and details of these studies are discussed in chapter 8.2 of document UNEP/POPS/POPRC.19/INF/11.

90.   In the EU funded project HBM4EU, TCP was measured in urine samples as a biomarker of chlorpyrifos and chlorpyrifos-methyl. Quality approved data were obtained from four countries in children (n=495) and four countries in adults (n=745). A provisional health-based guidance value of 0.02 mg/L for adults and 0.01 mg/L for children has been derived by Tarazona et al. (2022). This provisional HBM-GV for TCP relates to an intake limit that has been recently updated and reduced (EFSA 2019). Govarts et al. calculated hazard quotients (HQ) exposure values as the ratio of population level concentrations of a specific chemical at the geometric mean and the 95th percentile to the corresponding health-based guidance value. A HQ below one suggests that levels of exposure to the specific chemical in question may not be a concern at the population level. For TCP, the detection frequency in adults was 83.6% and in children 99.8%, and the HQs at geometric mean are <1 in children and adults, but in children the HQ at the 95th percentile exceeds 1 (Govarts et al. 2023). 7.3% of the children tested exceeded the guidance value of 0.01 mg/L (Tarazona et al. 2022). Further details are presented in chapter 8.2 of document UNEP/POPS/POPRC.19/INF/11.

91.   Giffin et al. (2022) studied chlorpyrifos concentrations in air in agricultural areas at a banana plantation. Chlorpyrifos concentrations in air samples collected at and around the plantation were correlated with urine samples from pregnant women working and living in the area. Air concentrations were detected in 98% of the samples with a median concentration of 0.016 $\mu g/m^3$. While noting limitations regarding sample size and correlation coefficients, the authors demonstrated for each 0.001 $\mu g/m^3$ increase of chlorpyrifos in air, a 1.5% increase was observed in the chlorpyrifos metabolite TCP in urine, thus demonstrating that women working and residing in the area of the banana plantations were exposed to airborne chlorpyrifos which further suggest that inhalation is a relevant exposure pathway.

92.   In a study by Yoshida et al. (2000), indoor air was measured after chlorpyrifos application as a termiticide for several consecutive years. Levels in the dining room ranged from 0.007 – 0.41 $\mu g/m^3$, the estimated combined daily intake of chlorpyrifos from air and rice was 3 – 4 $\mu g/d$, which is below the recommended reference dose (RrD) of 3$\mu g/kg$ bw/d, if no further uptake occurs.

93.   In the EU, the maximum residue level (MRL) for food was lowered to 0.01 mg/kg in 2020, after the non-renewal of the substance registration (Commission Regulation (EU) 2020/1085 (EC 2020)). However, MRL values are not toxicologically based threshold values. The Scientific Committee on Health, Environmental, and Emerging Risks (SCHEER) agreed with the adoption of the general drinking water standard for pesticides of 0.1 $\mu g/L$ for chlorpyrifos (SCHEER 2022).

94.   The Norwegian pesticide residues monitoring programmes in 2018–2021 detected chlorpyrifos above the EU MRL in dried beans, coriander leaves, pears, table grapes, wheat flour, oranges, parsley, and organic sesame seeds (Mattilsynet 2019, Mattilsynet 2020, Mattilsynet 2021, Mattilsynet 2022)). Pesticide residue testing in Colombia of various food produce showed one detection of chlorpyrifos in 24 samples and in 31.6% of the raw cow's milk samples (Mesa et al. 2013, Restrepo et al. 2014). In Egypt, chlorpyrifos was detected in 5 of 15 samples of buffalo milk collected from vendors in three areas of Assiut city, the concentrations exceeded the 2008 MRL of 0.1 mg/kg set by the European Commission (Shaker and Elsharkawy 2015). Further details are presented in chapter 8.2 of document UNEP/POPS/POPRC.19/INF/11.

95.   In issuing the final rule in response to a court order (https://www.regulations.gov/document/EPA-HQ-OPP-2021-0523-0001), the US EPA found that it could not "determine that there is a reasonable certainty that no harm will result from aggregate exposure to [chlorpyrifos] residues," when taking into consideration then-currently available information and then-currently registered uses of chlorpyrifos. EPA's evaluation indicated that registered uses of chlorpyrifos result in exposures exceeding the safe levels of exposure, and thus do not meet the statutory safety standard. Although risks from food exposure alone did not present risks of concern, "EPA [was] unable to conclude that risk from aggregate exposure from the use of chlorpyrifos meets the safety standard". Therefore, EPA revoked the tolerances for chlorpyrifos and is currently working to cancel associated food uses.

5.   Hazard assessment for endpoint of concern

96.   Chlorpyrifos induces irreversible inhibition of acetylcholinesterase (AChE) in the central and peripheral nervous system (World Health Organization et al. 1986, Colovic et al. 2013, Giesy 2014), and toxic effects in non-target organisms (US EPA 2006). Consequently, the Reregistration Eligibility Decision of chlorpyrifos from 2006 (US EPA 2006), as well as EFSA (2019) and a more recent Registration Review from September 2020 (US EPA 2020a) report concerns about acute and chronic risks to birds, mammals, fish, aquatic and terrestrial invertebrates. It should be noted that marine and semi-aquatic mammals such as manatees, whales, dolphins, sea otters and sea lions lack the paraoxonase 1 enzyme needed to further metabolize chlorpyrifos and other organophosphate pesticides (Meyer et al. 2018). This makes these marine mammals possibly more susceptible to toxic effects than terrestrial species for which toxicological studies are available. Also, there is evidence of developmental neurotoxicity effects in

humans due to the exposure to chlorpyrifos and occurring at doses lower than that causing 20% inhibition of AChE, see chapter 5.2.1.

5.1   Hazard assessment for the environment

5.1.1   Hazard assessment for aquatic organisms

97.   Chlorpyrifos displays high acute and chronic toxicity to aquatic organisms. According to the Globally Harmonised System of Classification and Labelling, the EU has classified chlorpyrifos in 2008 as Aquatic Acute Tox 1, with the hazard phrase "H400-very toxic to aquatic life"; and Aquatic Chronic Tox 1, with the hazard phrase "H410-very toxic to aquatic life with long lasting effects" with an M-factor of 10 000 (Annex VI of Regulation (EC) No 1272/2008), that accounts for the high toxicity to be applied to the concentration of chlorpyrifos in a mixture[14].

98.   In Spain (2017), a review of laboratory studies performed with the active ingredient chlorpyrifos according to the OECD 203 guideline for acute effects (i.e., lethality) identified rainbow trout (*Oncorhynchus mykiss)* as more sensitive than fathead minnow (*Pimephales promelas)*. Spain (2017) reports a 96 h LC_{50} (lethal concentration for 50% of the exposed animals) value of 8 µg/L for a test performed with "Dursban" (trade name of chlorpyrifos, 99.9% purity, see Table 1). When considering studies from literature not strictly following the OECD test guideline 203 but performed under similar conditions, lower 96 h LC_{50} values are reported. Accordingly, 96 h LC_{50} values ranging from 1.3 to 520 µg/L are reported in Clark et al. (1985). The authors identified the estuarine fishes *Menidia menidia, M. peninsulae, M. beryllina* and *Leuresthes tenuis* as the most sensitive species, with 96 h LC_{50} values ranging from 0.53 to 4.2 µg/L. However, there is no strict evidence in sensitivity differences between saline and/or freshwater fish species. As described in the US EPA's biological evaluation for chlorpyrifos Endangered Species Act (ESA) (US EPA 2022b) threshold concentrations were estimated using species sensitive distributions (SSDs) to calculate the 5th percentile hazardous concentration (HC05); using mortality data from acute exposures. For direct effects, the HC05 is used to estimate the threshold representing a chance of one in a million of mortality to an individual[15].

99.   US EPA 2022 reviewed data from 40 fish species and recorded LC_{50} values ranging from 0.17–7,012µg/L[16] (see table 2–3 in US EPA (2022b), where the majority of values were from 96-hour studies). *Chirostoma jordani* was the most sensitive species from a 1-day study (LC_{50}=0.17 µg/L; Dzul-Caamal et al., 2012, in US EPA (2022b)). US EPA (2022b) calculated a HC05 of 1.44 µg/L for freshwater and estuarine/marine fish together. The results supported separating the data into separate SSDs for freshwater (HC05 = 5.94 µg/L) and estuarine/marine (HC05 = 0.79 µg/L) fish. Based on data ranging from 0.53 to > 860 µg/L collected for 25 fish species, Giesy et al. (2014) used an SSD to calculate an HC05 of 0.812 µg/L.

100.   Studies looking at chronic toxicity usually expose animals to sub-lethal concentrations. However, in the case of chlorpyrifos, because of its high toxicity, lethality often remains the most sensitive endpoint recorded in chronic tests, despite the low concentrations tested in such studies. Only few studies performed in laboratory conditions similar to those of the OECD 210 guideline, i.e., focusing on sub-lethal effects and on the early life stages of the species tested, record effects at concentrations slightly lower but still in the same range as lethality. For the estuarine fish *Leuresthes tenuis*, Goodman et al. (1985) reported No observed effect concentration (NOEC) values of 0.14 and 0.3 µg/L for embryo weight and lethality respectively. Jarvinen and Tanner (1982) determined NOEC values of 1.6 and 3.2 µg/L for weight and lethality of *Pimephales promelas* fry exposed to Dursban technical grade for 32 days. The lowest NOEC estimated for chronic mortality is 0.3 µg/L. This endpoint was assessed for embryo lethality in *Leuresthes tenuis* in a 35-days exposure design (Goodman et al. 1985).

101.   A substantial quantity of data is available for aquatic exposure of amphibians to chlorpyrifos. Fryday and Thompson (2012) summarised 96-h LC_{50} values ranging from 0.80 to 14.6 mg/L for four species of amphibians at different life stages (embryos, larvae, tadpoles, or not reported). The US EPA's biological evaluation for chlorpyrifos ESA reviewed 10 studies for 8 species and the values ranged from 0.215 µg/L for the African clawed frog *Xenopus laevis* to 500 µg/L for the foothill yellow legged frog *Rana boylii*. The LOAEC of 0.215 µg/L for the African clawed frog *Xenopus laevis* was used by the US EPA to set the sublethal threshold for aquatic-phase amphibians (US EPA 2022b).

102.   Invertebrates, especially crustaceans and insects, are the most sensitive taxa to chlorpyrifos among aquatic organisms. Considering only tests performed in an OECD 202 acute test design, European Commission (2005) and

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[14] 'M-factor' means a multiplying factor. It is applied to the concentration of a substance classified as hazardous to the aquatic environment acute category 1 or chronic category 1, and is used to derive by the summation method the classification of a mixture in which the substance is present (EC 2008).

[15] The HC05 is the Hazardous Concentration at the 5th percentile. This value is derived using the Species Sensitivity Distribution (SSD). SSDs are generated by fitting a statistical or empirical distribution function to the proportion of species affected as a function of stressor concentration or dose. This is EPAs current endpoint for Biological Evaluations. For the Endangered Species Act (ESA) analysis, EPA uses a second endpoint, the "Threshold concentration".

[16] https://www.epa.gov/endangered-species/biological-evaluation-chapters-chlorpyrifos-esa-assessment.

Spain (2017) identified *Daphnia magna* as the most sensitive species with a 48-h LC_{50} of 0.1 µg/L. This endpoint is in the same range as the 96-h LC_{50} of 0.138 µg/L determined for the macroinvertebrate *Hyalella azteca* (Brown 1997a). Note that higher mortality is observed for *H. azteca* in chronic exposure design (i.e., 10-days lethal dose (LD_{50}) of 0.037 and 0.058 µg/L are reported in Brown (1997b) and Hasenbein et al. (2015), respectively). When referring to non-OECD tests with similar set ups, Giddings et al. (2014) identified *Daphnia ambigua* as the most sensitive species with an LC50 of 0.035 µg/L. Using an SSD approach, the authors calculate HC5 values of 0.034 µg/L for crustacea and 0.087 µg/L for insects, based on effective concentration (EC_{50}) values collected for 23 and 17 species, respectively, that met criteria for inclusion in the analysis. The HC5 values for invertebrates are based on EC_{50s} while fish was based on LC_{50s} which also may contribute to the difference when comparing both trophic levels.

103.   Reproductive studies following the OECD 202 test design with *Daphnia magna* found no effect on reproduction or mortality at the concentration of 0.056 µg/L. However, 100% mortality occurred within 21 days for the next tested concentration of 0.1 µg/L (Adema 1990). Similar studies performed on the marine shrimp *Mysidopsis bahia*, reported a NOEC of 0.0046 µg/L based on mortality in the parental population. Treatment related effects were apparent at 10 ng/L and above after males and females were paired on Day 14 (Sved et al. 1993).

104.   Under the EU Water Framework Directive (WFD), the European Commission has established a Technical Guidance for deriving an Environmental Quality Standards (EQS) which covers both human health and ecosystems (EC 2018). The WFD main objective is to protect European waterbodies by preventing and reducing pollution and promoting sustainable water use. In this framework, EQS are established to protect the aquatic organisms and indirectly predators feeding in the aquatic environment and human health via the drinking water and food consumption. More information on WFD and EQS is presented in chapter 9.1.1 of document UNEP/POPS/POPRC.19/INF/11.

105.   For chlorpyrifos, the long-term standard expressed as an annual average concentration (AA-EQS), based on chronic toxicity data, is compared against available monitoring data in this risk profile (see chapter 5.4). The current AA-EQS is 0.03 µg/L for freshwater and marine waters (EC 2013). The European Commission proposed to revise the current AA-EQS for chlorpyrifos to take into account the latest scientific evidence on toxicity for aquatic organisms and for humans (EC 2022) on the basis of a scientific dossier. The Scientific Committee on Health, Environmental, and Emerging Risks (SCHEER) reviewed the dossier and supported an AA-QS of 0.46 ng/L for fresh water and 0.046 ng/L in marine waters (SCHEER 2022). Another standard that is used in this risk profile for hazard assessment is the QS biota value which may be derived to protect both organisms living in aquatic systems and those feeding upon them. The lowest, most protective QS for chlorpyrifos is 1.3 µg/kg for biota (SCHEER, 2022). More details on the derivation of EQS and QS values are presented in chapter 9.1.1 of document UNEP/POPS/POPRC.19/INF/11.

5.1.2   Hazard assessment for terrestrial organisms

106.   Chlorpyrifos shows high acute toxicity to terrestrial vertebrates, especially to birds (Solomon et al. 2014). Considering the current state of science and technology, the rapporteur member state Spain proposed in the EU RAR (Spain 2017) to revise the LD_{50} of 13.3 mg/kg bw initially recorded in a peer review study (Schafer et al. 1983) on the Japanese Quail (*Coturnix coturnix*) to the LD_{50} of 39.24 mg/kg bw from a study that followed the OECD 223 guideline for the Bobwhite quail (*Colinus virginianus*). Both tests were oral studies performed with chlorpyrifos as technical grade. When tested as product, chlorpyrifos indicates a slightly higher toxicity compared with the LD50 of 39.24 mg/kg bw for the active substance endpoint for Emulsified Concentrate (EC) or Capsule Suspension (CS) formulations. Spain (2017) reports LD_{50} values of 19.92 and 17.5 mg/kg bw for *Colinus virginianus* in EC and CS formulations, respectively. High toxicity for birds is confirmed in repeated dose dietary studies. Dietary studies (i.e., 5 days feeding followed by 3 days observation) performed on the mallard duck *Anas platyrhynchos* calculated a LC_{50} of 71 mg/kg bw/d (European Commission 2005).

107.   When the substance is administered by gavage in mammals, European Commission (2005) reports acute oral LD_{50} ranging from 66 to 192 mg/kg bw in rats and from 64 to 71 mg/kg bw in mice. The lowest LD_{50} of 64 mg/kg bw was confirmed by EFSA (2011) to assess the acute toxicity of chlorpyrifos for wild mammals.

108.   Long-term and reproductive toxicity studies identified effects on the nervous system, including depression of AChE in the red blood cell (RBC) and the nervous system in mammals. EFSA (2017) sets the lowest no observed adverse effect levels (NOAELs) for adult animals at 0.1 mg/kg bw/d for an RBC AChE inhibition observed in a two-year chronic toxicity study in dogs and rats at 1 mg/kg bw/d. A significant decrease in RBC AChE was also observed at the same dose level in a two-generation reproductive toxicity study in rats, confirming the parental NOAEL of 0.1 mg/kg bw/d. In the reproductive toxicity study in rats, Spain (2017) reports an offspring NOAEL of 1 mg/kg bw/d based on decreased growth and slight but statistically significantly increased mortality of the pup. For birds, no reproductive impairment was reported in a study with the mallard duck (*Anas platyrhynchos*) at a dose level of 2.885 mg/kg bw/day (European Commission 2005). Additionally, to these classical reproductive endpoints usually recorded in OECD test designs, Eng et al. (2017) recently demonstrated that sub-lethal endpoints such as migratory activity and orientation are highly relevant to describe the risk to granivorous birds. In their paper, the authors focused on a granular formulation and reported that wild songbirds consuming 7.4 µg chlorpyrifos/g bw/d over 3 days could

suffer impaired condition, migration delays and improper migratory direction, which could lead to increased risk of mortality or loss of breeding opportunity.

109.   Chlorpyrifos is a broad-spectrum insecticide. Therefore, toxic effects on non-target arthropods, especially pollinators, exist. Chlorpyrifos is highly acutely toxic to the honeybee *Apis mellifera*. The highest toxicity is identified when the substance is administered via contact. Bell (1994) measured an acute LD_{50} of 0.068 µg/bee in a test performed with Dursban F (97.4% purity) (trade name for chlorpyrifos). For comparison, the lowest LD_{50} estimated for oral toxicity is 0.15 µg/bee (Bell 1993).

110.   In addition to acute toxicity, Spain (2017) reports recent studies on chronic toxicity of chlorpyrifos for bees and bee brood. These tests follow the recommendations of Decourtye et al. (2005) and EFSA and Panel on Plant Protection Products and their Residues (2013) to evaluate among others the chronic mortality following a 10-day exposure at very low concentrations, or the OECD test guideline 237 to assess potential lethal or sublethal effects affecting the bee brood and development. Accordingly, for chlorpyrifos technical Nöel (2015) calculated a 10 d-LC_{50} of 0.002 µg/bee/day. For bee brood development, Deslandes (2014) determined a no observed effect dose (NOED) of 0.018 µg/bee for larvae.

111.   Chlorpyrifos has been extensively tested on non-target arthropods. Laboratory tests reported in Spain (2017) indicate that chlorpyrifos is very harmful for beneficial arthropods. When exposed to fresh dry residues of an EC formulation (EF-1042) on glass plates, the 24h-lethal rate 50 (LR_{50}) of the beneficial aphid parasite *Aphidius colemani* (Hymenoptera: Braconidae) was determined to be < 1 ppm (Mead-Briggs 1997). The high acute toxicity of chlorpyrifos to Braconidae is confirmed by tests performed in a topical (i.e., contact) design (e.g., 24h-LR_{50} values of 3.21 and 3.62 ppm for *Bracon brevicornis* and *Chelonus blackburni*, respectively). Acute LR_{50} values < 1 ppm were also reported from topical applications for the beneficial aphids *Acyrthosiphon kondoi, A. pisum* (Homoptera: Aphididae) as well as for the brown lacewings *Austromicromus tasmaniae* (adults: Neuroptera: Hemerobiidae). Further acute LR_{50} values of 1 ppm or less are reported in Spain (2017) from topical applications for the damselflies *Enallagma spp.* and *Ischmura spp.* (nymph: Odonata: Coenagrionidae) and larvae of Trichopteran species *Hydropsyche* and *Chematopsyche spp.* (Trichoptera: Hydropsychidae).

112.   Among Coleoptera, the lady beetle *Coccinella undecimpunctata* was the most sensitive species tested (LR_{50}=1.9 ppm). A LR_{50} of 24 ppm is reported by Siegfried (1993) for larva of the European corn borer pest *Ostrinia nubilalis* (Lepidoptera: Crambidae).

113.   The acute toxicity of chlorpyrifos tested as EC formulation (EF 1042=Dursban 480) on the redworm *Eisenia foetida* in an artificial soil (OECD 207) delivers a 7-days LC_{50} of 313 ppm corresponding to about 137 mg/kg soil (European Commission 2005). However, additionally to acute effects, chlorpyrifos appears to have a high chronic toxicity to earthworms. In a 56 days study following the OECD 222 design (earthworm reproduction test), De Silva et al. (2009) detected effects of the technical chlorpyrifos on the reproduction of *E. foetida* at concentration around and lower than 1 mg/kg soil. Compared to the earthworms, chlorpyrifos has a higher chronic toxicity to soil macro-organisms such as collembola and mites. A test on the springtail *Folsomia candida* (Collembola) conducted with technical chlorpyrifos following an OECD 232 design reports a 28-d NOEC mortality of 0.075 mg/kg soil (Witte 2014). When looking at sub-lethal effects, the NOEC is 0.024 mg/kg soil for effects on reproduction of *Folsomia candida*.

5.2   Hazard assessment for human health

114.   Chlorpyrifos is classified as Acute Tox. 3 under UN GHS criteria, with the following hazard phrases for single dose exposure: "H301-Toxic if swallowed"; and repeat exposure: "H370-Causes damage to organs (nervous system), H372-Cause damage to organs through prolonged or repeated exposure (nervous system, adrenal gland) [17].

115.   Studies on airborne chlorpyrifos have demonstrated toxicity in laboratory animals after repeated doses. Adult male CF-1 mice were intranasally administered with chlorpyrifos (3–10 mg/kg bw/d) three days a week, for 2 weeks. Behavioral and biochemical analyses were conducted 20 and 30 days after the last intranasal chlorpyrifos administration, respectively. No significant behavioral or biochemical effects were observed in the 3 mg/kg chlorpyrifos intranasal exposure group. However, animals exposed to 10 mg/kg chlorpyrifos showed anxiogenic behavior and recognition memory impairment, with no effects on locomotor activity. In addition, the intranasal administration of 10 mg/kg chlorpyrifos altered the redox balance, modified the activity of enzymes belonging to the cholinergic and glutamatergic pathways, and affected glucose metabolism and cholesterol levels in different brain areas. Taken together, these observations suggest that these biochemical imbalances could be responsible for the neurobehavioral disturbances observed after intranasal administration of chlorpyrifos in mice (Gallegos et al. 2023). Toxicity has also been demonstrated in humans.

116.   Recently in 2022, the US EPA published a notice of intent to cancel for certain products containing chlorpyrifos stating that "chlorpyrifos has been found to inhibit an enzyme that leads to neurotoxicity, including

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[17] https://www.nite.go.jp/chem/english/ghs/m-nite-2921-88-2e.html.

potential neurodevelopmental effects in children." The 2021 US EPA tolerance revocation impacts the following uses: terrestrial food crops and greenhouse food crops, food handling establishments, and commercial livestock uses. In 2000, the chlorpyrifos registrants reached an agreement with EPA to voluntarily cancel all residential use products except those registered for containerized ant and roach baits.

117.   EFSA (2019), stated that the criteria are met for the classification of chlorpyrifos as toxic for the reproduction, Repro 1B, H360D 'May damage the unborn child' in accordance with the criteria set out in Regulation (EC) No 1272/2008 after taking into consideration the following evidence: DNT study outcome (reduction in cerebellum height – that could not be explained by the maternal AChE inhibition), the epidemiological evidence showing an association between chlorpyrifos exposure during development and neurodevelopmental outcomes, and the overall analysis of the published literature (*in vivo*, *in vitro* and human data).

118.   Mohammed et al. (2014), Buntyn et al. (2017) and Carr et al. (2017) showed that male and female rat pups treated by oral gavage with chlorpyrifos at 0.5 mg/kg/day during post-natal days (PND) 10–16 exhibited behavioral anomalies when tested on PND 25. Decreased anxiety was evident through increases in number and percent of open arm entries, time and percent time spent in open arm of a plus maze, occurrences of crawling over/under, motor activity, play-fighting and time spent playing (Mohammed et al. 2014). In a subsequent study, pups were treated by gavage on PND 10–15 with 0, 0.5, 0.75 or 1 mg/kg/day chlorpyrifos (6–8/sex/dose) (Carr et al. 2017). Forebrain AChE inhibition was noted at the highest tested dose, setting the lowest observed effect level (LOEL) for brain AChE inhibition at 1.0 mg/kg/day. Behavioral testing showed decreased times to emergence from a dark container into a novel environment at 0.5 mg/kg/day in both sexes. This behavior was associated with decreased anxiety. The data confirm earlier findings from this group showing that chlorpyrifos treatment generated behavioral effects at doses lower than those inhibiting brain AChE (1.0 mg/kg bw/day). The LOEL for decreased anxiety in PND 25 pups was 0.5 mg/kg/day.

119.   A study by Lal et al. (2022) determined that repeated oral administration of chlorpyrifos in Wistar rats at 50 mg/kg bw for 28 consecutive days showed an alteration in biochemical enzymes such as alanine transaminase (ALT), aspartate aminotransferase (AST), and serum acetylcholine (AChE) when compared to the control group. AChe levels decreased and other enzymes levels increased.

120.   According to the US EPA 'Chlorpyrifos Human Health Risk Assessment' (HHRA), hazard characterization for chlorpyrifos and its oxon is based on adverse effects in animals and humans related to AChE inhibition and potential for neurodevelopmental effects (US EPA 2020b).

121.   Severe poisoning in humans causes neurotoxic effects such as slurred speech, tremors, ataxia, convulsions, depression of respiratory and circulatory centres by cholinesterase inhibition and subsequent overstimulation of the nervous system. Coma and death may result from respiratory failure due to the combination of bronchoconstriction, bronchorrhea, central respiratory depression, and weakness/paralysis of respiratory muscles. These collective symptoms are referred to as the cholinergic syndrome or the cholinergic toxidrome (Jokanović and Kosanović 2010).

5.2.1 Developmental neurotoxicity

Animal experiments

122.   Hoberman (1998) examined the effect on developmental neurotoxicity by daily oral gavage of chlorpyrifos in pregnant rats (25/dose) during gestation and the perinatal period (GD 6–PND 11) at doses of 0, 0.3, 1, and 5 mg/kg bw/day. The study was performed according to the US EPA guideline OPPTS 870.6300 and the OECD guideline 426; with some deviations, including a shortened exposure period (gestation day 6 to lactation day 11, rather than lactation day 21), and a lower number of pups included for neuropathology, learning and memory, and behavioral ontogeny assessments. Maternal effects were observed at 5 mg/kg bw/day, with decreased body weight gain, food consumption, brain, RBC and plasma cholinesterase inhibition, and manifestation of clinical signs (fasciculations, hyperpnea and hyperactivity). The critical maternal effect was a decrease in the RBC cholinesterase at all dose levels (maternal LOAEL: 0.3 mg/kg bw/day). The offspring showed signs of toxicity at the high dose (5 mg/kg bw/day), such as decreased viability index (day 1–5), bodyweight and food consumption. Developmental landmarks were also delayed at the high dose. Unlike observations in dams, brain AChE was not altered in offspring. Developmental neurotoxicity was transiently manifested with changes in the brain weight, decreased layer thickness in brain areas (PND 12), and increased latency of the auditory startle response at PND 23. All effects were resolved in the adult period (PND 60–71). Morphometric measurements for nine brain regions in PND 12 pups revealed statistically reduced cerebellar dimensions in high dose males, with male brain weights 11.5% lower than concurrent controls. A chlorpyrifos-mediated impact on cerebellar growth in these males was considered possible. Similar morphometric measurements were conducted in PND 66–71 adults, revealing statistically reduced parietal cortex dimensions in females dosed with 1 and 5 mg/kg (4% and 5%, respectively; p < 0.05). A developmental LOEL of 1 mg/kg/day was suggested based on reduced parietal cortex and hippocampal dimensions in PND 66-71 (Hoberman, 1998). Morphometric observations were not made at 0.3 mg/kg/day; consequently, a discrete NOEL could not be determined (EFSA 2019).

123.   The developmental neurotoxicity study (Hoberman 1998) was re-evaluated by Mie et al. (2018) based on the full study report, including the raw data. Mie et al. (2018) expressed each brain regional measurement relative to brain weight in order to demonstrate the absence of a sensitive target region. Based on the re-analysis of the raw data, it was found that low- and mid-dose effects (decreased cerebellum height in PND 11 pups) were statistically significant, and consistent in both sexes. The absence of a statistically significant effect in cerebellum height in the high dose group, was attributed to a significant decrease in brain weight (observed at the high-dose only). Therefore, it was concluded by the authors that indications of developmental neurotoxicity were observed at all dose levels tested in the study.

124.   The re-evaluation of the study by Mie et al. (2018) was considered by EFSA's statement on human health assessment of chlorpyrifos. In the statement it was mentioned that the decrease in cerebellum height corrected by brain weight was considered an adverse effect indicating a damage of the developing brain. The structural changes in the developing rat brain found in regulatory studies are consistent with human data (EFSA 2019).

In vitro **studies**

125.   Through an international collaboration, a battery of *in vitro* assays has been developed to evaluate critical processes of neurodevelopment. In 2020, US EPA presented data from the battery for organophosphates (OPs) (including chlorpyrifos) as a case study. This included data from a microelectrode array-based network formation assay (MEA NFA) and high-content imaging (HCI) assays of neural cells for processes, such as proliferation, apoptosis, and synaptogenesis. The data obtained demonstrate that chlorpyrifos was active in the assays. Moreover, *in vitro* to *in vivo* extrapolation (IVIVE) approaches using high-throughput toxicokinetic (HTTK) models were utilized to approximate new approach methodology (NAM)-derived administered equivalent doses (AEDs). The comparison demonstrate that NAM-derived AEDs were greater than or in some cases approximated doses that inhibit AChE (US EPA 2020c).

126.   More recent studies have determined that neurotoxicity occurs in both humans and laboratory animals. Studies conducted in India to help determine the acute effects of chlorpyrifos within farmers and allied agricultural workers resulted in adverse effects such as acute cholinergic crisis, respiratory failure, acute renal failure, and seizures, which indicates the potential effects and mode of action (Acharya and Panda 2022). Using an *in vitro* model, blood-brain barrier cells (HCMEC/D3) were exposed to concentrations of 10 micromolar (μM) and 30 μM of chlorpyrifos, Deepika et al. (2022) observed that chlorpyrifos has the highest potential to compromise the blood-brain barrier compared to other pesticides i.e., permethrin and cyfluthrin.

127.   A report by Masjosthusmann et al. (2018) concluded that developmental neurotoxicity *in vitro* test battery results of chlorpyrifos and its metabolite, chlorpyrifos oxon, mirror the broad effect spectrum observed in *in vivo* studies. Chlorpyrifos was active in the neural progenitor cells NPC/UKN assays and has altered rNNF and UKN2 without affecting NPC5. This supports the assumption that multiple, yet unknown modes of action (MOA) drive neurodevelopmental toxicity of OPs. Several *in vitro* studies have observed effects of chlorpyrifos and chlorpyrifos-oxon on neuronal growth in tissue culture, including decreased axonal length and inhibition of neurite outgrowth (Eaton et al. 2008).

128.   Based on the weight of evidence from animal studies and *in vitro* mechanistic studies it could be concluded that many of the neurodevelopmental effects of chlorpyrifos are secondary to inhibition of AChE in target tissues. In addition, available *in vitro* studies suggest that alternative mechanisms are active. At present, many challenges still exist with respect to *in vitro* to *in vivo* extrapolation (IVIVE) in the context of developmental neurotoxicity, including consideration of internal dosimetry at various life-stages, and physiological changes during pregnancy and lactation, which present difficulties with establishing dose concordance between effects in *in vitro* and in *vivo studies*.

Human studies

129.   Epidemiological evidence suggesting associations between chlorpyrifos exposure during neurodevelopment and adverse health effects is derived from three cohort studies conducted by the Columbia Center for Children's Environmental Health (CCCEH), the Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS) and Mt Sinai Children's Environmental Health Centre. These studies were considered the most robust available epidemiological evidence by several Agencies (US EPA, 2020, CalEPA 2018, EFSA 2019).

130.   In 2011, the Columbia Center for Children's Environmental Health (CCCEH) published the results of a study examining the potential association between foetal cord blood levels of chlorpyrifos and neurodevelopmental outcomes (Rauh et al. 2011). A cohort of 535 pregnant non-smoking women (aged 18-35) were enrolled in the study. The study started in 1997 to evaluate effects of prenatal exposure to ambient and indoor pollutants on birth outcomes, neurocognitive development, and procarcinogenic damage among mothers and newborns from minority communities in New York City. The authors also performed magnetic resonance imaging studies on 40 cohort children (5.9–11.2 years old) to see if chlorpyrifos exposure *in utero* affected brain morphology (Rauh et al. 2012). Numerous morphological differences were reported in the children in the high chlorpyrifos exposure group, including enlarged superior temporal lobe, posterior middle temporal lobe, and inferior postcentral gyri bilaterally, as well as enlarged superior frontal gyrus, gyrus rectus, cuneus, and praecuneus along the mesial wall of the right hemisphere. These children also showed frontal and parietal cortical thinning and an inverse dose–response relationship between

chlorpyrifos in cord blood and cortical thickness. The CCCEH cohort study was initiated while chlorpyrifos was allowed for indoor use; note that all indoor uses of chlorpyrifos were voluntarily cancelled by the end of 2001 (US EPA 2001), resulting in a difference in exposure before and after the removal from the marketplace.

131.   Rauh et al. (2015) conducted a follow-up study to assess children from the same cohort at 11 years of age. A total of 271 children were assessed for neurological development and motor function. In the set of children exposed to chlorpyrifos there was significant association to tremor in the dominant arm (p=0.015), tremor in either arm (p=0.028), tremor in both arms (p=0.027), and marginal association with tremor in non-dominant arm (p=0.055).

132.   The US EPA concluded that the 3 US cohort studies (CCCEH, CHAMACOS, and Mt. Sinai) provide the most robust available epidemiological evidence (US EPA 2016). However, several limitations and uncertainties associated with the epidemiological studies have been identified as part of Scientific Advisory Panel reviews (FIFRA SAP, 2012; FIFRA SAP, 2016), particularly with respect to the exposure measures.

133.   In 2020 US EPA revised the human health risk assessment of chlorpyrifos in which the toxicological points of departure (PODs) are derived from 10% RBC AChE inhibition, using a physiologically-based pharmacokinetic pharmacodynamic (PBPK-PD) model. The US EPA stated that these PODs are protective for neurotoxic effects related to AChE inhibition and potential downstream neurotoxic effects. This assessment relied on the previous documents developed for chlorpyrifos (US EPA 2014), an updated drinking water assessment, and animal toxicity literature review. Five new laboratory animal studies were reviewed, and it was concluded that while one study (Carr et al. 2017) provides strong support for the conclusion that effects on the developing brain may occur below a dose eliciting 10% AChE inhibition, it was not robust enough for deriving a POD (US EPA 2020b). US EPA concluded, that despite several years of study, peer review, and public process, the science addressing neurodevelopmental effects remains unresolved (US EPA 2020a) and there continues to be uncertainty in the human dose-response relationship for neurodevelopmental effects from chlorpyrifos exposure.

134.   US EPA (2016) and CalEPA (2019) reviewed additional epidemiological studies that despite differences in study location and design support the association of adverse neurodevelopmental outcome with Chlorpyrifos or OP exposure (Bouchard et al., 2010; Fortenberry et al., 2014; Furlong et al., 2014; Shelton et al., 2014; Zhang et al., 2014, Fluegge et al. 2016, Wickerham et al. 2012, Silver et al. 2016, 2017, 2018. In July 2018, California EPA published their "Final Toxic Air Contaminant Evaluation of Chlorpyrifos" CalEPA concluded that results from the CCCEH cohort study (along with two further cohort studies on OPs within indoor environments by the Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS) and Mt. Sinai (see UNEP/POPS/POPRC.19/INF/11, chapter 9.2.2) have showed associations of indoor and outdoor exposure to chlorpyrifos during pregnancy with adverse neurodevelopmental outcomes in children, including changes in brain morphology, delays in cognitive and motor functions, and problems with attention, and tremors. While EPA decided not to use the low-dose animal studies to derive a POD, California's Department of Pesticide Regulation (CDPR) derived a POD based on a review of low-dose animal model studies published in 2015-2018 (CalEPA 2018).

135.   In July 2019, EFSA published a statement based on a peer review of health impacts for chlorpyrifos (EFSA 2019). The epidemiological evidence was discussed as showing associations between chlorpyrifos exposure and adverse effects for neurodevelopment. The three US cohort studies (CCCEH, CHAMACOS, and Mt. Sinai studies) were also considered within the review. EFSA concluded that using different biomarkers of exposure, the studies show that prenatal exposure to organophosphates (OPs) produces a consistent pattern of early cognitive and behavioral deficits. The experts also discussed other epidemiological evidence from the public literature and considered that the results from some of these studies (mainly from CCCEH study, (Engel et al. 2011, Rauh et al. 2012, Silver et al. 2017) contribute to the evidence of developmental neurotoxicity effects in humans due to the exposure to chlorpyrifos and occurring at doses lower than that causing 20% inhibition of AChE. EFSA also identified uncertainty regarding concerns about possible genotoxic potential effects. EFSA concluded that because of the "unclear genotoxic potential", as well as neurodevelopment effects, supported by the epidemiological data indicating effects in children, toxicology reference values could not be set for chlorpyrifos.

5.3   Conclusions on hazard assessment

136.   Chlorpyrifos is a known, potent *in vivo* inhibitor of acetylcholinesterase. Laboratory studies clearly demonstrate that chlorpyrifos is highly toxic to aquatic communities with acute adverse effect concentrations from 0.812 to 1.44 µg/L (HC$_5$-LC$_{50}$) for fish and lower values for aquatic invertebrates with HC5 values of 0.034 µg/L for crustacea and 0.087 µg/L for insects, based on EC$_{50}$ values. In chronic laboratory studies, adverse effect concentrations are lower than the acute effect concentrations, the lowest value being a NOEC of 4.6 ng/L for the shrimp *Mysidopsis bahia*. The lowest NOEC for fish is 0.3 µg/L.

137.   Chlorpyrifos also shows high acute toxicity to terrestrial vertebrates, especially to birds, with an LD$_{50}$ value of 39.24 mg/kg bw for Japanese quail. For mammals, LD$_{50}$ values from 64 to 71 mg/kg bw in mice are reported. Values for chronic toxicity are considerably lower, with e.g., a NOAEL of 0.1 mg/kg bw/day observed in a 2-year dietary study in rats.

138.   In rats and mice, effects on the developing nervous system include altered cognition, motor control, and behavior. These studies, along with epidemiological analyses, suggest that chlorpyrifos has the potential to affect the developing nervous system. The structural changes in the developing rat brain found in regulatory studies at a very low dose are consistent with human data.

139.   Human cohort studies evaluated pre- and post-natal exposure to chlorpyrifos in mother-infant pairs and birth and developmental outcomes in neonates, infants, and children. The results suggest an association of exposure to chlorpyrifos during pregnancy with adverse neurodevelopmental outcomes in children, including changes in brain morphology, delays in cognitive and motor functions, problems with attention, and tremors.

140.   US EPA concluded that, while there are data that indicate an association between chlorpyrifos and neurodevelopmental outcomes, there remains uncertainty in the dose-response relationship and the levels at which these outcomes occur. EFSA concluded that no reference values could be set, and thus no risk assessment conducted, due to uncertainties relating to genotoxicity potential, neurotoxic effects noted in the DNT study (observed at the lowest dose tested), and findings in epidemiological studies. EFSA identified this as a critical area of concern (EFSA 2019).

5.4   Comparison of exposure levels and effect data

5.4.1   Near point sources and source regions

141.   Chlorpyrifos has been found in breast milk sampled from women, as well as in placenta, in various parts of the world, both in agricultural and non-agricultural areas. Chlorpyrifos and/or its metabolites have been detected in urine, blood, human plasma and saliva, including from pregnant women. The EU-funded project HBM-4EU, which collected data on 495 children in four countries, with a detection frequency of 99.8%, has concluded that exposure in 7.3% of children tested exceeded a provisional health-based limit value of 0.01 mg/L for TCP (Govarts et al. 2023). While levels of metabolites might not always be correlated with chlorpyrifos exposure, these findings give reason for concern, considering the neurodevelopmental effects in children associated with exposure during pregnancy. The conclusions by the US EPA on uncertainty in the dose-response relationship for neurodevelopmental effects and by EFSA that no reference value could be set for such effects represent additional areas of concern. A recent US EPA evaluation indicated that currently registered uses of chlorpyrifos result in aggregate exposures exceeding the safe levels of exposure.

142.   The use of chlorpyrifos as a termiticide in and under residential buildings has been banned in several countries but is still common practice in many others. The extended persistence at high application rates (see chapter 3.1.2) leading to stable levels of chlorpyrifos in indoor air for several years (Yoshida et al., 2000), in combination with the possibility of neurodevelopmental effects in newborns and children at levels below 10% AChE inhibition, is a concern.

143.   When considering source areas, concentrations of chlorpyrifos in the environment higher than the current EU AA-EQS value (0.03 µg/L) have been measured in surface water, for example, in Canada, New Zealand and Europe, acknowledging that the comparison is made between single measurements and a limit value for annual averages (see UNEP/POPS/POPRC.19/INF/11, chapter 8.1).

5.4.2   Remote regions

144.   Concentrations of chlorpyrifos measured in biota in remote regions are compared to the quality standard (QS) in biota (see 5.1.1). In addition to the limitations to the monitoring data mentioned in 4.2.1, the monitoring results from tissue subtypes or environmental compartments are different to those specified for the QS value for biota; and single data points (e.g., maximum concentrations) are used for comparisons. While the average chlorpyrifos concentrations in fish and ringed seal blubber are below the QS biota value, the highest concentrations measured in some of the monitoring studies exceed the QS biota value. Average chlorpyrifos levels in polar cod (muscle) (3.8 ± 2.4 ng/g ww) in a fjord of NE Greenland and maximum levels in ocean polar cod (muscle) (max 3.8 ng/g ww) exceeded the QS whole body biota value, with the average levels in the ocean polar cod (muscle) being close to the limit value (0.9 ± 0.7 ng/g ww). With regards to the monitoring data for fish and ringed seal from the Canadian Arctic/sub-Arctic generated by ongoing projects of the Northern Contaminants Program, the highest concentrations measured in some of the samples of burbot liver, lake trout muscle and lake whitefish muscle, as well as in the ringed seal blubber samples, exceed the QS biota value (see table 3). The geometric mean concentrations for all fish and the ringed seal blubber are below the QS biota value.

145.   The concentrations of chlorpyrifos measured in lakes and marine water in remote regions are generally below the current annual average EQS (AA-EQS) value of 0.03 µg/L in the EU (Directive 2013/39/EC). Some detections in seawater and in fresh water exceed the revised annual average Environmental Quality Standards (AA-EQS) value of 0.46 ng/L for fresh water and 0.046 ng/L for marine water, which are proposed as updated AA-EQS values in the EU (SCHEER 2022) based on the latest scientific and technical knowledge (EC, 2022) (see UNEP/POPS/POPRC.19/INF/11, Table 12, Chernyak et al. (1996) and Zhong et al. (2012a)). Of the seven pesticides measured in glacial meltwater, only chlorpyrifos was found in concentrations that may indicate concern as indicated

by exceedance of the toxicity exposure ratio for aquatic invertebrates representing the most sensitive species (Rizzi et al., 2019).

6.   Synthesis of information

146.   Chlorpyrifos is considered sufficiently persistent in some environments to justify its consideration within the scope of the Convention, and it shows moderate bioaccumulation in aquatic and air-breathing organisms. In combination with high toxicity, even moderate bioaccumulation can lead to body burdens that elicit adverse effects. Though long-range transport is not predicted by modelling results using OECD Pov and LRTP Screening Tool, chlorpyrifos has been found far away from known sources in various abiotic and biotic compartments. This indicates that long-range environmental transport occurs.

147.   The concentrations of chlorpyrifos measured in lakes and marine water in remote regions are generally below the current annual average EQS (AA-EQS) value of 0.03 µg/L in the EU (Directive 2013/39/EC) although it has been found in lake water in the Antarctica (Bhardwaj et al. 2019). Some detections in seawater and in glacial meltwater in the Alps exceed the revised value of 0.46 ng/L for freshwater and 0.046 ng/L for marine water, (SCHEER 2022), based on the latest scientific knowledge. When considering source areas, concentrations of chlorpyrifos higher than the current and proposed EU AA-EQS value have regularly been measured in surface water.

148.   Although the levels of chlorpyrifos measured in biota in remote regions are relatively low, concentrations measured in some lake whitefish in the Canadian Arctic and in polar cod in northeast Greenland would exceed the proposed QS biota value of 1.3 µg/kg. Such value is established in the EU to protect wildlife from exposure via the food chain and human health from adverse effects resulting from the consumption of chemical-contaminated fishery food.

149.   *In vivo* animal studies provide evidence of developmental neurotoxicity at doses below those causing cholinesterase inhibition. Effects on the developing nervous system include altered brain morphology, cognition, motor control, and behavior in rats and mice.

150.   Epidemiological evidence suggests an association of exposure to chlorpyrifos during pregnancy with adverse neurodevelopmental outcomes in children, including changes in brain morphology, delays in cognitive and motor functions, problems with attention, and tremors. These findings, consistent with those of the animal studies, suggest that chlorpyrifos has the potential to affect the developing nervous system. The exposure of newborns and children in households where chlorpyrifos was used as a termiticide at high application rates is a concern.

151.   US EPA concluded that there is uncertainty in the human dose-response relationship for neurodevelopmental effects from chlorpyrifos exposure and that registered uses lead to exceedance of safe levels of aggregated exposure. EFSA in their latest evaluation concluded that toxicology reference levels could not be set for chlorpyrifos for human health risk assessment. Both EFSA and US EPA have identified risks of concern for human health from exposure to chlorpyrifos. The EU funded human biomonitoring project HBM4EU recently concluded that exposure levels of TCP in 7.3% of nearly 500 children tested exceeded a health-based guidance value specifically set for the project.

7.   Concluding statement

152.   Chlorpyrifos production and use declined in some regions such as Europe or North America following regulatory measures such as bans or restrictions but has still a wide application range in many countries worldwide, including in residential applications.

153.   Chlorpyrifos can be persistent in marine water, in some soils and in deeper sediment layers. Monitoring data from the Arctic and Antarctic demonstrate that chlorpyrifos can be transported over long distances to remote regions. Since degradation of chlorpyrifos is temperature dependent, it is expected to persist in these regions for a considerable length of time. In addition, chlorpyrifos is found in dated sediment cores in Arctic and sub-Arctic lakes. In conclusion, chlorpyrifos is considered sufficiently persistent in some environments to justify its consideration within the scope of the Convention.

154.   Chlorpyrifos shows moderate bioconcentration, which, in combination with high toxicity, may lead to body concentrations that elicit adverse effects, thus may be of concern.

155.   Chlorpyrifos has been detected frequently in various abiotic compartments of remote areas in the Arctic and Antarctic, as well as in in apex predators of the Arctic including polar bears, demonstrating its ability to undergo long-range transboundary transport. Potential routes of transport include atmospheric transport in the gas or particulate phase and transport via water in rivers and/ or ocean currents.

156.   Chlorpyrifos is a known, potent *in vivo* inhibitor of acetylcholinesterase. Laboratory studies clearly demonstrate that chlorpyrifos is highly toxic to both aquatic organisms as well as terrestrial vertebrates. *In vivo* animal studies provide evidence of developmental neurotoxicity at doses below those causing cholinesterase inhibition. Epidemiological evidence suggests an association of exposure to chlorpyrifos during pregnancy with adverse

neurodevelopmental outcomes in children, including changes in brain morphology, delays in cognitive and motor functions, problems with attention, and tremors. These findings, consistent with those of the animal studies, suggest that chlorpyrifos has the potential to affect the developing nervous system.

157.   While the concentrations of chlorpyrifos measured in biota in remote areas are generally below adverse effect levels for chronic toxicity found in laboratory aquatic and terrestrial species, it should be noted that levels of chlorpyrifos in fish and ringed seal blubber in remote regions (see table 3) have been measured at levels that exceed EU environmental quality standards to protect wildlife. Likewise, the concentrations of chlorpyrifos measured in lakes and marine water in remote regions are generally low, but some detections in sea water and in glacial fresh water exceed the revised annual average Environmental Quality Standard of the EU to protect freshwater and marine aquatic wildlife. Chlorpyrifos was found in glacial meltwater in concentrations that may indicate concern as indicated by exceedance of the toxicity exposure ratio for aquatic invertebrates representing the most sensitive species.

158.   POP substances have the potential to contaminate remote areas that should be protected from further contamination by hazardous substances resulting from human activity, because of the intrinsic value of pristine environments. These specific concerns occur particularly with substances that can be shown to persist for long periods and to bioaccumulate in biota and which can give rise to toxic effects after a longer time and over a greater spatial scale than substances without these properties. These effects may be difficult to detect at an early stage because of long-term exposures at normally low concentration levels, and long life cycles of species. Thus, concentrations of chlorpyrifos in biota from the Arctic and Antarctica and in humans indicate a potential for adverse effects in wildlife and in humans.

159.   Based on evidence of its persistence, potential for bioaccumulation, toxicity to aquatic organisms and terrestrial animals (including humans) and the widespread occurrence in environmental compartments including remote regions, it is concluded that chlorpyrifos is likely, as a result of long-range environmental transport, to lead to significant adverse human health and/or environmental effects such that global action is warranted.

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