Chlorpyrifos

Draft risk profile

February 2023

Table of contents

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.

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 or 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 these 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. Fish BCF above 5000 are observed in early life stages. In combination with high toxicity, even moderate bioaccumulation may lead to body concentrations that elicits adverse effects, thus may be a serious concern.

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. Chlorpyrifos is classified as Acutely Toxic, Category 3 under the criteria for the United Nations Globally Harmonised System (UN GHS), 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), H373: May cause damage to organs through prolonged or repeated exposure (eye)”. It induces irreversible inhibition of acetylcholinesterase in the central and peripheral nervous system. Epidemiological analyses, in combination with animal toxicity studies, 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.

8. Chlorpyrifos is highly toxic to aquatic communities, especially for aquatic invertebrates and early life stages of fish. Chlorpyrifos also shows high acute toxicity to terrestrial vertebrates, especially to birds, and mammals.

9. Although the concentrations of chlorpyrifos measured in the remote environment are generally below adverse effect levels found in laboratory studies for aquatic organisms and terrestrial vertebrates, i*n vivo* animal studies provide evidence of developmental neurotoxicity at doses below those causing cholinesterase inhibition. Effects on the developing nervous system include altered cognition, motor control, and behaviour in rats and mice. These studies, along with epidemiological evidence, suggest that chlorpyrifos has the potential to affect the developing nervous system at low doses. The European Food Safety Authority (EFSA) in their latest evaluation concluded that reference values could not be set for chlorpyrifos for human health risk assessment. The United States Environment Protection Agency (US EPA) found “it could not determine that there is a reasonable certainty of no harm from aggregate exposure to chlorpyrifos — including food, drinking water, and residential exposure — based on available data and considering its registered uses. EPA’s evaluation indicated that registered uses of chlorpyrifos result in exposures exceeding the safe levels of exposure, and thus have the potential to result in adverse effects." (EPA press

release from 25 February, 2022[1]) Therefore, concentrations found in biota in remote regions, as well as in human biomonitoring studies are of concern and should be reduced because of high uncertainties to attain an acceptable risk.

10. 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, it is concluded that chlorpyrifos is likely, as a result of its long-range environmental transport, to lead to significant adverse human health effects such that global action is warranted.

[1] https://www.epa.gov/newsreleases/epa-takes-next-step-keep-chlorpyrifos-out-food-protecting-farmworkers-and-childrens

1. Introduction

1.1 Chemical identity

11. Chorpyrifos is an organophosphorous pesticide. Figure 1 and Table 1 provide details of the chemical structure and identity for chlorpyrifos.

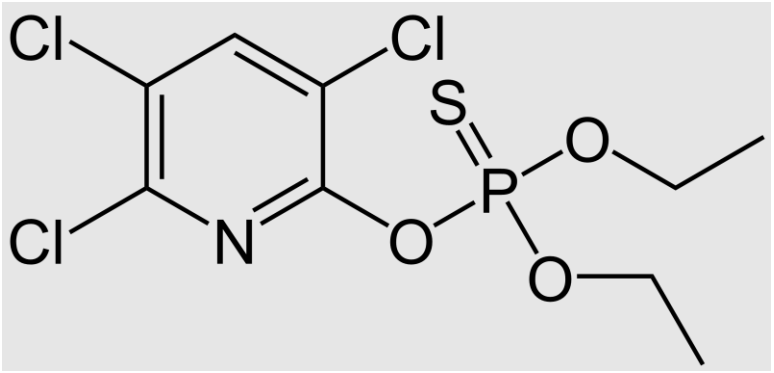

Figure 1. Structural formula of chlorpyrifos (Credit: Andreas Buser, Switzerland.)

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

12. Table 2 reports the main physicochemical properties of chlorpyrifos, additional information can be found in Table 1 in INF-document. The vapour pressure value indicates that it can volatilise. 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	European Commission (2005) WHO (2009) Mackay et al., (2014) WHO (2009) WHO (2009)

Property	Value	Source
	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, as cited in 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)
Organic carbon/water partition coefficient (K_{OC})	Commerce loam 7300 Tracy sandy loam 5860 Catlin silt loam 4960 8,500	US EPA's biological evaluation for ESA (Appendix 3-1) Mackay et al., (2014)

Transformation products

13. 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 and TMP are not exclusive to chlorpyrifos but are also formed from chlorpyrifos-methyl and triclopyr (Health Canada, 2016). For information on chemical identity, physico-chemical properties and environmental hazard information please see paragraphs 1-3 of document INF-document.

1.2 Conclusion of the POPRC regarding Annex D information

14. 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.

15. The POPs Review Committee 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 Commitee 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

16. 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

17. 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 Turkey (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 (with exemptions), 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, 2020; US EPA, 2022). In the European Union 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). In India chlorpyrifos has been registered under the Insecticides Act of 1968 since 1977. All identified information on national-level regulations can be found in Table 2 in INF-document .

2. Summary information relevant to the risk profile

2.1 Sources

2.1.1 Production, trade, stockpiles

18. 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 for example, in the presence of sodium carbonate (ATSDR, 1997).

19. 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 organophosphorus pesticides in China, chlorpyrifos has become one of the most dominant insecticides used in the country (Chen et al., 2012). While the use of chlorpyrifos on vegetables in China was banned in 2016, it is noted that under the China Pesticide Information Network, that there are still presently 1,127 registered chlorpyrifos based products for other applications, second only to avermectin (1,651) and imidacloprid (1,362) (AgNews, 2020).

20. It is understood that 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. 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 export value were chlorpyrifos 97% TC, chlorpyrifos 40% EC (Emulsified Concentrate) and chlorpyrifos 95% TC.

21. 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 (for example, 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.

22. 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 (product/active) in 2020–2021.

23. The non-renewal of chlorpyrifos authorisation 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.

24. As presented in European Commission (2017), according to the Food and Agriculture Organisation 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 Turkey), Near East (Lebanon), Africa (Burundi, Malawi, Madagascar and Senegal), Latin America and the Caribbean (Ecuador) and Asia (Thailand, Bangladesh, Myanmar and Malaysia). The total volume of import into these markets in 2015 was estimated to be ~7,000 tonnes (European Commission, 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, Turkey import quantities followed a clear trend to increase 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 production showed an increase from 2009 (1,467 tonnes) to 2014, when it reached a peak of 12,989 tonnes. As of 2014, the 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 chlorpyrifos and from 2,449 to 16,452 tonnes used domestically over the considered period. (Agrochemical Marketing Reports available at (ibama.gov.br)).

2.1.2 Uses

25. Chlorpyrifos is a broad-spectrum chlorinated organophosphate insecticide and has been used for pest control on various crops as well as lawns and ornamental plants (John & Shaike, 2015). Pesticide products containing chlorpyrifos are registered for use on many agricultural crops, including corn, soybeans, alfalfa, oranges, apples, bananas, wheat, and walnuts (US EPA, 2020a; Foong et al, 2020). 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).

26. In the USA, for the period 1987–1998, it was estimated that, of the ~9500 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.[2]

27. 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 authorised as a plant protection product (Sweden, 2022; Norway 2022). In January 2020, the European Commission adopted implementing Regulation EU 2020/18,[3] meaning that the European Union (EU) Member States must withdraw all authorisations 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.

28. 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 INF-document.[4]

29. 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 their vectors.[5]

[2] https://www.epa.gov/ingredients-used-pesticide-products/chlorpyrifos.

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

[4] 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).

[5] 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).

30. The use of chlorpyrifos as a termiticide was phased-out in the USA in 2000. Although several other countries also have phased out the use of chlorpyrifos in termite control, it is still used as a termiticide in India (India, 2020), as stated above, and Australia, as well as in a number of African states such as Zambia and Zimbabwe (Rother, 2020). However, in Australia a review is currently underway, on the basis of concerns related to toxicology, work health and safety, chemistry, residues and environment (Australia, 2019).

31. In China the total domestic consumption of the substance applied on several crops (mainly rice, vegetables, fruits and cotton) in 2017 was reportedly ~18,000 tonnes (CCPIA, 2022). However, chlorpyrifos was prohibited for use on vegetables in China from December 2016 (CCPIA, 2022).

2.1.3 Releases and emissions to the environment

32. Upon its application as a pesticide, chlorpyrifos is directly released to the environment and can be further distributed by several potential pathways. It either adheres to the soil particles or sediment, leaches 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 volatilisation (Nandhini et al., 2021; Das et al., 2020).

33. Only limited data exists to capture potential emissions to environment during production. ATSDR (1997) 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.

34. 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). 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 dataset review, chlorpyrifos emissions values above zero were reported in nine countries;[6] however, only one country reported the pollutant's release from agricultural activities, while three countries reported the pollutant's release from riverine load.

35. 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.

3. Environmental fate

3.1 Persistence

36. 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 in INF-document, together with more detailed information.

37. Various studies examining the route of degradation have been assessed in the European 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 and mobile and is eventually degraded to CO_2 and to non-extractable residues.

3.1.1 Environmental distribution and abiotic degradation

38. Vapour pressure and Henry's Law constant (for values see Table 1) indicate that chlorpyrifos is volatile. Volatilisation plays a role in the overall dissipation process in the field. In the US, 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).

39. In summary, chlorpyrifos photolytical degradation 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

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

generally longer (16–210 d) and at pH >9 shorter (0.1–10 d). High losses due to volatilisation as reported by some studies are also noteworthy. Detailed information on abiotic degradation can be found in INF-document.

40. The European Union Risk Assessment Report – EU RAR (Spain, 2017) lists seven studies on soil leaching behaviour (column leaching studies) (Reeves & O'Connor, 1994a, 1994b; Pike and Getzin, 1981; Racke, 1993; Somasundram et al., 1991; 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, The results all show that chlorpyrifos is strongly bound to soil. Chlorpyrifos is expected to be immobile to slightly mobile in soils as indicated by K_{OC} values ranging from 2,785–31,000 (Health Canada Pest Management Regulatory Agency Proposed Re-Evaluation Decision (PRVD2019-05)).

3.1.3 Biotic degradation

41. No reliable degradation half lives in **water** could be secured, since in all of the studies that were reviewed, volatilisation contributed considerably to dissipation. In aquatic systems, the primary routes of dissipation of chlorpyrifos from the water phase is volatilisation and partitioning to the sediment (10–52%) (Australia, 2022). Where the remaining chlorpyrifos in the test system permits the estimation, a degradation half-life (DT50) of 75 d at 8°C was calculated, showing that chlorpyrifos can be considered persistent in open sea water, at 8°C (Swales, 2003).

42. 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, 2017b) and PMFAI, 2022.

43. According to the European draft renewal assessment report (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.

44. 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 (up to 40% of the applied test substance). TCP is weakly bound to soil and highly mobile (K_{OC} 27–389), with increasing mobility as the pH increases. Degradation decreases in soils with low water contents, and in experiments at lower temperatures.

45. 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, 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 INF-document.

46. Half-lives reported for chlorpyrifos degradation in **aerobic 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.

47. 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 (Dabrowski et al., 2002; Gebremariam et al., 2012; Readman et al., 1992). 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 (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, 1997). This process can contribute to persistency and may transport considerable amounts of chlorpyrifos from water to particulate matter such as suspended sediment. Such mechanisms can explain the many findings of chlorpyrifos in groundwater and surface water (see INF-document).

48. 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 (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). Since degradation of chlorpyrifos is temperature dependent, 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 can be considered persistent in some environments.

3.2 Bioaccumulation

49. For chlorpyrifos, experimental and estimated log K_{OW} values between 4.7 and 5.2 have been reported, indicating potential bioaccumulation in aquatic. 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. For an overview of all bioconcentration studies assessed for this dossier, please see INF-document, Table 10.

50. 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 some species in early life stages (for example El-Amrani et al. (2012): BCF of 5011 in eluthero embryos of zebrafish (*Danio rerio*)).

51. 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 (please see INF-document). Balmer et al. (2019) further illustrated 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.

52. 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

53. Chlorpyrifos has been detected in many different environmental matrices in remote regions; in Arctic air, snow, lake sediment, fresh water, sea water, marine fog and ice, as well as in ice-cores (Balmer et al., 2019; Bigot et al., 2017; Chernyak et al., 1996; Garbarino et al., 2002; Hermanson et al., 2005; Hermanson et al., 2020; Hermanson et al., 2021; Hung et al., 2013; Jantunen et al., 2007, as cited in Hoferkamp et al., 2010; Jantunen et al., 2015; Landers, 2008; Muir et al., 2004; Pućko et al., 2015; Pućko et al., 2017; Rice & Chernyak, 1997; Ruggirello et al., 2010; Zhong et al., 2012), in Antartic air, ice and sea-ice meltwater (Bigot et al., 2017; Hermanson et al., 2021), 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, 2020b). The results of these monitoring studies, which have been published in scientific literature, are summarized in chapter 3.4 Exposure.

54. Chlorpyrifos is also widely detected in remote areas far away from point sources and without any agricultural use, in various biotic compartments such as in caribou, seals and polar bears in the Arctic (see chapter 3.4 on exposure). Potential routes of transport include atmospheric transport in the gas or particulate phase, and transport via water in rivers and/or ocean currents.

55. 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 is shown in Figure 1 of the INF-document. The figure illustrates that chlorpyrifos is widely detected in remote areas.

56. Particulate chlorpyrifos is more recalcitrant to atmospheric degradation and has been detected in several studies. However, the available data indicate that its percentage is low.

57. Based on physico-chemical properties and modelling results, transport in the water phase is expected to be relevant for chlorpyrifos. In the water compartment, chlorpyrifos will sorb preferentially to suspended solids (see 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 also occurs via water.

58. Though long-range transport is not predicted by modelling results using OECD Pov and LRTP Screening Tool, (see INF-document), the compound has been found far away from point sources in various abiotic and biotic compartments. This indicates that long-range environmental transport occurs.

3.4 Exposure

3.4.1 Abiotic matrices

59. Chlorpyrifos has been detected globally, in all continents and in all compartments, including air, freshwater, saltwater, 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 the INF-document.

60. In the Arctic, chlorpyrifos has been measured in air, snow, lake sediment, fresh water, sea water, marine fog and ice (Balmer et al., 2019; Bigot et al., 2017; Chernyak et al., 1996; Garbarino et al., 2002; Hermanson et al., 2005; Hermanson et al., 2020; Hermanson et al., 2021; Hung et al., 2013; Jantunen et al., 2007, as cited in Hoferkamp et al., 2010; Jantunen et al., 2015; Landers, 2008; Muir et al., 2004; Pućko et al., 2015; Pućko et al., 2017; Rice & Chernyak, 1997; Ruggirello et al., 2010; Zhong et al., 2012), as well as in Antartic 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 6 fog condensates; the highest concentration was 5 ng/L. Chlorpyrifos was the third most abundant chemical identified at most sampling points. Among the five pesticides analysed, chlorpyrifos was the most frequently identified contaminant in sub-surface sea water with levels ranging from 18 to 67 pg/L in 6 of 9 samples. Chlorpyrifos was measured at 170 pg/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 (Yong 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, 2020b). The results of these monitoring studies, which have been published in scientific literature, are summarized in Table 12 in INF-document.

61. Comparative analyses of chlorpyrifos and other current use pesticides and pesticides listed as POPs (for example endosulfan, chlordane and DDT) in ice-cores in the Arctic and Antarctica have shown that chlorpyrifos is among the most abundantly detected pesticides (Ruggirello et al., 2010 and Hermanson et al., 2021). Winter snow from four glacial sites on Svalbard was analysed for atmospheric deposition of 36 organochlorine pesticides (OCPs) and 7 industrial compounds (OCICs). Chlorpyrifos dominated OCP flux at three of the sites and was the second highest at the fourth site (Hermanson et al., 2020). Chlorpyrifos concentrations were highest in sea water in the Canadian Arctic Archipelago (Jantunen, et.al., 2015) when compared to different organochlorine pesticides, some of them POPs (endosulfan and chlordane). The studies cited above are discussed in more detail in the INF document.

62. 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., (2010). 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 was increasing 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 organophosphorus 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 5.9 and 9.6 pg/g, in a range of <MDL to 25.6 pg/g. The studies cited above are discussed in more detail in the INF document.

63. 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., 2010). The studies cited above are discussed in more detail in the INF document, as are studies that discuss various mechanism of long-range environmental transport of chlorpyrifos (Bigot et al., 2017, Chernyak et al., 1996, Pućko et al., 2015 and Zhong et al., 2012)

64. Detections of chlorpyrifos in air, freshwater, saltwater, 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 the INF document. Some of the monitoring results presented in the INF document come from regional and national monitoring programmes.

3.4.2 Biota data

65. Chlorpyrifos has been detected in biota samples from around the world, including the Arctic. Muir et al., 2022 compiled, in a draft paper to inform this risk profile, the monitoring data in fish and marine mammal samples from the Canadian Arctic/sub-Arctic generated by ongoing projects of the Northern Contaminants Program (https://science.gc.ca/site/science/en/northern-contaminants-program). Details on these projects are available on the NCP database at the Arctic Institute of North America (https://www.aina.ucalgary.ca/ncp/). In addition, ringed seal blubber and Arctic cod (whole body) samples from 2007-08 reported in Morris et al. (2016) were included. Detection frequencies of chlorpyrifos ranged from zero in Arctic grayling (N=2 samples) to 52% in Arctic cod (N=29; results from Morris et al. (2016)) (Table 3). Largest geometric mean chlorpyrifos concentrations (ng/g wet wt) were found in lake whitefish (*Coregonus clupeaformis*) and muscle while burbot liver had the highest maximum concentration (8.2 ng/g wet weight). These values can be related to environmental quality standards (EQS) for fish (see chapter 4.1.1 for further details on EQS): 2.207 ng/g biota ww in fish should not be exceeded to ensure the protection of biota and organisms feeding from marine waters. This is exceeded in some of the higher values in burbot liver, lake trout muscle and lake whitefish muscle (see table 3 and 6).

Table 3. Concentrations of chlorpyrifos (CPY) in Arctic biota samples (ng/g ww), detection frequency (DF), and % lipid results for fish (Canada, 2022, adapted)

Species/tissue		Date	DF (%)	Arith Mean*	Geo mean*	range	Arith Mean	range
	N			CPY	CPY	CPY	% lipid	% lipid
Arctic char muscle	123	2005-2021	16%	0.05	0.01	<0.001 – 0.58	3.9	0.5 – 10.9
Arctic cod (WB)**	29	2007-2010	52%	0.10	0.03	<0.01 – 0.62	7.1	2.3 – 14.8
Arctic grayling muscle	2	2019	0%	1.10	1.04	<1.5 – 1.45	3.0	2.5 – 3.6
Burbot liver	82	2013-2021	23%	0.41	0.05	<0.003 – 8.23	36.1	0.1 – 59.1
Lake Trout muscle	186	2013-2021	14%	0.12	0.03	<0.001 – 2.57	7.4	0.5 – 21.6
Lake Whitefish muscle	4	2019	50%	1.36	0.56	<0.16 – 4.03	2.5	2.1 – 3.1
Ringed seal blubber	200	2007-2016	18%	0.46	0.12	<0.008 – 4.50		

*Arithmetic and geometric means include non-detect results substituted with ½ DL

** WB = whole body

66. Temporal trends in concentrations of chlorpyrifos in ringed seals were evaluated by plotting the results versus year of collection (Figure 2). Detected concentrations in the samples from 2011 to 2016 for all locations 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). Lack of data after 2016 precludes any firm conclusions about temporal trends in seals.

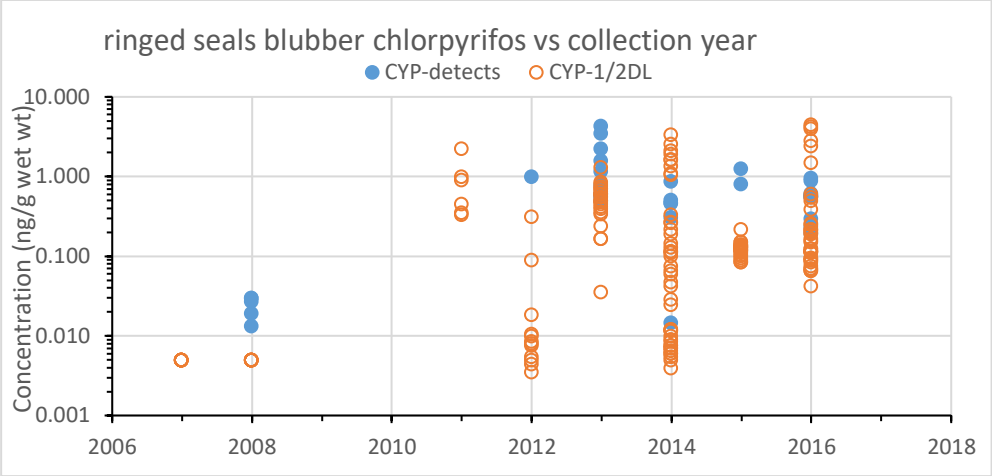

Figure 2. Chlorpyrifos results, including non-detects substituted with ½ detection limit (DL), in ringed seal blubber plotted by sampling year. Results from 2007 and 2008 are from Morris et al. (2016)

67. During the Western Airborne Contaminant Assessment Project (WACAP), the contamination of the vegetation was investigated during 2003 and 2005 (Landers, 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 (Hoferkamp et al., 2010; Landers et al., 2008).

68. 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 wet weight among the four lakes.

69. 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.

70. 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. All other results were below the limit of detection in a total of 59 samples of fish, seabirds, seabird eggs, and seals.

71. 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.

72. 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 lipid weight (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.

73. In 1997 and 1998 blood samples from sea otters (*Enhydra lutris* ssp.) in California and Alaska, USA were analysed for POPs and other chemicals of concern (Jessup et al., 2010). Recovery rates were > 90% and the detection limit was 4 ng/g lw with capillary gas chromatography. The lipid percentage of serum ranged from 0.6 to 1%. No chlorpyrifos contamination was reported for Alaskan sea otters. For Californian sea otters, a range from below LOD

to 342.6 ng/g lw chlorpyrifos was reported. 40 individuals were sampled. Significant differences were found at the three sampling locations in California.

74. 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 12 showed no contamination with chlorpyrifos. The remaining individuals 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.

75. Chlorpyrifos was detected in songbird spp. feet, in animals collected from Toronto in the spring. 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 a limit of detection of 0.1 pg/mg feet weight. In the collection year 2011, chlorpyrifos ranged in feet samples from nondetectable to 1.2 pg/g feet weight. With sufficient duration of low-dose exposure, chlorpyrifos might persist and bioaccumulate (Alharbi et al., 2016). Owl carcasses were sampled for tissues (heart, liver, and kidney). Chlorpyrifos was detected in the livers of two of the Megascops spp. (n=5), collected in 2018-2019 in Brazil, in an area with mixed agriculture and forests (Dal Pizzol et al., 2017).

76. Sixty wild boars (*Sus scrofa*) from north-western Spain were sampled for POPs, and organophosphate pesticides including 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 nondetectable (n.d.) to 1.7 ng/g, and in liver, concentrations ranged from n.d. to 29 ng/g l.w. or n.d. to 3.2 ng/g (Gonzalez-Gomez et al., 2021).

77. 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). The results from another Norwegian screening programme from 2017 have shown 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 (Screening Programme 2017 AMAP Assessment Compounds). Chlorpyrifos was otherwise not detected in air, bird, polar bear, or mink sampled in the Arctic in Norway in 2017, or 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 µg/kg dw (Screening programme 2016 Suspected PBT compounds). Chlorpyrifos was also measured in one of 11 rat liver samples (2.4 µg/kg dw), and was otherwise below the limit of detection in all samples of cod liver (15), fish fillets (16), shore crab (3), and winkie (2) that were analysed.

78. Chlorpyrifos and its transformation product chlorpyrifos oxon were detected in needles of potted ponderosa pines at three sites in California in 1994 (Aston & Seiber, 1997). Needle compartments were analysed 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[7]. 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[8] was estimated as 9800.

3.4.3 Human exposure

79. 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 the INF document. Breast-milk is considered an important medium for exposure of chlorpyrifos to infants, particularly when considering neurodevelopmental effects of the pesticide.

Table 4: Human biomonitoring data

Concentrations in milk are measured as chlorpyrifos, in urine as TCP

Human biomonitoring data					
Weldon et al. (2011)	California breasts milk	2002-2004	Median (range) 0.0245 (0.0129 – 0.23)	LOD 0.151 - 0.256 pg/g	Breastfeeding mothers from urban (n=21) and rural

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

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

Human biomonitoring data					
			ng/g milk (urban) 0.028 (0.0128 – 0.107) ng/g milk (rural)	milk DF 100%	communities (n=13) in California
Hartle et al. (2018)	USA breast milk	2018	Range 4.2 to 54.6 pg/g median 20.5 pg/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)	MDL0.01 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 endosulfan concentrations were the highest followed by chlorpyrifos
Brahmand et al. (2019)	Iran, breast milk and urine	2017	Milk: mean cpy 1.3 ± 0.6 µg/L urine: mean cpy metabolite 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 and plasma	2013	Median 0.1 ng/mL Range < LOD – 0.46 ng/mL	LOD 0.22 ng/mL milk	Breastfeeding mothers from agricultural area (n=33)

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

80. An Acceptable Daily Intake (ADI)/ Provisional tolerable daily intake (PTDI) was set by FAO/WHO at 0–0.001 mg/kg bw, which equals the acceptable daily intake for infants set by EFSA (2014) at 0.001 mg/kg bw. A more recent review by EFSA did not establish a reference value as there were considerable uncertainties for dose-response relationship concerning neurodevelopmental effects (EFSA, 2019), as well as due to remaining uncertainties regarding a genotoxicity potential (EFSA, 2019). In the EU, a maximum residue level (MRL) of 0.01 mg/kg was set in 2020, after the non-renewal of the substance registration.

81. 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, which is a metabolite of both chlorpyrifos and chlorpyrifos-methyl, and can also be taken up from the environment itself, thus it is not possible to establish the exact origin of the exposure. Results and details of these studies are discussed in the INF document.

82. 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, 2020, 2021, 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 maximum residue level of 0.01 mg/kg set by the European Commission (Shaker and Elsharkawy, 2015). Further details are presented in the INF-document.

3.4.4 Conclusion

83. 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 to those reported for the POP endosulfan in landlocked arctic char and ringed seals in the Canadian Arctic (Weber et al. 2010).

84. Human biomonitoring data show exposure to chlorpyrifos at a level of concern, considering the PTDI of 0.01 mg/kg set by FAO.

4. Hazard assessment for endpoint of concern

85. Chlorpyrifos induces irreversible inhibition of acetylcholinesterase (AChE) in the central and peripheral nervous system (Colovic et al., 2013; Solomon et al., 2014; WHO, 1987), 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 invertebrates 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 4.2.2.

4.1 Hazard assessment for the environment

4.1.1 Hazard assessment for aquatic organisms

86. 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" (Annex VI of Regulation (EC) No 1272/2008(CLP Regulation)).

87. Under the EU Water Framework Directive, the European Commission has set an Environmental Quality Standard (EQS) which covers both human health and ecosystems (EC, 2018). The current value of an annual average concentration (AA-EQS) of 0.03 µg/L (EC, 2015, EU, 2013) is under review in 2023 to take into account the latest scientific evidence on toxicity for aquatic organisms and for humans. It has been proposed to lower the EQS to $0.46*10^{-3}$ µg/L for fresh water and the marine environment. As part of the review, it is also concluded that the value of 0.128 µg/kg biota wet weight (ww) and 2.207 µg/kg biota ww in bivalves and fish, respectively, should not be exceeded to ensure the protection of biota and organisms feeding from marine waters. The maximum allowable concentration in water (MAC-EQS) is set at 0.1 µg/l. It should be noted that the EQS also has the objective to protect humans from exposure via food.

88. Laboratory studies performed with the active ingredient chlorpyrifos according to the OECD 203 guideline for acute effects (i.e., lethality) identify *Oncorhynchus mykiss* as the most sensitive fish species tested. 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 DOW, 99.9% purity, see Table 1). For fish, based on data available in Spain (2017) there is no evidence for higher toxicity of the active ingredient when formulated, although no test with EC formulations (Emulsified Concentrate), the most common formulations in agriculture, are available. When considering studies from the 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 0.53 to 520 µg/L are reported in J. R. 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. Based on data ranging from 0.53 to > 860 µg/L collected for 25 fish species, Giesy et al., (2014) used species sensitivity distribution (SSD) to calculate a hazardous concentration for 5% of species (HC_5-LC_{50}) of 0.812 µg/L. This means that at the concentration of 0.812 µg/L already 5% of the fish species included in the SSD reach their LC_{50}, which clearly demonstrates the high acute toxicity of chlorpyrifos to fish. US EPA's biological evaluation for chlorpyrifos Endangered Species Act (ESA) reviewed data from 40 fish species and recorded 96-hour LC_{50} values ranging from 0.17–7,012µg/L[9] (see table 2–3 in ESA) with *Chirostoma jordani* being the most sensitive species (LC_{50}=0.17 µg/L; Dzul-Caamal et al., 2012's biological evaluation for chlorpyrifos ESA calculated a hazardous concentration for 5% of species (HC_5-LC_{50}) of 1.44 µg/L for both freshwater and estuarine/marine fish.

89. 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, Hansen, Cripe, et al., (1985b) 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 35 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., 1985b).

90. A substantial quantity of data is available for aquatic exposure of amphibians to chlorpyrifos. Fryday and Thompson (2012) report 96-h LC_{50} < 1 mg/L for the *Xenopus laevis* and *Bufo bufo gargarizans* (0.564 from Richards

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

and Kendall (2002) and 0.800 mg/L from Yin et al., (2009), respectively). The US EPA's biological evaluation for chlorpyrifos ESA reviewed 10 studies for 8 species and recorded lowest observed adverse effect level (LOAEL) values for anticholinesterase effects ranging from 0.215 - 500 µg/L for the African clawed frog *Xenopus laevis* and the foothill yellow legged frog *Rana boylii* respectively. The NOAEL of 0.215 µg/L was used by the US EPA to set the sublethal threshold for aquatic-phase amphibians (US EPA's biological evaluation for chlorpyrifos ESA).

91. Invertebrates, especially crustaceans and insects, are the most sensitive taxa among aquatic organisms. Considering only tests performed in an OECD 202 acute test design, European Commission (2005) and Spain (2017b) identified *Daphnia magna* as the most sensitive species with a 48-hours Effect concentration (EC_{50}) of 0.1 µg/L. This endpoint is in the same range as the 96-hours EC_{50} of 0.138 µg/L determined for the macroinvertebrate *Hyalella azteca* (Brown et al., 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 et al., (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 EC50 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 EC50 values collected for 23 and 17 species, respectively. The HC5 for invertebrates are based on EC50s while fish was based on LC_{50s} which also increased the factor difference when comparing both trophic levels.

92. 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 and DeRuiter, 1990). Similar studies performed on the marine shrimp *Mysidopsis bahia*, reported a NOEC of 4.6 ng/L. based on mortality and growth impairment occurring at concentrations of 10 ng/L and above (Sved, 1993).

4.1.2 Hazard assessment for terrestrial organisms

93. 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 calculated according to 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 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 dietary studies, which represent a more realistic exposure scenario. Dietary studies (i.e., 5 days feeding followed by 3 days observation) performed on the mallard duck *Anas platyrhynchos* calculated a LD_{50} of 71 mg/kg bw (European Commission, 2005).

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

95. 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 by DOW 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.

96. Chlorpyrifos has been designed to control a wide variety of foliage- and soil-borne insects. It is a broad-spectrum insecticide and thus toxic effects on non-target arthropods, especially pollinators, exist. Chlorpyrifos is highly acutely toxic to the honeybee *Apis millefera*. The highest toxicity is identified when the substance is administrated via contact. Bell (1994) measured an acute LD_{50} of 0.068 µg/bee in a test performed with Dursban F (97.4% purity). For comparison, the lowest LD_{50} estimated for oral toxicity is 0.15 µg/bee (Bell, 1993).

97. 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 (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.

98. 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 (for example, 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 for the beneficial aphids *Acyrthosiphon kondoi, A. pisum* (Homoptera: Aphididae) as well as for the brown lacewings *Austromicromus tasmaniae* (Neuroptera: Hemerobiidae). Further acute LR_{50} values of 1 ppm or less are reported in Spain (2017) for the damselflies *Enallagma spp.* and *Ischmura spp.* (Odonata: Coenagrionidae) and larvae of Trichopteran species *Hydropsyche* and *Chematopsyche spp*. (Trichoptera: Hydropsychidae).

99. 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 the European corn borer pest *Ostrinia nubilalis* (Lepidoptera: Crambidae).

100. 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 be highly chronically toxic 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 the animals. These effects observed at laboratory level were confirmed by field data.

4.2 Hazard assessment for human health

101. 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).

102. Studies on airborne chlorpyrifos have demonstrated toxicity in laboratory animals. Adult male CF-1 mice were intranasally administered with chlorpyrifos (3–10 mg/kg/day) three days a week, for 2 weeks. Behavioural and biochemical analyses were conducted 20 and 30 days after the last intranasal chlorpyrifos administration, respectively. No significant behavioural or biochemical effects were observed in the 3 mg/kg chlorpyrifos intranasal exposure group. However, animals exposed to 10 mg/kg chlorpyrifos showed anxiogenic behaviour 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. 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 women working and living in the area. Air concentrations were detected in 98% of the samples with a median concentration of 15.62 nanograms per cubic meter (ng/m^3). The authors demonstrated for each 1 ng/m^3 increase of chlorpyrifos in air, a 1.5% increase was observed in the chlorpyrifos metabolite TCP, 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.

103. On December 14, 2022, the US EPA published a notice of intent to cancel (NOIC) for certain products containing chlorpyrifos stating that “chlorpyrifos has been found to inhibit an enzyme that leads to neurotoxicity, including potential neurodevelopmental effects in children.” The US EPA tolerance revocation includes terrestrial food crops, food handling establishments, commercial livestock uses and (implied) indoor residential uses except for containerised ant and roach bait.

104. EFSA 2019, suggested that 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 would be appropriate 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).

105. 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 (Jokanovic and Kosanovic 2010).

4.2.1 Cholinesterase inhibition

106. 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).

4.2.2 Developmental neurotoxicity

Animal experiments

107. Mohammed et al., (2015), 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 behavioural 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., 2015). 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. Behavioural testing showed decreased times to emergence from a dark container into a novel environment at 0.5 mg/kg/day in both sexes. This behaviour was associated with decreased anxiety. The data confirm earlier findings from this group showing that chlorpyrifos treatment generated behavioural 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.

108. 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 behavioural 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).

109. 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 that indications of developmental neurotoxicity were observed at all dose levels tested in the study.

110. The re-evaluation of the study by Mie et al., (2018) was considered by EFSA's statement on human health assessment of chlorpyrifos (2019). 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 (as cited in EFSA, 2019).

***In vitro* studies**

111. US EPA developed a new approach methodology (NAM) for fit-for-purpose evaluation of developmental neurotoxicity using organophosphate pesticides (OPs) (including chlorpyrifos) as a case study. This includes a development of a microelectrode array network formation assay (MEA NFA) and high-content imaging (HCI) assays of neural cells to understand key processes relevant to neurodevelopment 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).

112. More recent studies have determined that neurotoxicity occurs in both humans and laboratory animals. Studies conducted in India determined chlorpyrifos poisonings in farmers and allied agricultural workers resulted in adverse effects such as acute cholinergic crisis, respiratory failure, acute renal failure, and seizures (Acharya and Panda (2022). Plasma pseudocholinesterase levels with less than 1,000 units per liter (U/L) were far less that the reference dose ranges of 3930-10,800 U/L and 4620 – 11,500 U/L for females and males, respectively. The significance is that the pseudocholinesterase enzyme is responsible for breaking down acetylcholine and is inhibited by chlorpyrifos. The persistence of acetylcholine leads to over-stimulation of post-synaptic nerves, muscles, and exocrine glands leading to adverse outcomes. 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 acetylcholine (AChe) when compared to the control group. AChe levels decreased and other enzymes levels increased. 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.

113. A report by Masjosthusmann et al. (2020) 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 (D. L. Eaton et al., 2008).

114. 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. although available *in vitro* studies suggest that alternative mechanisms are possible. 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 and risk assessments

115. 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.

116. In 2011, the Columbia Center for Children's Environmental Health (CCCEH) published the results of a study examining the potentialon 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 new-borns 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.

117. 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 eitrher arm (p=0.028), tremor in both arms (p=0.027), and marginal association with tremor in non-dominant arm (p=0.055).

118. In July 2018, California EPA published their "Final Toxic Air Contaminant Evaluation of Chlorpyrifos" (CalEPA, 2018) which reviewed several additional epidemiological studies (Bielawski et al., 2005; Corrion et al., 2005; Fluegge et al., 2016; Ostrea, Jr. et al., 2012; Ostrea, Jr. et al., 2006; Posecion et al., 2006; Silver et al., 2015; Silver et al., 2017; Wickerham et al., 2012). 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 INF document) 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.

119. The US EPA concluded that the 3 US cohort studies (CCCEH, CHAMACOS, and Mt. Sinai) provide the most robust available epidemiological evidence (US EPA, 2016a). 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.

120. In July 2019, the European Food Safety Authority (EFSA, 2019), published a statement based on a peer review of health impacts for chlorpyrifos. 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 behavioural 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" such effects, as well as neurodevelopment effects, supported by the epidemiological data indicating effects in children, toxicology reference values could not be no safe exposure level can be set for chlorpyrifos.

121. 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 state 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, 2020a). US EPA concluded, that despite several years of study, peer review, and public process, the science addressing neurodevelopmental effects remains unresolved (US EPA, 2020b). US EPA concludes there is uncertainty in the human dose-response relationship for neurodevelopmental effects from chlorpyrifos exposure.

122. In 2019, EFSA concluded that significant uncertainties were linked to the neurodevelopmental laboratory toxicity studies, where effects were observed at the lowest dose tested in rats (consistent with a decrease in cerebellum height corrected by brain weight) and based on other uncertainties, no human health toxicological reference values could in any case be set, meaning that no "safe threshold" could be derived for human health risk assessment, and thus no ADI can be set.

4.3 Conclusions on hazard assessment

123. 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.

124. In rats and mice, effects on the developing nervous system include altered cognition, motor control, and behaviour. 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 are consistent with human data.

125. US EPA concluded that effects on the developing brain may occur below a dose eliciting 10% AChE inhibition and that there is uncertainty in the human dose-response relationship for neurodevelopmental effects from chlorpyrifos exposure. 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. This represents a critical area of concern. (EFSA, 2019).

126. 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 EC50 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.

127. 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 lower, with for example, a NOAEL of 0.1 mg/kg bw/day observed in a 2-year dietary study in rats.

5. Synthesis of information

128. Chlorpyrifos can be considered persistent in some environments and it shows moderate bioaccumulation in aquatic and air-breathing organisms. In combination with high toxicity, even moderate bioaccumulation can lead to body concentrations 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 point sources in various abiotic and biotic compartments. This indicates that long-range environmental transport occurs.

129. The concentrations of chlorpyrifos measured in lakes and marine water in remote regions are generally below adverse effect levels found in laboratory studies for aquatic organisms and terrestrial vertebrates, or below the annual average EQS (AA-EQS) values of 0.03 µg/L for surface water and 0.1 µg/L for the maximum allowable concentration (MAC-EQS). It should be noted that EQS values are under review with the objective to lower them. In glacial meltwater in the Alps, aquatic toxicity exposure ratios (TERs) for CPY ranged from 1.42 (Forni Glacier) to 52.6 (Lys Glacier), indicating an unacceptable level of risk for aquatic invertebrates. When considering source areas, concentrations of chlorpyrifos higher than the effect levels have, however, been measured in surface water, for example, in Canada, New Zealand and Europe.

130. The levels of chlorpyrifos measured in biota in remote regions are relatively low. Nevertheless, concentrations measured in lake whitefish in the Canadian Arctic and in polar cod in northeast Greenland have exceeded the proposed EQS value of 2.207 µg/kg biota ww in fish that should not be exceeded to ensure the protection of biota and organisms feeding from marine waters (including humans). In remote regions, Indigenous peoples of the Arctic can be at increased health and livelihood risks from chlorpyrifos exposure as contaminants can affect food, animal and plant species that are important to their traditional ways of life.

Table 5: Comparison of environmental levels with effect levels (proposed EQS)

Organism	**Measured level [ng/g ww]**	**EQS [ng/g]**	**Organism**
lake whitefish muscle (geom. mean)	0.56*	0.128	bivalves
lake whitefish muscle (max)	4.03	2.207	fish
polar cod, fjord, liver, mean	5.9		
polar cod, fjord,liver, max	21.2		
polar cod, fjord,muscle, mean	3.8		
polar cod, fjord,muscle, max	23.1		
polar cod, fjord, muscle, 2nd highest conc	9,5		

* geometric mean of n=4 samples, includes 50% non-detect results substituted with ½ DL

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

132. 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.

133. US EPA concluded that there is uncertainty in the human dose-response relationship for neurodevelopmental effects from chlorpyrifos exposure. EFSA in their latest evaluation concluded that toxicology reference levels could not be set for chlorpyrifos for human health risk assessment. Therefore, concentrations found in human biomonitoring studies (including in breast milk in some countries) are of concern and should be reduced because of high uncertainties on the level of acceptable risk.

134. The toxicity and ecotoxicity profile of chlorpyrifos, its current wide and dispersive use in high volumes, including in residential applications, and the evidence for long range transport to remote regions give rise to concerns on toxicological risks to human health and to aquatic and terrestrial organisms, also in remote regions.

6. Concluding statement

135. 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.

136. 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.

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

138. 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.

139. 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.

140. While the concentrations of chlorpyrifos measured in remote areas are generally below adverse effect levels for acute and chronic toxicity found in laboratory studies for aquatic organisms and terrestrial vertebrates, it should be noted that these levels are under review to lower them. When considering source areas, concentrations of chlorpyrifos higher than the effect levels have regularly been measured in surface water.

141. 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 may, as a result of long-range environmental transport, lead to significant adverse human health effects such that global action is warranted.

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