

# **Chlorpyrifos**

## **Draft risk profile**

**April 2022**



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## Executive summary

- 1 The POPs Review Committee at its seventeenth meeting concluded that chlorpyrifos fulfilled the screening criteria in Annex D (decision POPRC-17/4) and 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. In 2008 chlorpyrifos products were authorised for use in more than 88 countries. Usage as a biocide was phased-out in the European Union by Commission Decision (2007/565/EC) by 2008 (European Union, 2007). A decision on phasing out most non-agricultural applications was adopted by the EPA in 2000 (US EPA, 2006). However, usage as a biocide, e.g., for termite control in buildings, is still practiced in other countries. For example, use for termite control is still recommended by the Indian authorities (India, 2020).
- 3 Chlorpyrifos was first produced commercially in 1965 by Dow Chemical Company. While a number of methods for the commercial preparation of chlorpyrifos have been reported, a common method is the by reaction of 3,5,6-trichloro-2-pyridinol with diethyl phosphorochloridothioate under basic conditions e.g. in the presence of sodium carbonate (ATSDR, 1997). While data are not available on total global production volumes, data from the CCPIA (Annex E, 2022) indicated that, in terms of volume of use, prior to 2007, global use was about 10,000 tonnes/year. It is indicated that, following the prohibition of five highly toxic organophosphorus pesticides in China, chlorpyrifos has become the dominant insecticide used in the country (Chen et al., 2012), with the global use now estimated to be 50,000 tonnes/year (CCPAA, 2022). It is understood that China and India are currently two of the biggest producers of chlorpyrifos globally.
- 4 Environmental degradation half-lives of chlorpyrifos range from a few days to several years, depending on application rate, ecosystem type, soil or sediment characteristics, and other environmental factors, including temperature. 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. In addition, chlorpyrifos is found in dated sediment cores in Arctic and sub-Arctic lakes (Landers, 2008). Thus, chlorpyrifos can be considered persistent in some environments according to the definition of the Stockholm Convention.
- 5 The log  $K_{ow}$  for chlorpyrifos indicates potential bioaccumulation. The combination of a log  $K_{ow} > 2$  and a log  $K_{oa} > 5$  indicates potential bioaccumulation in air-breathing organisms. Chlorpyrifos has been found in biota at different trophic levels in the remote regions, globally in apex predators and in human breast milk at levels concerning for offspring. Based on current data available, a BCF of  $> 5000$  cannot be concluded. Fish studies show moderate bioaccumulation with BCF in the range of 1000 to 2000 at concentrations showing toxic effects. BCF above 2000 are observed in early life stages. In combination with high toxicity, even moderate bioaccumulation can lead to body concentrations that elicit adverse effects, thus it is a serious concern. Based on high toxicity in fish and other species such as invertebrates, amphibians, birds and mammals including humans, in combination with a moderate BCF and a BSAF above 6 for soil organisms, chlorpyrifos meets the second criteria (ii) for bioaccumulation in other species, high toxicity and ecotoxicity of Annex D. Based on the reasons stated above, we conclude that chlorpyrifos fulfils the criteria for bioaccumulation.
- 6 While modelling results do not predict long-range transport, chlorpyrifos is widely detected in remote areas far away from point sources and/ or agricultural use. Potential routes of transport include atmospheric transport in the gas or particulate phase, transport via water in rivers and/ or ocean currents. Chlorpyrifos has been found far away from point sources, in various abiotic and biotic compartments of remote areas such as in caribou, seals and ice bears in the Arctic and sea-ice meltwater and air of Antarctica. Thus, chlorpyrifos is considered to meet the criterion of the Stockholm Convention on long-range environmental transport.
- 7 Chlorpyrifos has been detected in air samples, both in regions close to application areas and in remote locations far from application areas, as it can be carried with the wind (Mackay et al., 2014).
- 8 Epidemiological evidence in combination with animal studies are evidence for developmental neurotoxicity (DNT) of chlorpyrifos in humans. Additionally, chlorpyrifos exhibits acute and chronic effects at very low and environmentally relevant concentrations. It is highly toxic to aquatic communities, early life stages of fish and aquatic invertebrates, bees, birds and mammals. The ecotoxicological and toxic properties of chlorpyrifos lead to adverse effects for human health and the environment



9 Some of the text included in this version for the first commenting round may have to be moved to the INF-document due to space limitations.



# 1. Introduction

10 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), which was considered by the Persistent Organic Pollutants Review Committee (POPRC) at its seventeenth meeting held in Geneva, Switzerland, in January 2022. The conclusion of that meeting determined that chlorpyrifos meets the criteria set-out under Annex D of the Stockholm Convention, warranting that chlorpyrifos move to the next stage of the review process.

11 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. In 2008 chlorpyrifos products were authorised for use in more than 88 countries. Usage as a biocide was phased-out in the European Union by Commission Decision (2007/565/EC) by 2008 (European Union, 2007). A decision on phasing out most non-agricultural applications was adopted by the EPA in 2000 (US EPA, 2006). However, usage as a biocide, e.g., for termite control in buildings, is still practiced in other countries. For example, use for termite control is still recommended by the Indian authorities (India, 2020).

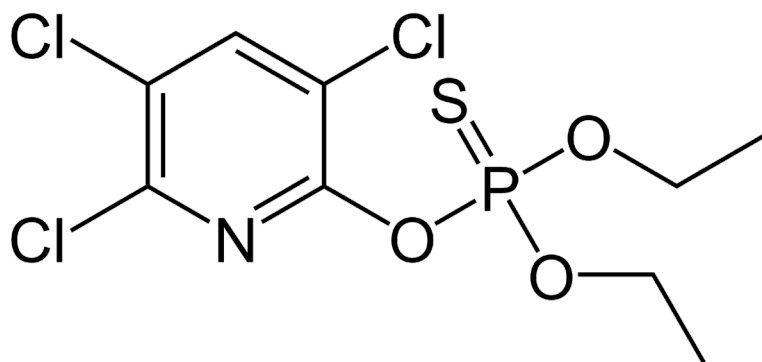
12 In 2020 US EPA revised the human health risk assessment of chlorpyrifos. This assessment substantially relies on the previous documents developed for chlorpyrifos (US EPA, 2016), an updated drinking water assessment, and animal toxicity literature review. Risks were identified for workers; also, potential risks were found for drinking water. According to the US EPA (2017) exposure to chlorpyrifos is also linked to the delay of mental development of young children.

13 In 2019, the renewal of the approval of chlorpyrifos for use as active substance in plant protection products has been denied in the European Union (European Union, 2020), following the risk assessment carried out by Member States and the European Food Safety Authority (EFSA, 2019). EFSA concluded that the approval criteria, which are applicable to human health as laid down in Article 4 of Regulation (EC) No 1107/2009 are not met. The decision was based on uncertainty regarding genotoxic potential and potential neurodevelopmental toxicity of chlorpyrifos. Furthermore, chlorpyrifos is banned in Morocco (ONSSA, 2020), Saudi Arabia, Sri Lanka (PIC Database, 2021), Indonesia (Indonesia, 2019) and Switzerland (Switzerland, 2019).

## 1.1 Chemical identity

14 Figure 1 (below) provides details of the chemical structure for chlorpyrifos. Additionally, Table 1 and 2 provide further details about the chemical identity of chlorpyrifos and its physical properties. Information on the major degradation products of chlorpyrifos was already provided previously within the information document at the seventeenth POPRC meeting (see UNEP/POPs/POPRC.17/INF/4).

**Figure 1. Structural formula of Chlorpyrifos**



Credits: Andreas Buser, CH



**Table 1. The chemical identity of Chlorpyrifos.**

<b>CAS number:</b>	2921-88-2
<b>CAS chemical name:</b>	O,O-diethyl O-(3,5,6-trichloro-2-pyridyl) phosphorothioate
<b>IUPAC name:</b>	O,O-Diethyl O-3,5,6-trichloro-2-pyridinyl phosphorothioate
<b>EC number:</b>	220-864-4
<b>Smiles code</b>	CCOP(=S)(OCC)Oc1nc(Cl)c(Cl)cc1Cl
<b>Molecular formula:</b>	C <sub>9</sub> H <sub>11</sub> Cl <sub>3</sub> NO <sub>3</sub> PS
<b>Molecular weight:</b>	350.59 g/mol
<b>Synonyms:</b>	chlorpyriphos; chlorpyrifos-ethyl; chlorpyriphos-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
<b>Trade names:</b>	Dursban, OMS 0971, Lorsban, Brodan, Killmaster, Pyrinex, Suscon, Coroban, Terial, Danusban, Durmet, Eradex

## Physical and chemical properties

15 Table 2 reports the main physicochemical properties of chlorpyrifos. The vapour pressure value indicates that it can volatilise. It has a low water solubility. The log Kow value shows that it can adsorb and/or absorb to organic material and the logKoc 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) ILO & WHO (2014)
Odour	Mild mercaptan (experimental, 99.6 % purity)	European Commission (2005)
Melting/freezing point [°C]	41 – 42 (experimental at 97- 99 % purity) 42 at 99.9 % purity	European Commission (2005) Spain (2017)
Thermal decomposition point [°C] (decomposition before boiling)	170 – 180 Experimental data	European Commission (2005) Spain (2017)
Vapour pressure [Pa]	3.35 * 10 <sup>-3</sup> 25°C (purity 99.8%) 1.43 * 10 <sup>-3</sup> 20°C (purity 99.8%) 1.0 * 10 <sup>-3</sup> Experimental, 25°C (purity 98%) 2.3 * 10 <sup>-3</sup>	European Commission (2005) European Commission (2005) WHO (2009) Compiled by Mackay et al. (2014)
Water solubility [mg/L]	1.05 at 20°C, in unbuffered solution, no pH dependency reported 0.39 at 19.5°C, pH not cited (98 % purity) 0.73 0.941 (20°C, pH unknown, guideline EEC Method A6/OECD 105) Dow 0.588 (20°C, pH not stated, guideline OECD 105 flask method) Makhteshim, as cited in WHO (2009)	European Commission (2005) WHO (2009) Mackay et al. (2014) WHO (2009) WHO (2009)
n-Octanol/water partition coefficient, K <sub>ow</sub> (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 – 5.267 at 25°C	European Commission (2005) WHO (2009) Gebremariam et al. (2012) Gebremariam et al. (2012)
n-Octanol-air partition coefficient K <sub>oa</sub> (log value)	8.882 (estimated) 8.34	US EPA (2012) Mackay et al. (2014)



Property	Value	Source
Air/water partition coefficient (log K <sub>AW</sub> )	-3.922 Experimental database	US EPA (2012)
Organic carbon/water partition coefficient (K <sub>OC</sub> )	8,500 (EPA gives 5,860, 4,960, 7,300) Log is 3.93	Mackay et al. (2014)

## Transformation products

16 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). For information on chemical identity, physico-chemical properties and environmental hazard information please see table 1 and text of the INF-document.

## 1.2 Conclusion of the POPs Review Committee regarding Annex D information

17 The POPs Review Committee 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 UNEP/POPS/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.

## 1.3 Data sources

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

1. The proposal submitted by the European Union (UNEP/POPS/POPRC.17/5);
2. Annex E 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: Australia, Austria, Belarus, Canada, Egypt, Monaco, Netherlands, Republic of Korea, Sweden, Thailand, The United Kingdom, Uzbekistan, China Crop Protection Industry Association (CCPIA), International Pollutants Elimination Network /Alaska Community Action on Toxics (IPEN/ACAT), Pesticide Action Network, Pesticides Manufacturers & Formulators Association of India (PMFAI), United States of America.
3. Reports and other grey literature as well as information from peer-reviewed scientific journals;

## 1.4 Status of the chemical under national regulations and international forums

19 The US EPA has performed numerous human health risk assessments over the years as well as a link to the ecological risk assessment and released a biological evaluation for chlorpyrifos in 2021. Chlorpyrifos has been used as a pesticide since 1965 in both agricultural and non-agricultural areas, however in 2000 all outdoor residential uses and most out-door non-residential uses were eliminated (US EPA, 2006). On 28 February 2022, all chlorpyrifos tolerances will expire pursuant to the final rule. Therefore, chlorpyrifos application to food commodities results in food being considered adulterated; distribution of adulterated food in interstate commerce is unlawful under the FFDCA. The non-agricultural, non-food uses will remain registered as chlorpyrifos undergoes registration review, a program that re-evaluates all pesticides on a 15-year cycle. (USA, 2022; US EPA, 2022).

20 Since 2000 multiple re-evaluations of chlorpyrifos were performed in Canada, which assessed the health and some environmental risks, the latest being performed in 2007. A subsequent final phase of re-evaluation was intended to update the current health risk assessment for the remaining registered products based on additional information identified since the 2007 health re-evaluation. The Pest Management Regulatory Agency requested these additional health data from chlorpyrifos registrants. As the registrants of chlorpyrifos products were unable to fulfill these data requirements, Health Canada cancelled the remaining pest control products containing chlorpyrifos, and is phasing out sale by registrants and retailers by 10 December 2021 and 2022 respectively and use for all chlorpyrifos products by 10 December 2023 (Canada, 2022).



21 Chlorpyrifos is in the European Union prohibited to be marketed for use as active substance in plant protection products since 2020 and in biocidal products since 2008 (Regulation (EC) No 1107/2009, Regulation (EU) No 528/2012)<sup>1</sup>.

22 According to harmonised classification in EU (Regulation (EC) No 1272/2008), chlorpyrifos is classified as H301 (toxic if swallowed), H400 (very toxic to aquatic life) and H410 (very toxic to aquatic life with long lasting effects) (Norway, 2022).

23 In the Netherlands chlorpyrifos has been authorised since 1971. At present it is registered for its use as an active ingredient in a few formulations controlling crawling insects (in specific spaces), moths (protecting woollen fabrics), and cabbage maggots (on cabbage varieties). The Health Council of the Netherlands published a health hazard assessment in 2003 (The Netherlands, 2022).

24 In the UK, chlorpyrifos is not authorised for use as a plant protection product. Additionally, in the UK there are no products containing chlorpyrifos as the active ingredient registered for use as a biocide. (UK, 2022)

25 In Egypt, chlorpyrifos will be banned at the end of 2022 with a restriction for the use in cotton. (Egypt, 2022)

26 The New Zealand EPA has assigned the following GHS hazard classifications to chlorpyrifos<sup>2</sup>: Acute toxicity cat.2 (H310), acute toxicity cat.3 (H301), acute toxicity cat.4 (H332), Eye irritation cat.2 (H319), Reproductive toxicity Cat.2 (H361), STOT single exp. cat.1 (H370), STOT repeat exp. cat.1 (H372) Aquatic acute cat.1 (H400), Aquatic chronic cat.1 (H410). The classification of Reproductive toxicity Cat.2 has been legally applied to formulated products but not yet to the active ingredient and will be applied during the current reassessment. Chlorpyrifos is allowed for use in New Zealand. Specifically, the use as wettable power, liquid and granulates is allowed for use across a different number of crops such as grasses, orchard fruits and vegetables. In total 17 products containing Chlorpyrifos are registered for use in New Zealand. Plant protection products were reassessed (re-registration) by the EPA in 2013 and approvals were retained with additional controls/restrictions added<sup>3</sup>. Chlorpyrifos and chlorpyrifos-methyl are currently being reassessed as plant protection products by the Environment Protection Agency of New Zealand. Non-plant protection uses, such as veterinary medicines and in urban pest management, were reassessed in 2016 and the approvals were revoked (New Zealand, 2022).

27 Australia is currently reviewing chlorpyrifos-ethyl on the basis of concerns related to toxicology, work health and safety, chemistry, residues and environment. Several assessment reports, including an update report published in 2019 are available<sup>4</sup>. Proposed regulatory action is expected to be published in mid-2022 (Australia, 2022).

28 In China, in order to reduce the residual risk, chlorpyrifos is listed in the “Pesticide Management Regulations” and is prohibited from being used on vegetables since December 31, 2016 (CCPIA, 2022).

29 In Thailand, chlorpyrifos is regulated under the Hazardous Substance Act. Household and public health pesticides containing chlorpyrifos as active ingredient are classified as type 4 hazardous substances (under the responsibility of Thai FDA), which have high degrees of hazard or risks arising either from their applications or intrinsic properties. Thus, their manufacturing, import, export or possession is prohibited (Thailand, 2022).

30 In India, chlorpyrifos has been registered under the Insecticide Act of 1968 since 1977. The registration of chlorpyrifos undergoes strict scrutiny and adherence to regulatory data requirement under the scheduled act for complete safety. Labelling of chlorpyrifos follows the Insecticide Rules 1971, where chlorpyrifos falls under Category II with a yellow color code and caution as “POISON” to represent the level of toxicity as Highly toxic (PFMAI, 2022). Additionally, seven formulations are registered for use in India under the Insecticides Act, 1968. It is also approved to be used for desert locust control on crops, acacia and other trees in concentrations of 240 grams active substances per hectare.

<sup>1</sup> [https://ec.europa.eu/food/plants/pesticides/approval-active-substances/renewal-approval/chlorpyrifos-chlorpyrifos-methyl\\_en](https://ec.europa.eu/food/plants/pesticides/approval-active-substances/renewal-approval/chlorpyrifos-chlorpyrifos-methyl_en)

<sup>2</sup> <https://www.epa.govt.nz/database-search/chemical-classification-and-information-database-ccid/view/F20DCF7B-634B-4FF3-B3C8-015E4C2E7FA7>

<sup>3</sup> [APP201045-APP201045-Decision-Amended-with-s67As-and-APP202142-2015.07.28.pdf \(epa.govt.nz\)](#)

<sup>4</sup> Report year 2000: <https://apvma.gov.au/sites/default/files/publication/14746-chlorpyrifos-irr-toxicology.pdf>

Supplementary assessment Report available at <https://apvma.gov.au/node/26831>

Update report available at <https://apvma.gov.au/node/50111>



31 According to the Agency for Quarantine and Plant Protection of the Republic of Uzbekistan, chlorpyrifos and preparations containing chlorpyrifos in the amount of 15 units are included in the "List of chemical and biological means of combating pests, plant diseases and weeds, defoliant and plant growth regulators approved for use in agriculture of the Republic of Uzbekistan". In the same list chlorpyrifos is categorized as hazard class III (moderately hazardous) for humans and preparations based on it belong to classes II and III. The Ministry of Health of the Republic of Uzbekistan plans to take measures for the phased restriction and decommissioning of chlorpyrifos. (Uzbekistan, 2022)

32 Chlorpyrifos is registered in accordance with the Law of the Republic of Belarus on Quarantine and Plant Protection (December 25, 2005 No. 77-Z) and is included in the State Register of Plant Protection Products and Fertilizers Permitted for Use on the Territory of the Republic of Belarus. Due to a toxico-ecological assessment of insecticides based on chlorpyrifos it has been classified as highly hazardous (Belarus, 2022).

33 In Argentina, the information on the human health and environmental effects of chlorpyrifos was reviewed in 2021, concluding that the risks posed by its use are unacceptable (Argentina, 2021).

## 2. Summary information relevant to the risk profile

### 2.1 Sources

#### Production, trade, stockpiles

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

35 While data are not available on total global production volumes, data from the CCPIA (2022) indicated that, in terms of volume of use, prior to 2007, global use was about 10,000 tonnes/year. It is indicated that, following the prohibition of five highly toxic organophosphorus pesticides in China, chlorpyrifos has become the dominant insecticide used in the country (Chen et al., 2012), with the global use now estimated to be 50,000 tonnes/year (CCPAA, 2022).

36 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 t, of which 11,000 t was used domestically, 12,000 t was exported and 1,000 was stockpiles (PMFAI, 2022). Data of 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. The products with highest export value were chlorpyrifos 97% TC, chlorpyrifos 40% EC and chlorpyrifos 95% TC. In 2017 the total domestic consumption of the substance applied on several crops (mainly rice, vegetables, fruits and cotton) was reportedly ~18,000 tonnes.

37 Production of chlorpyrifos in the USA has taken place for the last 50 years. It has been marketed under many trade names including Brodan®, Detmol UA® Dowco 179®, Dursban®, Empire®, Equity®, Eradex®, Lentrek®, Lock-On®, Lorsbanv®, Pageant®, Piridane®, and Stipend® (ATSDR, 1997). While volumes of chlorpyrifos production in the USA have not been provided, production in the USA 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 t (US EPA, 2006) while annual use between 2014 and 2018 was ~2,300 t (US EPA, 2020). The majority of chlorpyrifos products registered for residential treatments were voluntarily cancelled or phased out by the registrants between 1997 and 2001 (US EPA, 2006). Furthermore, applications for use have reportedly declined due to State-level restrictions (e.g. in California), reduced production and the development of alternative products. It is also noted that several manufacturers have voluntarily halted production in the USA in recent years.

38 In Canada, no production is reported. All sales and use of chlorpyrifos active ingredient and most chlorpyrifos end-use products are being imported into Canada. Annual sales of chlorpyrifos in Canada, expressed as volume of active ingredient sold were 133 t in 2020. Australia (2022) reported importing 2131 t of chlorpyrifos (product/active).

39 The withdrawal of chlorpyrifos for use in the European Union in 2020 is expected to have resulted in the ceasing of use, and therefore production or imports of chlorpyrifos in European countries. It is also reported that chlorpyrifos is not produced or used in Norway (Norway, 2022). The United Kingdom (2022) reported no data on production of chlorpyrifos. 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.



40 As presented in European Commission (2017), according to the FAO, chlorpyrifos has been imported from 2008 to 2015 by 12 developing countries and economies in transition from 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 t (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 increased trend over this time-period, despite some slight decreases for some years.

## Uses

41 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 (EM & Shaik, 2015). Pesticide products containing chlorpyrifos are registered for use on many agricultural crops, including corn, soybeans, alfalfa, oranges, wheat, and walnuts. 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, 2020).

42 In the USA, for the period 1987-1998, it was estimated that, of the ~9500 t of chlorpyrifos used annually, approximately 25% was used on corn, 25% for termite control and 12.5% on turf (US EPA, 2006). 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 approximately 4,500 t of chlorpyrifos were removed from the market (US EPA, 2006). Of the 2,300 t of chlorpyrifos reported to be used annually in the USA from 2014-2018, soybeans, alfalfa and corn made up nearly 50% of the total volume of chlorpyrifos used, with soybeans accounting for nearly 25% of total volume applied (US EPA, 2020). In August 2021 the US EPA ended the use of chlorpyrifos products on all food products nationwide. EPA will next proceed with registration review for the remaining non-food uses<sup>5</sup>.

43 In January 2020, the European Commission adopted implementing Regulation EU 2020/18<sup>6</sup>, meaning that 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 has been widely used since 1971, however, since the EU ban, alternative insecticides are being developed. In Sweden, chlorpyrifos was never approved as a plant protection product (Sweden, 2022). At the same time, in Belarus it 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).

44 PMFA (2022) reported that, of the 24,000 t of chlorpyrifos produced in India in 2021, 11,000 t 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 below<sup>7</sup>:

**Table 3. Overview of the specific products, crops and target pests approved for use in India. Source: PMFA (2022)**

Product	Crop	Pest
Chlorpyrifos 10.00% G	Rice (Paddy)	Yellow stem borer, Leaf folder, Gall midge
Chlorpyrifos 20.00% EC	Rice (Paddy)	Hispa
Chlorpyrifos 50.00% EC	Rice (Paddy)	Yellow stem borer, Leaf roller
	Cotton	Bollworms
Chlorpyrifos 01.50% DP	Rice (Paddy)	Yellow stem borer, Green leaf hopper, Brown plant hopper, Leaf folder, Gall midge, Grass hopper

<sup>5</sup> <https://www.epa.gov/newsreleases/epa-takes-next-step-keep-chlorpyrifos-out-food-protecting-farmworkers-and-childrens>

<sup>6</sup> <https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32020R0018&rid=7>

<sup>7</sup> 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)



Product	Crop	Pest
	Bengal gram	Pod borer ( <i>Helicoverpa armigera</i> )
Acetamiprid 00.40%+Chlorpyrifos 20.00% EC	Rice (Paddy)	Stem borer, Brown plant hopper, White backed plant hopper
Bifenthrin 03.00%+Chlorpyrifos 30.00% w/w EC	Rice (Paddy)	Stem borer, Leaf folder
Chlorpyrifos 50.00%+Cypermethrin 05.00% EC	Cotton	Aphid, Jassids, Thrips, Whitefly, Spodoptera litura, Spotted bollworm, Pink bollworm, American bollworm
	Rice (Paddy)	Yellow stem borer, Leaf folder
Chlorpyrifos 16.00%+Alphacypermethrin 01.00% EC	Cotton	Spotted bollworm, Pink bollworm, American bollworm
Acetamiprid 00.40%+Chlorpyrifos 20.00% EC	Rice (Paddy)	Stem Borer, Brown plant hopper and White backed plant hopper

45 Other chlorpyrifos products are used in India for non-agricultural purposes, namely to protect buildings from termite attack at pre and post construction stages; to control adult mosquitoes and their vectors; and to protect wood from termites and borers within households<sup>8</sup>.

46 The use of chlorpyrifos as a termiticide was phased-out in the USA in the year 2000. Although several other countries also have phased out the use of chlorpyrifos in termite control, chlorpyrifos is still used as a termiticide in India (India, 2020), as stated above, and Australia (Australia, 2000), as well as in a number of African states such as Zambia and Zimbabwe (Rother). However, in Australia a review process for chlorpyrifos usage as termiticide is in progress (Australia, 2019).

47 As noted above, use of chlorpyrifos in China has been reported on rice, vegetables, fruits and cotton, however chlorpyrifos was prohibited for use on vegetables in China from December 2016 (CCPIA, 2022).

## Releases and emissions to the environment

48 Upon its application as a pesticide, chlorpyrifos follows several potential pathways. It either adheres to the soil particles, leaches through the soil into groundwater, reaches the aquatic environment through runoff irrigation water, or travels through the air (Nandhini et al., 2021; Das et al., 2020; Gebremariam et al., 2012).

49 Between 2007 and 2017, in Europe, emissions of chlorpyrifos to water were recorded 24 times in 5 countries with a total of 27.6 kg as reported under the Regulation on the European Pollutant Release and Transfer Register (E-PRTR). In 2016, according to a Water Framework Directive dataset review, chlorpyrifos emissions above 0 values were reported in 6 countries; however, only one country reported the pollutant's release from agricultural activities, while 3 countries reported the pollutant's release from riverine load.

## 3. Environmental fate

### 3.1 Persistence

50 According to the European draft renewal assessment report (RAR) (Spain, 2017a) and US EPA (2006), chlorpyrifos appears to degrade slowly in soil under both aerobic and anaerobic conditions. It has a low water solubility and a high soil binding capacity. Information on leaching and adsorption/desorption indicate that parent chlorpyrifos in soil or sediment is largely immobile. The pesticide agent can contaminate surface water via spray drift at the time of application or 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. However,

<sup>8</sup> 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)



under some conditions, dissolution in runoff water may be significant. All half-lives mentioned in the following chapters are listed in tables 2-7 in the INF-document.

51 Various studies examining the route of degradation have been assessed in the European RAR for chlorpyrifos (Spain, 2017b). 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% in soil. Other minor metabolites, 2-Methoxy-3,5,6-trichloropyridine (TMP, max 2.9 %AR), 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 eventually degraded to CO<sub>2</sub> and to non-extractable residues.

## Environmental distribution

52 According to UNEP (2012), chlorpyrifos may be volatile with regard to its vapour pressure and its Henry's Law constant (for values see the table 2). It is concluded that volatilisation plays a role in the overall dissipation process in the field.

### Soil photolysis

53 The RAR (Spain, 2017b) lists four studies on soil photolysis (Havens et al., 1992; Racke et al., 1994; Walia et al., 1988; Yackovich et al., 1985). In the study by Havens et al. (1992), the half-life of chlorpyrifos in soil was calculated to be 30 h ( $r^2=0.94$ ) and 28.5 hours ( $r^2=0.96$ ) for light and dark respectively indicating that photolysis is not a significant degradation process for chlorpyrifos. The half-life for the main metabolite TCP was calculated to be 17.7 days in light, and could not be calculated in the dark since levels increased throughout the study period.

54 Racke et al. (1994) determined the photodegradation rate and identified the photodegradates of the main metabolite (TCP) of both chlorpyrifos and chlorpyrifos-methyl on soil surface. Approximately 50% of the applied TCP degraded during the first 8 hours of sunlight exposure, the half-life was calculated to be 14.1 days ( $R^2 = 0.820$ ). The major photoproduct of TCP was CO<sub>2</sub> (40% AR at 30 days) and small amounts of polar and non-extractable residues were also formed. The study author suggests that these polar residues may represent transient intermediates to CO<sub>2</sub>.

### Hydrolytic degradation

55 The RAR for chlorpyrifos (Spain, 2017b) lists five studies on hydrolysis in pure water. The hydrolysis of chlorpyrifos has been found by P.J. McCall (1986) to be independent of pH below pH 7 with a half-life of approximately 72 days. At alkaline pH, hydrolysis is dependent on pH with a measured half-life for chlorpyrifos of 16 days at pH 9, 25°C in this study. Under conditions encountered in the environment, where other dissipative processes act on the chemical, hydrolysis will tend to be a minor route for dissipation of the chemical. For an overview of pH dependant degradation of chlorpyrifos please see the INF-document table 2.

56 Meikle and Youngson (1978) conducted a study to evaluate the hydrolysis rates at different pH and temperature values, and the fate of chlorpyrifos in water. In buffered distilled water at 25°C and pH 8.1, 6.9 and 4.7, the half-life was 23.1, 35.3, and 62.7 days, respectively. A comparable aqueous hydrolysis half-life at 35 °C and pH 4.7 of 15.75 days has been reported.

57 Macalady and Wolfe (1985) determined the hydrolysis of various organophosphorothioate insecticides in sediment-water samples to define the role of hydrolysis in the sediment-sorbed state. For chlorpyrifos, the observed rate constants were the same in the sediment and aqueous phases and similar in magnitude to those found for natural water samples.

58 In spite of some shortcomings, the study by Hui et al. (2010) supports the conclusions of other studies that chlorpyrifos is relatively stable in an acidic medium, but the rate of degradation increases with increasing pH. The half-life is also influenced by temperature.

59 WHO (2009) provides hydrolysis characteristics of chlorpyrifos. The half-lives in buffers at 25°C were 72 d at pH 5 and pH 7, and 16 d at pH 9 (guideline EPA Sub. N 161-1; source: Dow). The half-lives in buffers at 30°C were 72 d at pH 4.0, 40 d at pH 7.0, and 24 d at pH 9.0 (guideline EPA test method CS5000; source: Makhteshim).

60 A comprehensive discussion on chlorpyrifos hydrolysis data may be found in an evaluation by Mackay et al. (2014). These authors compiled studies from different sources. One major source for that evaluation was a review by Racke (1993). Reported half-lives for hydrolysis in distilled and natural waters at pH values between 5 and 9 (environmentally relevant pH) were between 1.5 d and 142 d. The Henry's Law constant of 1.11 Pa.m<sup>3</sup>/mole (Mackay, 2014) is high enough that volatilisation from water should occur. Early laboratory half-lives of 8-24 hours in open beakers of distilled water are too short for hydrolysis and thought to reflect volatilisation. Aeration of 10 L of



a 50 ppb solution at 80 mL/minute left less than 15% of the applied dose after 24 hours. In (Schimmel et al., 1983, cited in Racke 1993 and Australia, 2000a), 63% of applied chlorpyrifos were recovered from resin traps attached to jars holding aerated seawater solutions. Mackay et al. (2014) reported an overall mean hydrolysis half-life of 46 d and a geometric mean half-life of 29 d. Half-lives at pH <5 were generally longer (16 - 210 d) and at pH >9 shorter (0.1 - 10 d). The authors also report that the chlorpyrifos hydrolysis half-lives are influenced by the presence of copper ions (increased hydrolysis rate) and suspended solids (decreased hydrolysis rate).

### Direct and indirect photochemical degradation in water

61 The European Union RAR for chlorpyrifos (Spain, 2017b) lists eight studies on direct photochemical degradation in water, one of which (Adam (2015)) also deals with indirect photochemical degradation. The study by Batzer et al. (1990) was carried out according to US EPA 161-2, using a mercury lamp as irradiation. As chlorpyrifos is more stable toward hydrolysis in acid than in alkaline solution, the influence of hydrolysis in the irradiated samples was minimized by the use of buffered solutions at pH 7. The half-lives were estimated in Jackson (1994) and amounted to 14.6 days for mid-summer at 20°N, and to 29208 days (80 years) for midwinter at 60°N. It should be noted that the long half-lives calculated for winter at northerly latitudes are unrealistic since they do not account for seasonal changes and assume that sunlight intensity does not vary from mid-winter conditions.

62 Adam (2015) concluded that chlorpyrifos is degraded by direct and indirect photolysis with net half-lives of 7.2 and 2.9 days natural summer sunlight at latitudes 30 to 50°N. For irradiated samples, it was not possible to completely avoid volatilisation of the test item from the water phase. The review by Racke (1993) cites the study by P.J. McCall (1986) who investigated photolytic degradation (0.35 - 0.38 ppm) in an aqueous buffer (pH 5) and reported a photolysis half-life of 52 days upon exposure to an artificial light source (general Electric Chroma lamps). In the study of Meikle et al. (1983), photolysis half-lives observed ranged from 9.4 to 15.6 days (corrected for hydrolysis) and 7.8 to 11.0 days (uncorrected for hydrolysis). This study is considered as additional information. Dilling (1984) estimated half-lives for chlorpyrifos of 31 – 43 d in summer and 345 d in winter in pure water. In river water, summer half-life was estimated at 980 d for average light attenuation coefficients for ten river water samples from south-east US.

63 Although photolysis can be a degradation pathway, this is limited to the upper centimetres of a water body, depending on turbidity.

64 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 in distilled and natural waters at pH values between 5 and 9 (environmentally relevant pH) were between 1.5 d and 142 d. Hydrolysis assessments performed in distilled water are of only limited relevance for natural waters due to high KOC of chlorpyrifos. High losses due to volatilisation as reported by some studies are also noteworthy.

## Biotic degradation

### Water

65 The European Union RAR for chlorpyrifos (Spain, 2017b) reports several studies on degradation in water. In a study by (Gassen, 2015) on aerobic mineralisation in surface water, conducted according to OECD TG 309, DT50 values of 21 and 46 d at 22°C were estimated. In all systems, up to 28.5% of unchanged parent was progressively lost from the test systems due to evaporation from the aqueous layer during the incubation period, thus the DT50 values do not refer to degradation alone, but rather to dissipation: loss through volatilisation as well as degradation. In Caviezel (2015) dissipation of chlorpyrifos was mainly caused by volatilisation from the surface water, reaching between 58.6% and 64.4% AR after 61 days of incubation, and to a lesser extent by biodegradation. Similarly, in another study on degradation in three static marine water systems Swales (2003) DT50s of 45 d in estuarine (15°C), 35 d in coastal (12°C) and 75 d in open sea water (8°C), respectively, were estimated, again with a rapidly declining 14C-mass balance which points to substantial volatilisation. With a Henry's law constant of 1.1 Pa m<sup>3</sup>mol<sup>-1</sup> at 20°C, these observations are plausible. The Henry's Law constant is high enough that volatilisation from water should occur. Early laboratory half-lives of 8-24 hours in open beakers of distilled water are too short for hydrolysis and thought to reflect volatilisation. Aeration of 10 L of a 50 ppb solution at 80 mL/minute left less than 15% of the applied dose after 24 hours. The most compelling evidence is the recovery of 63% of applied chlorpyrifos from resin traps attached to jars holding aerated seawater solutions (Schimmel et al., 1983, cited in Racke 1993 and Australia, 2000a). All half-lives mentioned here are listed in Table 2.

66 Daam et al. (2008) investigated the dissipation of chlorpyrifos in outdoor freshwater microcosms in Thailand. The application rate was 1 µg/L active ingredient. 7 d after application about 30% of the initial chlorpyrifos could be detected, and after 28 d 10%. This can only in part be attributed to degradation, since the concentrations in sediment



increased to about 10% of the applied active ingredient after 28 d. Volatilisation and adsorption to biomass were not measured but cannot be excluded. The dissipation of 14C-chlorpyrifos in estuarine outdoor microcosms in Vietnam studied by Nhan et al. (2002) and Pablo et al. (2008) found chlorpyrifos dissipation half-lives of < 1 d (probably due to dilution processes) and about 5 d, respectively. Mackay et al. (2014) summarised that the dissipation half-life of chlorpyrifos in natural waters under field conditions is about 4 - 10 d (geometric mean 5 d). Since in field studies or open test systems volatilisation contributes considerably to the overall dissipation, the results of these outdoor microcosm studies are considered less relevant.

67 The DT50 values listed here probably overestimate degradation in water, since volatilisation contributes considerably to dissipation. Thus, with a DT50 of 75 d at 8°C, following the criterion of a half-life >2 months mentioned in Annex D, chlorpyrifos can be considered persistent in water, especially at lower temperatures. 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).

## Soil

68 For the assessment of route and rate of degradation of chlorpyrifos, numerous studies are available, both published papers and proprietary studies conducted for registration purposes. Many of these studies have been conducted according to the OECD test guideline 307 (OECD, 2002), which is the current mandatory standard in the EU, but also according to US guidelines and older guidelines such as the BBA guidelines. 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 European Union RAR (Spain, 2017b) and PMFA, 2022.

## Laboratory studies – rate of degradation

69 De Vette and Schoonmade (2000) and B. Clark (2013) have conducted studies on route and rate of degradation in four soils each. The degradation kinetics have been re-evaluated by Abu (2015) according to FOCUS degradation kinetics (FOCUS, 2006)<sup>9</sup>. Degradation half-lives range from 5.96 d – 110.3 d at 20°C. Although the soil used by Bidlack (1979) was stored for several months, the DegT50 values are in the same range as other studies (11 – 141 days). All half-lives mentioned here are listed in table 4 of the INF-document. There, one column is included with DT50 values normalised to 12°C to illustrate reduced degradation in more temperate regions.

70 Degradation in soil is temperature-dependant (Getzin, 1981), with DegT50 values ranging from 6 weeks (42 d) at 35°C through 13 weeks (91 d) at 25°C to 25 weeks (175 d) at 15°C in one soil (silt loam), which is just below the trigger value in Annex D of the Stockholm Convention (SSC, 2018). At 5°C, the temperature associated with some Arctic environments, the DegT50 would be expected to be in the order of 50 weeks, given that Getzin's (1981) figures show an approximate doubling of the value for each 10 degrees lowering of temperature. Racke et al. (1994) also reported that degradation half-lives doubled with each decrease of 10 °C.

71 As observed degradation process, hydrolysis in alkaline soils and a combination of hydrolysis and biodegradation in acidic soils is assumed. Degradation decreases in soils with low water contents, and in experiments at lower temperatures. The major transformation product of chlorpyrifos in soil was TCP (up to 40% of the applied test substance).

72 Chai et al. (2013) studied the degradation of chlorpyrifos in three humid tropical soils from Malaysia and found that degradation was fastest in moist soils ( $t_{1/2}$  53.3 - 77.0 days), compared to dry ( $t_{1/2}$  49.5 - 120 days) and wet soils ( $t_{1/2}$  63.0 - 124 days). Degradation increased markedly with temperature and decreased with higher chlorpyrifos dosages (5-fold) which are often applied in the tropics due to severe insect infestations. Degradation and mineralization rates decreased 2-fold.

73 Chlorpyrifos is strongly bound to soil and non-mobile (mean KOC 8500 mL/g). The major metabolite TCP (a weak acid) is weakly bound to soil and highly mobile (KOC 27 – 389 mL/g), with increasing mobility as the pH increases.

## Field studies

74 In general, DT50 values in field studies are lower than in laboratory studies. However, it has to be kept in mind that in field studies, the DT50 refers to dissipation, not degradation, since the test is not done in a closed system and losses due to volatilisation etc. are not accounted for (Mackay et al., 2014). Fontaine (1987) investigated three soils (see INF-document table 6), and Old (2002a, 2002b, 2002c) investigated four soils. Dissipation half-lives were in the range 5 to 89 days. Following application, volatilisation is expected to contribute significantly to early losses of

<sup>9</sup> FOCUS is a tool for the estimation of half-lives used for the evaluation of pesticides in the EU



chlorpyrifos from soil surfaces (up to 25 % within 24 – 48 hours) and plant surfaces (80 % within 24 – 48 hours) (Australia 2022)

### Degradation of chlorpyrifos at application rates used for termite control

75 The review by Giesy et al. (2014) compiled and evaluated a large number of studies on soil degradation of chlorpyrifos. The work relied mainly on a previous review by Racke (1993). Half-lives for dissipation from soils via all pathways ranged from 1.1 to 1576 d. The highest half-life values were reported for the highest application rates (up to 1000 mg/kg, for control of termites). They are based on investigations by Racke (1993) who observed that the increase in application rate from typical agricultural use (10 mg/kg) to that for urban termiticide application (1000 mg/kg) resulted in a dramatically decreased rate of dissipation. These results were confirmed by a study by Murray et al. (2001). These authors found that the degradation rate of chlorpyrifos was strongly retarded at an initial soil concentration of 1000 mg/kg as compared to lower soil concentrations of 100 and 10 mg/kg in the same soils. The degradation followed a logarithmic function. The derived average half-lives for the three concentrations in several Australian soils were 385 d, 155 d, and 41 d, respectively.

76 Baskaran et al. (1999) performed a test under standard laboratory conditions (25°C, soil moisture 60% of the maximum water holding capacity) to determine the half-life of chlorpyrifos. The authors used termiticide application rates (1000 mg/kg) and dark conditions for a test with an Australian red-brown soil. Part of the losses of chlorpyrifos during the incubation period may have been due to volatilisation, but no trapping system for volatile compounds was installed. The observed degradation of chlorpyrifos was biphasic. Initially a fast degradation was measured for a two-month period. Subsequently, chlorpyrifos degraded at a slower rate. The degradation during the slower phase followed first-order kinetics. Half-lives of 315 – 462 d were estimated. The authors report that the transformation product TCP was found in the soil at levels corresponding to 29 % of the applied parent compound after 24 months.

77 Baker and Bellamy (2006) investigated the dissipation of chlorpyrifos applied at termiticide application rates in field plots in Arizona (USA) over a period of 5 years. The degradation was slower in covered plots, which may point to losses due to volatilisation in the open plots, thus leading to an overestimation of degradation. During the first year, the chlorpyrifos concentration decreased from 1420 µg/kg to 315 µg/kg soil (> 75 % dissipation). The estimated DT50(field) was below 3 months. For the covered plots the chlorpyrifos concentration was 1601 µg/kg at the study start and 813 µg/kg after one year (around 49 % dissipation; DT50(field) around 365 d).

78 Sardar and Kole (2005) conducted a laboratory experiment to study the dissipation of chlorpyrifos in an Indian alluvial soil. Test concentration corresponded to 1 kg, 10 kg and 100 kg per ha. The dissipation followed first order kinetics and the calculated half-lives ranged from 20 to 37 d at 28 °C. TCP was identified as primary transformation product (detected after 3 d, maximum level after 30 d). At all application levels TCP concentrations decreased afterwards and could no longer be detected after 120 d. TMP as secondary transformation product was detected during the study course, but also not after 120 d.

79 Although Wright et al., 1994 do not give a half-life, they do report that chlorpyrifos was detected in the soil of all houses investigated 8 years after application, at 1.8 – 396 ppm near exterior walls, and 1.3 - 439 ppm near interior walls. The initial application rate is not given.

80 The reduced degradation of chlorpyrifos at high application rates may not be a result of persistence as such but rather an effect of toxicity to microorganisms.

### Anaerobic degradation

81 An unpublished laboratory study (Bidlack, 1979) compared chlorpyrifos degradation in two soils used for rice growing held under anaerobic conditions (flooded) and under aerobic conditions (for 30 d) followed by anaerobic conditions. For a clayey soil an aerobic degradation half-life of 107 d was determined. The degradation under anaerobic and aerobic/anaerobic conditions yielded half-lives of 51 d and 58 d, respectively. For a loamy soil a half-life of 39 d was found under anaerobic and of 15 d for aerobic/anaerobic conditions as compared to 11 d under aerobic conditions.

### Sediment

82 Reeves and Mackie (1993) in (Spain, 2017b) have conducted a water-sediment study according to BBA Part IV Section 5-1, which was used before adoption of the OECD test guideline 308. They used a sandy loam from Brown Carrick Sediment and a clay loam from Auchingilsie Sediment. Due to low recoveries, the study cannot be considered fully valid, but it does give an indication: Chlorpyrifos degraded under aerobic aquatic conditions with DegT50 values in the total system of 22 and 51 days in the sandy loam and clay loam systems respectively (DT90 values 72 and 168



days). Dissipation was more rapid in the water layer, with DT50 values of 3 and 6 days respectively, this may be due either to adsorption to sediment, to volatilisation or to degradation. Significant levels of radioactivity were lost from the system. It was only partially retained by the connecting PVC tubing. This radioactivity was identified as volatile chlorpyrifos. Low levels of  $^{14}\text{CO}_2$ , < 1% AR, were formed during the incubation period. The principal degradation product was TCP, accounting for a maximum of 16.86% AR at 0 h in Sandy loam Total system and 9.89% AR at 100 d in Clay Loam Total system. In the study by Kennard (1996), chlorpyrifos was applied to the sediment (silty clay loam), not to the water. Here, too, significant amounts of radioactivity were lost. The half-life for chlorpyrifos in the test system (sediment and water) was 30.5 days, and only minimal mineralization to  $^{14}\text{CO}_2$  was observed. The major degradation product formed was TCP, which accounted for a maximum of 44% applied radioactivity in the total system at the end of the incubation period (36d). Another study was conducted by Kang (2015), with two sediment/water test systems. One was collected from Calwich Abbey Lake, the other from Swiss Lake, both in the UK. Samples were incubated for up to 150 days under aerobic conditions with associated overlying waters at a sediment/water ratio of 1:3 in the dark at  $20 \pm 2$  C. [ $^{14}\text{C}$ ] chlorpyrifos was applied at a nominal concentration of 0.50 mg/L. The raw data of this study was re-evaluated by Abu (2015), who estimated DegT50 values of 30.7 and 58.3 d for the total system.

83 Bondarenko and Gan (2004) investigated the degradation of chlorpyrifos in urban sediments from two creeks in southern California, USA. Under aerobic conditions, chlorpyrifos showed half-lives of 20.3 and 23.7 d, and under anaerobic conditions of 223 and 57.6 d, respectively. Half-lives were calculated for first-order degradation kinetics and based on measured concentrations at several time points. In this study, natural sediment was not topped up with original water but deionised water, no mass balance was reported and potential losses by volatilisation were not considered.

84 In a comparative marine water/sediment degradation study by Schimmel et al. (1983) the approximate half-life for chlorpyrifos was reported as 24 d (degradation was tested with 10 g of sediment and 100 mL of pesticide-seawater solution). No appreciable loss of chlorpyrifos was observed after 28 d in a control sample with formalin-treated (sterile) sediment. The authors therefore concluded that the degradation was caused by microorganisms. The chlorpyrifos half-life was lower in outdoor seawater solution exposures than in the indoor experiments (half-life of 4.6 d in systems exposed to sunlight). Although a high volatilisation rate was observed for chlorpyrifos from seawater (up to 63%), the loss was negligible in the presence of sediment in the test systems.

85 Laabs et al. (2007) conducted a semi-field study in microcosms to investigate the fate of chlorpyrifos in a Brazilian wetland and in parallel in a laboratory system for up to 50 d. The semi-field DT50 for chlorpyrifos in water microcosms was 7.0 d (laboratory test: 1.9 d) and the DT90 23.4 d (laboratory test: 6.2 d). The semi-field DT50 for chlorpyrifos in water/sediment microcosms was 36.9 d (laboratory test: 12.2 d) and the DT90 122 d (laboratory test: 40.5 d) for the total system. The respective semi-field DT50 for chlorpyrifos in the water phase of the water/sediment microcosms was 16.0 d (laboratory test: 3.2 d) and the DT90 53.2 d (laboratory test: 10.5 d) for the total system. An environmental fate review from Dow Chemical Company (Racke, 1993) gives a DT50 of 150 to 200 days in anaerobic pond sediments.

86 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. Its adsorption coefficients span two orders of magnitude in soils. Mean and median values for chlorpyrifos partition coefficients normalized to organic carbon, KOC, 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 KOC of 8,500.

87 From ATSDR (1997): ‘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 (Koc) of 973-31,000 ((Felsot & Dahm, 1979; Kenaga, 1980; P. J. McCall et al., 1980) in (Racke, 1993)). This suggests that chlorpyrifos in natural water ecosystems adsorbs strongly to suspended solids and sediments, and that this process may transport considerable amounts of chlorpyrifos from water to particulate matter. Several studies have reported very low concentrations of chlorpyrifos in surface waters.

## Other evidence of persistence

88 The Draft Assessment Report for EU approval (Spain, 2017b) lists seven studies on soil leaching behaviour (column leaching studies) (Reeves & O’Connor, 1994a, 1994b; Pike and Getzin, 1981; Racke, 1993; Fenoll et al. 2011; Rani et al., 2014 ). The results all show that chlorpyrifos is immobile in soil and is unlikely to leach to



groundwater. However, in several recent studies, chlorpyrifos has been detected in groundwater in spite of its high adsorptive capacity. Chlorpyrifos was detected in the majority of ground water and surface water samples collected along the Mediterranean coast of Turkey (Tuncel et al., 2008). The detection frequency of chlorpyrifos in drinking water well samples from the state of Rio Grande do Sul, Brazil, at times, exceeded that of surface water samples (Bortoluzzi et al., 2007). Chlorpyrifos was also detected in many samples taken from Australian water wells (Wightwick & Allinson, 2007). Gebremariam et al. (2012) found that desorption of chlorpyrifos from soils and sediments was low but not insignificant. His model predictions indicate that solid-phase chlorpyrifos will eventually partition to the aqueous phase if the soil or sediment is subjected to continuous desorption events in which they are exposed to water. Thus, although the leaching potential of chlorpyrifos is low due to high adsorptive potential, contaminated soils and sediments could be secondary long-term sources of pollution.

89 Dabrowski et al. (2002) found that the concentration of chlorpyrifos in the Lourens river, South Africa, increased from nondetectable to 0.19 µg/L after a rainfall event. Chlorpyrifos was only found in one of the water samples, but it was detected in a majority of the suspended sediment samples, with a maximum concentration of 152 µg/kg. The Lourens River site downstream of the farming area was identified as a site where potential toxic conditions could arise.

90 The strong association of chlorpyrifos with suspended sediments presents a potential migration route unique to aquatic environments and may explain reported detections of chlorpyrifos in water wells and marine sediments, also because sorbed chlorpyrifos is more persistent in sediments than in soils and water (Gebremariam et al., 2012; Readman et al., 1992; Tuncel et al., 2008).

91 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. In addition, chlorpyrifos is found in dated sediment cores in Arctic and sub-Arctic lakes (Landers, 2008). Although the concentrations in these sediments are low, they do not derive from local use of chlorpyrifos and can be dated back several decades. This also demonstrates the persistence of chlorpyrifos in sediments.

## Conclusion on persistence according to the criteria in Annex D

92 In the water degradation studies evaluated here, DT50 values range from 21 to 75 days at varying temperatures. Chlorpyrifos fulfils the criterion for persistence with half-lives in water greater than two months.

93 In soil, highest half-lives for the chlorpyrifos degradation were found at high application rates (100 - 1000 mg/kg). These are used for termite control, which is still an approved use in a number of countries. The reduced degradation of chlorpyrifos at high application rates may not be a result of persistence as such but rather an effect of toxicity to microorganisms. At application rates for agricultural uses (below 100 mg/kg), the half-lives found in literature and study summaries of proprietary studies span a wide range from 6 to 224 d, at varying temperatures. Normalised to 12°C to illustrate degradation in temperate regions, these values range from 12.7 to 483 days. Of the numerous soil studies evaluated here, around half the normalised DT50 values exceed the criterion for persistence in soil with half-lives greater than 6 months.

94 Half-lives reported for chlorpyrifos degradation in aerobic sediment degradation studies in the laboratory are below the Stockholm Convention threshold of 180 d (six months) for the total system. In most cases, an estimation of half-lives for the sediment alone cannot be done. For studies performed under anaerobic conditions, the half-life values reported were longer and the threshold was exceeded by some studies. Chlorpyrifos sorbs strongly to sediment and can remain there for a prolonged time. Thus, chlorpyrifos is frequently detected in run-off, associated with sediment (Dabrowski et al., 2002; Readman et al., 1992). The strong sorption of chlorpyrifos especially to sediments, where the adsorbed fraction may not be available to microorganisms, may explain the reported detections of chlorpyrifos in water wells and marine sediments. The frequent detection could be attributed in part to widespread use, but also to higher persistence where it is associated with sediment and where temperatures are lower.

95 Environmental degradation half-lives of chlorpyrifos range from a few days to several years, 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. In addition, chlorpyrifos is found in dated sediment cores in Arctic and sub-Arctic lakes (Landers, 2008). Thus, chlorpyrifos can be considered persistent in some environments according to the definition of the Stockholm Convention.



## 3.2 Bioaccumulation and toxicokinetics

### Bioaccumulation in laboratory studies

96 For chlorpyrifos log Kow values between 4.7 and 5.2 and log Koa values between 8.3 and 8.9 have been reported (see the INF-document table 1). These values indicate potential bioaccumulation in aquatic and air-breathing organisms.

97 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 many studies cannot be considered fully valid. For an overview of all bioconcentration studies assessed for this dossier, please see the INF-document table 8.

98 Regulatory assessments conducted by the US, Canada, Australia and the EU have determined a moderate bioconcentration factor (BCF) of < 5000 for chlorpyrifos in fish. Although the majority of fish studies conclude on a BCF < 2000, toxic effects occur during these experiments at very low doses. Toxicity is also observed for other aquatic organisms, birds and mammals and especially for humans.

99 The key BCF considered for the Draft Assessment Report for EU approval is  $1374 \pm 321$  in rainbow trout (*Onchorhynchus mykiss*) (report no ES-928 (J42) as summarized in Spain (2017b)). After a 30-day exposure to 0.3 µg/L chlorpyrifos under flow through conditions, a depuration phase of 16 days followed. Steady state was reached. This study was conducted according to EPA Guideline No. 72-6 and 165-4. Values were not normalized for lipid content or growth dilution. As the study was conducted with juvenile trout, growth dilution can lead to an underestimation of the BCF.

100 High bioaccumulation is documented for eleuthero embryos with kinetic BCF of 3548 and 6918 for zebrafish (*Danio rerio*) (El-Amrani et al., 2012) and 2187 for medaka (*Oryzias latipes*) (Alharbi et al., 2017). Exposure concentrations were 1 µg/L and 10 µg/L. The semi static exposure lasted 48 h, depuration lasted 24 h. Four pooled samples of 20 individuals were sampled for each concentration and the control at 0, 2, 6, 21, 29, 45, 48 h of exposure time and 2, 4 and 24 h of the depuration phase. Chlorpyrifos was analysed with high-performance liquid chromatography. Limit of detection (LOD) for chlorpyrifos in water samples was 0.5 µg/L and 3 ng/g for eleuthero embryos. The kinetic BCF was calculated, as steady state was not reached. BCF values were not normalized for lipid content in either experiment. The lipid content of eleuthero embryos is high with 11 – 20% average range (El-Amrani et al., 2012).

101 Deneer (1994), compared lab and field BCF for three-spined stickleback (*Gasterosteus aculeatus*) to investigate the feasibility of predicting the concentration of the organophosphorus insecticide chlorpyrifos in fish in outdoor mesocosms, using uptake and elimination rate constants determined in the laboratory. In the laboratory experiments, he found a lipid-based BCF of 21,000, or 1057 at 5% lipid. Also, a decrease of the elimination rate upon increasing exposure concentrations was found, which leads to an increase of the BCF with increasing exposure concentrations. The predicted values were all lower than the levels of chlorpyrifos found in fish from the outdoor mesocosms.

102 Other fish studies have produced BCF in a wide range, most studies however show toxic effects at low concentrations. Jarvinen et al. (1983) calculated a BCF of  $1673 \pm 423$  for the fathead minnow (*Pimephales promelas*). Toxic effects occurred in all concentrations and included significant mortality at 2.68 µg/L, growth reduction at 1.21 µg/L and reduced reproduction at 0.12 µg/L. For the same species Eaton et al. (1985) produced a lipid normalized BCF of 1150 at concentrations between 0.12 µg/L and 0.83 µg/L. Toxic effects included reduced reproduction and decreased body weight. Goodman et al. (1985) exposed early life stages of two silverside species to chlorpyrifos and determined a maximum BCF of 580. Significant mortality occurred at 1 µg/L and 2 µg/L. Following the same experimental set-up Goodman et al. (1985) produced a maximum BCF of 1000 using the californian grunion (*Leuresthes tenuis*). Here significant mortality and decreased body weight occurred at concentrations of  $0.63 \pm 0.11$  µg/L to  $2.8 \pm 0.48$  µg/L. In the sheepshead minnows (*Cyprinodon variegatus*) a maximum BCF of 1830 was determined (Cripe et al., 1986). Reduced body weight and increased mortality occurred at concentrations above 3.0 µg/L. Hansen et al. (1986) reported a maximum BCF of 5100 for the gulf toadfish (*Opsanus beta*). A decrease in body weight occurred at 18 µg/L and significant mortality at 150 µg/L. For details on these studies please refer to the chapter on bioaccumulation in the INF-document, §5 ff.

103 As demonstrated in the studies described above, toxicity to fish occurs at very low concentrations. These findings are supported by data from the EU RAR (Spain 2017) which gives a 96 h LC50 value of 8 µg active substance per litre (a.s./L) for rainbow trout in a test performed with Dursban. For the estuarine fish *Leuresthes tenuis*, Goodman, Hansen, Cripe, et al. (1985) reported NOEC values of 0.14 and 0.3 µg a.s./L for embryo weight and lethality respectively. Additionally, Giesy et al. (2014) calculated a species sensitivity distribution (SSD) for chlorpyrifos of 0.812 µg a.s./L. For more details see chapter 4 of this document. The concern of high bioaccumulation



is that the likelihood of body concentrations being reached that lead to toxic effect increase either with high bioaccumulation or with high toxicity.

104 Besides fish, other aquatic species are highly susceptible to chlorpyrifos. For *Daphnia magna* an EC50 of 0.1 µg a.s./L (Spain 2017a) and for *Xenopus laevis* (African clawed frog) a 96-h LC50 of 0.564 mg a.s./L (Richards and Kendall, 2002) was determined.

105 Toxicity in terrestrial species has also been demonstrated. For honey bees contact toxicity was identified as LD50 of 0.068 µg a.s./bee for Drusban (Bell (1994). A LD50 of 39.24 mg a.s./kg body weight (bw) was set for the Bobwhite quail (Spain 2017). Acute oral LD50 ranging 64 to 71 mg a.s./kg bw have been set for mice and ranging between 66 to 192 mg a.s./kg (bw) for rats (European Commission 2005). For further information on toxicity see chapter 3.4 of this document.

106 Bioaccumulation in sediment dwelling organisms has been measured for the oligochaete *Lumbriculus variegatus* (A. Jantunen et al., 2008). Four different sediments were tested in a 10-day static exposure with concentrations ranging from 0.06 to 1.1 µmol/kg dry weight. Steady state was not reached, which may lead to an underestimation of bioaccumulation potential. Bioaccumulation was measured as biota-sediment accumulation factors (BSAFs). BSAFs ranged from 6 to 99 depending on soil and chlorpyrifos concentration. This BSAF value indicates high bioaccumulation (ECHA, 2017).

107 In the earth worm species *Eisenia Andrei* Svobodová et al. (2018) measured BAF values at steady state following the experimental design of OECD 317. Both soil types were sterilized with gamma radiation and the nominal concentration was set to 5 mg kg<sup>-1</sup> soil dry weight to represent worst case scenarios. BAF under steady state were calculated as  $6.34 \pm 1.30$  and  $4.51 \pm 0.76$  for the different soils.

## Monitoring data concerning bioaccumulation

108 Chlorpyrifos has been detected in various biota samples from around the world, including the Arctic. During the Western Airborne Contaminant Assessment Project (WACAP), levels of chlorpyrifos were measured in national parks of the USA. Chlorpyrifos was detected 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 chlorpyrifos concentration. In the one-year white fir needles chlorpyrifos was not detected, while the mean concentration in the older needles amounted to 19.7 ng/g lw. The mean concentration in the pine needles was 11.6 ng/g lw in the first year and 20.5 ng/g lw in the second year (Landers, 2008).

109 Kurt-Karakus et al. (2011) detected chlorpyrifos in zooplankton collected from three remote inland lakes in Ontario in 2003 and 2004. Plankton were collected with a 250 µm net. With regard to lw the geometric mean of the overall BAF was 3300 while the corresponding medians were 270 to 16,200 for the individual lakes. The highest BAF found at the three lakes amounted to 117,000 referring to lipid weight. The uncertainty for plankton-based bioaccumulation is based on the high surface to volume ratio. Adsorption may occur and could skew bioaccumulation values.

110 A recent study in 2016, by Bonansea et al., investigated the accumulation of chlorpyrifos in the *Jenynsia multidentate* fish when exposed for 96 hours to different mixtures, namely: a mixture with chlorpyrifos individually of a 0.4 mg/L concentration, a technical mixture of concentrations 0.04mg/L of cypermethrin þ 0.4 mg/L of chlorpyrifos, and a mixture of commercial products with concentrations 0.04mg/L of cypermethrin þ 0.4mg/L of chlorpyrifos. The LOD level set for chlorpyrifos was 3 mg/kg. The mixture with only chlorpyrifos showed concentration <LOD the muscles and brain,  $67 \pm 49$  mg/kg in intestines,  $58 \pm 25$  mg/kg in liver, and  $42 \pm 31$  mg/kg in gills. The technical mixture showed chlorpyrifos concentrations <LOD in all fish parts. The commercial product mixture showed chlorpyrifos concentrations <LOD in brain,  $8 \pm 5$  mg/kg in muscles,  $50 \pm 29$  mg/kg in intestine,  $323 \pm 187$  mg/kg in liver, and  $11 \pm 6$  mg/kg in gills. Fish exposed to the individual chlorpyrifos showed BCFs in a range from 133 L/kg to 212 L/kg in the intestine, liver, and gills, indicating that the 2 compounds have the capacity to bioconcentrate in *J. multidentate*.

111 In the years 1997 and 1998 blood samples from sea otters (*Enhydra lutris ssp.*) in California and Alaska, USA were analysed for POP 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.



112 In 2005 the liver of river otters (*Lontra canadensis*) from New Jersey, USA were sampled for POP and other contaminants (Stansley et al., 2010). Analysis was performed with mass spectrometry. The sample size was 32, of which 12 showed no contamination with chlorpyrifos. The remaining individuals showed a mean concentration of 0.78 ng/g wet weight with a 95% confidence interval of 0.62 – 1.50 and a maximum of 6.91 ng/g.

113 During the winter of 2011, feathers of 23 blackbrowed albatross (*Thalassarche melanophris*) and 19 Cape petrels (*Daption capense*) were collected on the Patagonian Shelf of Argentina (Adrogué et al., 2019). They were analysed for different POP and chlorpyrifos using gas chromatography. The recovery rate was > 90% and the detection limit was between 0.08 and 0.33 ng/mL for different substances. Chlorpyrifos showed the highest concentrations of all substances analysed with  $58.64 \pm 27.31$  ng/g feather in male Albatross and  $84.88 \pm 50.57$  for male petrels.

114 The bioaccumulation of chlorpyrifos was investigated in the vegetation-caribou-wolf food chain in the Bathurst region (Nunavut) in Canada by Morris et al. (2014). The analytical recovery of chlorpyrifos from biota was low at  $52 \pm 17\%$ . The minimum detection limits (MDLs) were 0.18 ng/g lw for plants, 0.13 ng/g lw for caribou and 0.054 ng/g lw for wolves. The detection frequency for vegetation samples above the MDL was about 50% for lichen species and green plants and 80% for mushrooms. All concentrations were corrected for blanks and normalized to lipid-equivalents and reported as the geometric mean  $\pm$  standard errors (ng/g lw). For lichen the concentrations were  $0.25 \pm 0.21$  ng/g lw, for green plants including willow, mosses and grasses the concentrations were  $0.24 \pm 0.088$  ng/g lw and for mushrooms the concentrations were  $0.85 \pm 0.52$  ng/g lw. Chlorpyrifos was found in five caribou samples at  $0.40 \pm 0.16$  ng/g lw specifically in muscle but not in the liver and in one wolf liver below the MDL.

115 Morris et al. (2016) examined the polar bear and ringed seal food chains in three marine locations of Arctic Canada in the region Nunavut. Sampling took place in the years 2007, 2008 and 2010 at the sites Barrow Strait, Rae Strait and Cumberland Sound. The analytical recovery of chlorpyrifos from biota was only  $52 \pm 17\%$ . The MDL values for biota were not reported, the detection frequencies for samples above the MDL were reported. Concentrations were blank corrected and lipid normalized and given as geometric mean concentrations (ng/g lw) with the 95% confidence intervals. Chlorpyrifos was found in plankton at all three sites. The detection frequency above MDL varied between the three sites from 25% to 100% with mean concentrations of 0.41 ng/g lw (95%-CI 0.33–0.51), 0.33 ng/g lw (95%-CI 0.11–0.95) and 1.1 ng/g lw (95%-CI 0.010–131). Concentrations of chlorpyrifos were measured in Arctic char (*Salvelinus alpinus*) and capelin (*Mallotus villosus*) at Cumberland Sound with a detection frequency above MDL of 80% and 40% and concentrations of 0.11 ng/g lw (0.013–0.93) and 0.31 ng/g lw (0.017–5.5) respectively. Two samples of ringed seals at Barrow Strait showed concentrations above the MDL at 0.022 ng/g lw and 0.038 ng/g lw. Chlorpyrifos was most consistently detected in polar bear fat with detection frequencies above MDL of > 75% at all three sampling sites. Mean concentrations in polar bear fat were 0.022 ng/g lw (0.013–0.035), 0.032 ng/g lw (0.013–0.076) and 0.016 ng/g lw (0.0078–0.033) at the different sites.

116 During monitoring in Jaunpur, India, blood samples were taken from fish, chicken, goats and men near the river Gomti (Singh et al., 2008). Sample size was five. Chlorpyrifos, endosulfan, aldrin, and HCH and DDT isomers were analysed with gas liquid chromatography at recovery rates between 93.02 and 95.5% and a detection limit of 0.1 ppb. In fish, levels of chlorpyrifos in blood were 150 ppb similar to levels of lindane. For other species chlorpyrifos levels in blood were measured at 80 ppb in chicken, 70 ppb for goat and 40 ppb for men. These levels were comparable to the level of aldrin, a recognised POP, found in the blood of these species.

117 Urine is the most common matrix used for biological monitoring of OP insecticide exposure in humans (Barr and Angerer, 2006). In the case of chlorpyrifos, levels of the metabolite 3,5,6-trichloro-2-pyridinol (TCPY) have frequently been used as a biomarker of exposure to chlorpyrifos (see Andersen, 2019; Bevan et al., 20179). The vast majority of reported monitoring data in humans has been from studies analysing urine samples (; Albers et al., 2004; Atabila et al., 2018; Dalsager et al., 2018; Ismail et al., 2021; Koch and Angerer, 2001; Paglia et al., 2021; Phung et al., 2012; Wang et al., 2016; Ye et al. 2008; Ye et al. 2009).

118 Other studies investigate chlorpyrifos concentrations in blood samples or breast milk.

119 Chlorpyrifos and chlorpyrifos-methyl were found in breast milk sampled from women of agricultural and urban regions of California, USA (Weldon et al., 2011). Breast milk of 13 women from Salinas and 21 women from San Francisco was sampled between 2002 and 2007. Chlorpyrifos was detected in all samples with a mean of 40.5 pg/g milk, minimum of 12.9 and maximum of 223 pg/g milk in urban samples. In agricultural samples the mean was 139 pg/g milk, with a minimum of 12.8 pg/g milk and a maximum of 1070 pg/g milk.

120 In Pakistan, chlorpyrifos was detected in breast milk samples from 55% of women cotton pickers at 0.001 to 0.04 ppm, in 40% of chili workers at 0.0002 to 0.15 ppm, in 45% of okra pickers at 0 to 0.048 ppm, and in 30% of



berseem and wheat harvesters at 0.001 to 0.005 ppm. 20 women were sampled per crop. Pesticide recovery rates were between 85 and 100%. No limit of detection was given (Sheikh et al., 2014).

121 53 breast milk samples were analysed from women of the agricultural area of Punjab, India (Bedi et al., 2013). Samples were collected during November and December of 2011. Chlorpyrifos was found in 5.7% of samples at a median of 1664.2 ng/g lw. Authors stated this to be the first finding of chlorpyrifos in human breast milk in the area of Punjab, which could be explained by the current shift towards the extensive use of this pesticide in India. Three samples exceeded the acceptable daily intake for infants set by EFSA (2014) at 0.001 mg/kg bw.

122 Similar observations have been made for the region Bhopal (India), where the breast milk of 12 women was sampled (Sanghi et al., 2003). The detection limit was 0.01 mg/kg. Here, all samples tested positive for chlorpyrifos with a mean value  $\pm$  SE of  $0.230 \pm 0.024$  mg/kg and a range between 0.085 and 0.355 mg/kg. The consumption of 500 mL milk daily was calculated to exceed the acceptable daily intake for an infant by a factor of 41.

123 In a 2017 study conducted by Brahmand et al (2019) in Iran, breast milk and urine were examined in mothers and their infants under six months to determine chlorpyrifos and metabolite concentration levels. The samples (n=61) were taken from the households between August and November 2017. The mean concentration of chlorpyrifos in mother's breast milk samples was  $1.3 \pm 0.6$   $\mu$ g/L. The mean concentration of chlorpyrifos metabolite in mothers' and infants' urine was found to be  $2.1 \pm 1.4$  and  $1.4 \pm 0.7$   $\mu$ g/L, respectively.

124 Another study was conducted in Thailand in 2016 by Naksen et al. (2016) to examine pesticide residues in human plasma and breast milk. Samples were collected from 63 individuals, breastfeeding farmworkers (n=33) and their spouses (n=30). The LOD was set at 0.18 ng mL for chlorpyrifos. The concentration levels in the plasma samples had a range of <LOD to 0.66 ng mL, while the concentration levels in milk samples had a range of <LOD to 0.46 ng mL.

125 In a study by Casey (2005), a total of 26 breast milk samples, 52 plasma samples and 52 saliva samples were collected to examine the chlorpyrifos concentrations. The samples were put into two groups, namely, non-lactating, and lactating. The mean concentration of chlorpyrifos in breast milk was  $1.10 \pm 0.503$  ppb, and when above LOD set at 0.1 ppb, the range was 0.32 to 2.29 ppb. For the lactating group, the mean concentration of chlorpyrifos in plasma was  $0.186 \pm 0.299$  ppb, and when above LOD, the range was 0.066 to 0.972 ppb. In the non-lactating group, the mean concentration of chlorpyrifos in plasma was  $0.149 \pm 0.111$  ppb, and when above LOD, the range was 0.20 to 0.395 ppb.

126 In another study by Hartle et al. (2018), breast milk from 21 women in the US was analysed for chemical contaminants. The concentration of chlorpyrifos found in breast milk had a range of 4.2 to 54.6 pg/g with a median of 20.5 pg/g. Chlorpyrifos was persistent and kept high concentration values post milk pasteurization with a range of 3.5 to 34.4 pg/g and a median of value 3.7 pg/g.

127 Chlorpyrifos exposure during pregnancy has been linked to severe adverse effects on neurodevelopment in children. As discussed in chapter 3.4.1 of this dossier, animal studies and epidemiological studies confirm the developmental neurotoxicity of chlorpyrifos. Therefore, the exposure of pregnant women and new-borns via breastmilk gives rise to serious concern.

128 A study was conducted, between 1998 and 2001, with a sample of 230 African American and Dominican women living in an urban environment in New York, USA (Perera et al., 2003; Whyatt et al., 2002). Maternal blood (30–35 mL) was collected within 1 day postpartum and umbilical cord blood (30–60 mL) was collected at delivery. Chlorpyrifos was detected in 98% of the maternal blood with concentrations of 7.1 pg/g at a mean of  $4.8 \pm 5.5$  pg/g, with an LOD set at 0.5-1 pg/g. Chlorpyrifos was detected in 94% of the cord plasma samples with concentrations of 7.6 pg/g at a mean of  $4.7 \pm 6.5$  pg/g, with LOD set at 0.5-1 pg/g (Perera et al., 2003; Whyatt et al., 2002, 2004). In a study Cui et al. (2005), the capacity of blood proteins as a storage of chlorpyrifos was investigated. It was found that binding to blood proteins decreases the chlorpyrifos concentration in blood plasma which in turn reduces its toxicity. Binding to bovine serum albumin (BSA) was significantly stronger than binding to bovine hemoglobin (BHb). The authors noted that this process of protein binding with toxic insecticides could affect distribution, metabolism, and excretion of insecticides.

## Conclusion on bioaccumulation according to the criteria in Annex D

129 The log K<sub>ow</sub> for chlorpyrifos indicates potential bioaccumulation. The combination of a log K<sub>ow</sub> >2 and a log K<sub>oa</sub> >5 indicates potential bioaccumulation in air-breathing organisms. Chlorpyrifos has been found in biota at different trophic levels in the remote regions, globally in apex predators and in human breast milk at levels concerning



for offspring. Based on current data available, a BCF of > 5000 cannot be concluded. Fish studies show moderate bioaccumulation with BCF in the range of 1000 to 2000 at concentrations showing toxic effects. BCF above 2000 are observed in early life stages. In combination with high toxicity, even moderate bioaccumulation can lead to body concentrations that elicit adverse effects, thus it is a serious concern. Based on high toxicity in fish and other species such as invertebrates, amphibians, birds and mammals including humans, in combination with a moderate BCF in fish and a BSAF above 6 for soil organisms, chlorpyrifos meets the second criteria (ii) for bioaccumulation in other species, high toxicity and ecotoxicity of Annex D. Based on the reasons stated above, we conclude that chlorpyrifos fulfills the criteria for bioaccumulation.

### 3.3 Potential for long-range transport

130 The predicted atmospheric half-life of chlorpyrifos is mainly determined by the OH radical concentration. Gaseous chlorpyrifos does not exceed a half-life of two days. Particulate chlorpyrifos, however, is more recalcitrant to degradation by OH radical reaction and shows an atmospheric half-life up to 66.5 days. Modelling results indicate air and water as main media for chlorpyrifos transport. Chlorpyrifos has been measured in abiotic and biotic compartments of remote regions.

### Environmental fate properties and model results

131 The vapour pressure for chlorpyrifos has been estimated between  $1.0 \times 10^{-3}$  and  $3.35 \times 10^{-3}$  Pa (see INF-document table 1). Based on these values, chlorpyrifos in the atmosphere will exist mostly in the vapour phase and to a lesser extent the particulate phase.

132 For the vapour phase the dominant mechanism of degradation is based on a reaction with OH radicals (Zhou et al., 2010).

133 Using the Atmospheric Oxidation Program (AOPWIN; ver.1.89; (US EPA)), Simon (2001) calculated an OH radical reaction rate of  $9.16 \times 10^{-12}$  cm<sup>3</sup>/molecule-sec for chlorpyrifos. When applying atmospheric OH radical concentrations of  $0.5 \times 10^6$  molecules/cm<sup>3</sup> (European standard value) and  $1.5 \times 10^6$  molecules/cm<sup>3</sup> (US standard value) it becomes clear that the resulting atmospheric half-life depends on the atmospheric OH radical concentration used for calculation. For an OH radical concentration of  $0.5 \times 10^6$  molecules/cm<sup>3</sup>, the corresponding half-life is 4.1 hours. For an OH radical concentration of  $1.5 \times 10^6$  molecules/cm<sup>3</sup> as used in AOPWIN, the corresponding half-life is 1.4 hours.

134 Muir et al. (2004) replicated these results using AOPWIN in Epi Suite to calculate the half-life of chlorpyrifos. Applying an OH radical concentration of  $1.5 \times 10^6$  molecules/cm<sup>3</sup> the predicted half-life of chlorpyrifos amounted to 1.4 hours while an OH concentration of  $1.5 \times 10^5$  molecules/cm<sup>3</sup> resulted in a half-life of 14 hours. The authors noted, that the later scenario was realistic for spring in the northern hemisphere when chlorpyrifos may be applied early in the growing season. Atmospheric half-life is impacted by seasonal variations of OH radical concentration. Calculations indicate that a reduced OH radical concentration would result in a higher contribution of atmospheric transport.

135 Modelling results are confirmed by degradation experiments. In Muñoz et al. (2012) the atmospheric degradation of gas phase chlorpyrifos was observed in the European Photoreactor (EUPHORE). EUPHORE is a reaction chamber with about 200 m<sup>3</sup> volume covered with FEP foil which allows at least 80 % of outside radiation at wavelengths between 290–500 nm to penetrate the chamber. Over a period of five minutes 280 scans were conducted for FTIR spectroscopy. Additionally, solid-phase microextraction was used to monitor the reaction. The rate constant for the reaction of chlorpyrifos with OH radicals was determined as  $(9.1 \pm 2.1) \times 10^{-11}$  cm<sup>3</sup>/molecules-sec at  $29 \pm 5$  °C. The atmospheric half-life of chlorpyrifos was approximately 2 hours.

136 In the particulate phase, the reaction of chlorpyrifos with OH radicals is significantly reduced (ATSDR, 1997; El Masri et al., 2014). El Masri et al. (2014) measured a heterogeneous OH radical reaction rate of  $5.8 \times 10^{-12}$  cm<sup>3</sup>/molecules-sec at 25°C. For an OH radical concentration of  $0.5 \times 10^6$  molecules/cm<sup>3</sup>, the corresponding half-life of particulate chlorpyrifos is 66.4 hours. For an OH radical concentration of  $1.5 \times 10^6$  molecules/cm<sup>3</sup>, the corresponding half-life is 22.1 hours.

137 Socorro and co-workers showed that pesticides adsorbed to particulates may show an overall atmospheric half-life that exceeds values relevant for long range transport (Socorro et al., 2016). The heterogeneous OH oxidation of pesticides adsorbed on atmospheric particles is a very slow process suggesting that the pesticides can persist for a long time in the atmosphere prior to being either degraded or transferred to terrestrial and aquatic ecosystems.

138 Particulate phase chlorpyrifos was detected during monitoring in air from Spain (Borras et al., 2011; Coscollà et al., 2014) and the Czech Republic (Degrendele et al., 2016) and China (Li et al., 2014).



139 Zhong et al. (2012) assumed that the proportion of current-use pesticides including chlorpyrifos in the particulate phase is generally below 0.001 %. However, at several sites the authors measured distributions between vapour and particulate phase with a percentage of up to 4 % of chlorpyrifos in the particulate phase in oceanic air (see Zhong et al. (2012), supporting information).

140 As described earlier, chlorpyrifos binds strongly to soil and sediment (see chapter on persistence). Coscollà et al. (2014) hypothesize that chlorpyrifos adsorbed to soil particles could be transported by wind erosion as has been shown for other pesticides (Larney et al., 1999).

141 In summary, particulate chlorpyrifos appears to be more recalcitrant to atmospheric degradation. However, the percentage of particulate chlorpyrifos is below 10% in observed scenarios.

142 Once in the water compartment, chlorpyrifos bound to suspended solids and sediment is persistent (see chapter on persistence) and could be carried to remote regions in long range transport via oceanic currents (Ma et al., 2018). Chlorpyrifos bound to particles in the Arctic ocean have been measured by Bigot et al. (2017) and Morris et al. (2016).

143 The OECD Pov and LRTP Screening tool<sup>10</sup> was developed to screen and compare chemicals for potential long-range transport. This tool was used to model the characteristic travel distance and transfer efficiency of chlorpyrifos. The results do not indicate potential for environmental long-range transport<sup>11</sup>. However, the publications cited above show that transport of particulate chlorpyrifos via water and air are relevant.

### Presence in remote areas

144 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. In absence of an index including both water and atmospheric transport, the index of von Waldow based on the crop emission scenario is used as an indication of remoteness. A map generated by von Waldow et al. (2010) showing the resulting remoteness indices is shown in figure 1 of the INF-document; findings of chlorpyrifos in remote sections were manually plotted by the dossier drafters.

### Monitoring in abiotic compartments of remote regions

145 According to an AMAP report on Arctic Pollution (Nilsson & Huntington, 2009) chlorpyrifos has been found in fish samples in Alaskan parks, in surface water, ice and fog from the Bering and Chukchi seas, snow samples from Alaska, in air in the eastern Canadian archipelago, and in subarctic and Arctic lakes in Canada. In the following two sections results of monitoring studies published in scientific literature are compiled.

146 Chlorpyrifos was detected in Arctic marine fog, sea water and marine ice by Chernyak et al. (1996) (as cited in Hoferkamp et al. (2010)) who investigated current-use pesticides in the Bering and Chukchi marine ecosystems in the summer of 1993. The highest concentration found in fog condensates was 5 ng/L chlorpyrifos. Only chlorothalonil and metolachlor were found in higher concentrations at most sampling points. Among the five pesticides analysed, chlorpyrifos was the most frequently identified contaminant in sea water with levels ranging up to 67 pg/L. The highest concentration amounting to 170 pg/L was measured in melting ice, where only atrazine was found in higher concentrations. Chernyak et al. (1996) concluded that chlorpyrifos and other detected pesticides could accumulate at the ice surface either directly or as dry fall and snow accumulation. In this frozen condition the compounds would be stable in comparison with their behaviour in a dissolved state. The concentration in an interstitial air sample taken at the same expedition at Chukchi Sea near the Siberian coast amounted to 0.76 pg/m<sup>3</sup> in the vapour phase and 0.08 pg/m<sup>3</sup> bound to particles, while the level in the water phase of a corresponding fog sample was 0.08 ng/L ((Rice & Chernyak, 1997) as cited in Watts (2012)).

<sup>10</sup> OECD POV and LRTP Screening Tool, Version 2.2, 2009

<sup>11</sup> Input physico-chemical properties: log K<sub>ow</sub> 5.2, log K<sub>aw</sub> -3.9

Half-life data calculation 1: air 14 h, water 1800 h, soil 5376 h.

Results calculation 1: Pov = 320 d, CTD (air) = 276 km, CTD (water) = 171 km, TE = 7.86·10<sup>-2</sup>%.

Half-life data calculation 2: air 4.2 h, water 1080 h, soil 2640 h.

Results calculation 2: Pov = 158 x d, CTD (air) = 86 km, CTD (water) = 106 km, TE = 7.69·10<sup>-3</sup>%.



147 Garbarino et al. (2002) analysed current-use pesticides in snow cores that were collected over sea ice from four northwest Alaskan Arctic estuaries. The five sampling sites were situated at the Chukchi and Beaufort Seas. The samples represented the annual snowfall from the 1995/1996 cold season. Chlorpyrifos was detected in snow from three sites with concentrations estimated as 70 to 80 ng/L.

148 Hermanson et al. (2005) analysed the upper 40 m of an ice core from Austfonna (Svalbard Norway), the largest ice cap in Eurasia, for several current-use pesticides and others contaminants. There has never been outdoor agriculture on Svalbard. Chlorpyrifos first appears at Austfonna in 1972, it is one of 8 current-use pesticides with continuous profiles in the core. Its highest concentration amounting to 16.2 ng/L was found in sections of the core corresponding to the early to mid-1980s. Levels began to decline in the 1990s. The compound was not found in the surface layer of the core representing the period 1992 - 1998. All reported concentrations were blank corrected. The authors attributed the occurrence of chlorpyrifos to long-term atmospheric transport concluding that the actual OH radical reaction rate apparently is much slower than predicted from the literature because OH radical production is seasonal and often low in the Arctic.

149 Ruggirello et al. (2010) investigated the current use and legacy pesticide deposition to ice fields on Svalbard (Norway). Samples from a 125 m deep ice core drilled at Holtedahlfonna in 2005 were analysed. Chlorpyrifos was the only organophosphorus current-use pesticide that was detected continuously in the Holtedahlfonna ice core. It was first detected in 1971 - 1980 with a comparatively low input (64.8 pg/cm<sup>2</sup>/year) and decreasing trend until the mid-1990s. Then increasing rapidly reaching maximum concentrations in the time period of 1995 - 2005. During this period the flux peaked at 808 pg/cm<sup>2</sup>/year. The chlorpyrifos burden of the entire ice core accumulated between 1953 and 2005 amounted to 776 ng, higher than any other analysed compound. Chlorpyrifos made up about 34% of the total pesticide burden in the core. The method detection limit was 0.153 ng/L as calculated from three times the standard deviation of blanks. 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. Instead, results suggested that it is persistent in some Arctic conditions. The results of this study were compared with the results found by Hermanson et al. (2005). For this purpose, the concentration data determined at Austfonna were converted to core burdens. The comparative data showed that the chlorpyrifos as well as the alpha-endosulfan burden at Austfonna were much higher than that at Holtedahlfonna. The chlorpyrifos burdens differed by a factor of about 13. It was assumed that the general sources of these pesticides are different at least part of the time, and that Austfonna generally receives the greater input. Ten-year cumulative 5-day air mass trajectories confirmed the assumption that Austfonna had received more atmospheric flow from Eurasia than Holtedahlfonna. The greater Eurasian flow to Austfonna suggested that airflows over-populated and agricultural regions in northern Eurasia might be the source of greater burdens of some pesticides used there.

150 Ice cores collected from polar ice sheets at Site M, Dronning Maud Land, East Antarctica (Lat 75.00 S, Long 15.00 E), and Holtedahlfonna, Svalbard (Lat 79.13 N, Long 13.27 E), were analyzed for a net deposition of 25 organochlorine pesticides (OCPs) and 16 organohalogen (chlorine/bromine) industrial compounds (OHICs). Long-range atmospheric transport (LRAT) delivers contaminants to both sites, but the processes are different: Site M is affected by subsidence of air from the stratosphere to the Antarctic Plateau, while Holtedahlfonna is affected by air moving through the free troposphere. The sample from Site M is a composite core covering 1958–2000, while the Holtedahlfonna sample includes a historic record from 1953 to 2005 in six discrete samples. Chlorpyrifos was detected at the highest concentrations of any of the analyzed substances at both sites (Hermanson et al., 2021).

151 Winter snow from four glacial sites on Svalbard was analyzed 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)

152 Muir et al. (2004) investigated the levels of current-use pesticides in 30 North American lakes, of which six were located in the Canadian Arctic, between 1998 and 2001. The concentrations of chlorpyrifos in the six Arctic lakes ranged from < 0.017 ng/L to 1.6 ng/L with a mean value amounting to 0.27 ng/L. The difference between the mean chlorpyrifos level in arctic lakes and that in mid-latitude lakes was less than one order of magnitude (mean level in lakes receiving agricultural inputs: 0.65; mean level in lakes situated at least 50 km from agricultural areas: 0.82 ng/L). The levels in the seven sub-Arctic lakes were below detection limit.

153 In the Western Airborne Contaminants Assessment Program (WACAP) (Landers, 2008) levels of chlorpyrifos and its transformation product chlorpyrifos oxon (reported as total chlorpyrifos) were analysed in air, snow and lake sediments at several sites in the core parks covered by WACAP. In addition, air samples were collected in the secondary parks. 37 Passive air sampling devices were deployed in all parks in summer 2005 and retrieved one year later. Total chlorpyrifos (almost entirely as chlorpyrifos oxon) was detected in two parks situated in the temperate zone, but not at the sites in the Alaskan parks. Before the onset of spring snowmelt, beginning in 2003 and ending in



2005, snow samples were collected at 13 sites in seven core parks. Total chlorpyrifos was among the most frequently detected pesticides, being found in more than 90% of the samples. The mean concentrations of total chlorpyrifos in snow that were determined in spring 2003, ranged from 0.010 to 0.030 ng/L at the five sites in the three Alaskan core parks. Values below the limit of detection had been replaced by one-half of the detection limit to determine the mean levels. The deposition of total chlorpyrifos accumulated in snow in winter 2002/2003 amounted to 0.48 to 32 ng/m<sup>2</sup> (reported in Hageman et al. (2006)). WACAP also included an investigation on contaminations of lake sediment cores that provided information on the temporal changes of contaminant loadings in the eight core parks over about the last 150 years. Total chlorpyrifos was detected in lakes situated in the three Alaskan core parks. Results from Noatak National Preserve and Gates of the Arctic National Park and Preserve showed increasing contamination of lake sediments with chlorpyrifos until 2000, the most recent year represented by the sediment cores (Landers, 2008)

154 Jantunen et al. (2007) as cited in Hoferkamp et al. (2010) analysed samples from a 2007 cruise of the Labrador Sea. The measured concentrations of chlorpyrifos in air samples ranged from 0.36 to 30.4 pg/m<sup>3</sup>.

155 During a cruise in 2008 across the Beaufort Sea chlorpyrifos was measured in the air at  $3.1 \pm 1.9$  pg/m<sup>3</sup> and in the sea water at  $31 \pm 19$  pg/L (Pučko et al., 2015). These values were used to model the input of chlorpyrifos and other chemicals to the Beaufort Sea via melt ponds. Melt ponds occur during summer months as sea ice melts and act as input pathway for chemicals into the Arctic sea. The model suggested that 16 kg chlorpyrifos was released via meltponds each year, in comparison to 6 kg of alpha-endosulfan. This was estimated to be 4% of total chlorpyrifos contained in the upper layer of the Beaufort Sea region. Authors hypothesized that this phenomenon would increase with climate change.

156 Air samples collected between 2006 and 2009 at the Canadian High Arctic station of Alert in the Canadian Arctic showed a detection frequency of 19% for chlorpyrifos of 68 samples with a mean concentration of 0.39 pg/m<sup>3</sup> (Hung et al. as cited in Balmer et al. (2019)).

157 Marine boundary layer air and surface sea water samples were taken during an expedition of a Chinese research vessel from East China Sea to the high Arctic in 2010 (Zhong et al., 2012). Chlorpyrifos was also measured in blanks. The method detection limit was therefore set at mean blank value added to three times its standard deviation. Still chlorpyrifos was ubiquitously found in oceanic air and sea water with 100% detection frequencies. Along with alpha-endosulfan and dicofol it was the most abundant substance of the six current-use pesticides that were investigated in this study. Air concentrations ranged from 1 to 146 pg/m<sup>3</sup> in the gas phase. The levels of chlorpyrifos dissolved in sea water ranged from 0.1 to 111 pg/L. The highest levels in air and sea water were measured in samples from the Sea of Japan. A significant decline of air and water concentrations from East Asia toward Bering and Chukchi Sea was observed. Air-sea gas exchange data suggested that there was net deposition of chlorpyrifos into the North Pacific and the Arctic. The authors assumed Asian countries as sources of Chlorpyrifos and other detected pesticides for their long-range transport to the Arctic.

158 In 2012 Pučko et al. (2017) collected air, snow, sea-ice, melt-pond water and seawater from the Resolute Passage of the Canadian Arctic. Chlorpyrifos was found in more than 50% of the samples in all media. Concentrations are reported as mean  $\pm$  SD with  $4.8 \pm 1.3$  pg/L in snow,  $14.4 \pm 2.5$  pg/L in melt-pond water,  $14.1 \pm 6.0$  pg/L at surface level sea water,  $10.5 \pm 1.7$  pg/L at sea water of five-meter depth and  $0.10 \pm 0.04$  pg/m<sup>3</sup> for air.

159 Jantunen et al. (2015) conducted sampling cruises in the Canadian Arctic Archipelago in the years 2007, 2008, 2010, 2011 and 2013. The mean detection frequency across all years was 95% for chlorpyrifos in water with mean values  $\pm$  SD of  $13 \pm 12$  pg/L. In comparison other POP such as dieldrin and chlordane had 75%, endosulfan 97% mean detection frequency and concentrations in water of  $20 \pm 20$  pg/L,  $0.82 \pm 0.53$  pg/L and  $3.1 \pm 1.9$  pg/L respectively. For air the detection frequency was 85% with a mean value of  $1.1 \pm 1.3$  pg/m<sup>3</sup>. Temporal trends were derived from regression of the logarithmic concentration in the medium to the year. This was not significant for chlorpyrifos concentrations in water, but indicated that a 50% change in air concentration was reached in 1.5 years.

160 In the summer of 2015 seawater, sea ice and snow were collected from northern Greenland (Bigot et al., 2017). Chlorpyrifos was found in all media, at concentrations between 6.2 – 11.5 pg/L in snow, 5.2 – 12.0 pg/L in sea ice and at 0.74 – 1.0 pg/L in seawater. Chlorpyrifos was also found adsorbed to particles in sea ice and seawater, but at much lower concentrations. Bigot et al. (2017) also measured chlorpyrifos at the Davis Station in Antarctica at concentration exceeding the MDL in sea-ice meltwater at 7.3 pg/L and in air samples between 0.41 and 16.8 pg/m<sup>3</sup> (Supporting Information of Bigot et al. (2017)).

161 Chlorpyrifos was monitored as part of the Swedish national monitoring program for pesticides from 2002 to 2018 on agricultural sites (Boström, 2020). In Sweden, chlorpyrifos was never used as plant protection product, but as indoor biocide in products until 2009. Air samples from two sampling sites were collected with polyurethane foam between 2009 and 2018 and produced a detection frequency of over 90% for chlorpyrifos with median concentrations



of 0.002 ng/m<sup>3</sup>. Precipitation was sampled between 2002 and 2018 at four sampling sites. The detection frequency ranged between 12% to 56% with maximum concentrations ranging between 0.0001 and 0.01015 µg/L. Chlorpyrifos was not detected in surface water, groundwater or sediment. Based on these findings the authors hypothesised that the occurrence of chlorpyrifos in Sweden was based on long range transport.

162 A study analyzed a 102-m ice core taken from the Lys Glacier (Monte Rosa massif, Italy), and meltwater samples from six glaciers distributed along the Alpine Arc during the summer of 2016. Chlorpyrifos was detected in all samples, at concentrations ranging from 1.11 ng/L (in the ice core) – 70.3 ng/L (in 2016 melt water samples) (Rizzi et al., 2019).

## Monitoring in biotic compartments of remote regions

163 Within the WACAP the contamination of the vegetation was investigated in the twenty parks 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. Two-year-old conifer needles from Sitka spruce were also analysed. However, needle samples were not collected in the largely treeless Noatak National Preserve and Gates of the Arctic National Park and Preserve. In these needles mean level of total chlorpyrifos 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, 2008).

164 Furthermore, WACAP reported levels in fish caught at overall 14 lake sites located at the eight core parks (Landers, 2008). A wide age distribution and an even sex ratio (with distributions roughly equal at the various sites) were intended to be achieved (Ackerman et al., 2008). The WACAP fish monitoring included inter alia the investigation of lake trout (*Salvelinus namaycush*) from three lakes situated in the three Alaskan core parks and of whitefish (*Prosopium cylindraceum*) and burbot (*Lota lota*) from another lake in the Denali National Park. Since levels of current-use pesticides in fish were not reported in tabular form by Landers (2008) and Hoferkamp et al. (2010) the approximated mean contaminations from graphical illustrations is given here: total chlorpyrifos ranged from 0.041 to 0.1 ng/g wet weight among the four lakes.

165 A study from Norway included analyses of chlorpyrifos in several Arctic species like fish, seabirds 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. Vorkamp and Rigét (2014) noted that the concentrations in fish reported by Landers (2008) were partly lower than the detection limit in the Norwegian study. The following studies on biomonitoring in remote areas are also described in chapter 3.2 of this dossier, for details please refer to chapter 3.2.

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

167 Morris et al (2014) detected chlorpyrifos in the Canadian Arctic Archipelago in vegetation and mushrooms up to  $0.85 \pm 0.52$  ng/g lw. Additionally, chlorpyrifos was detected above the MDL in five of six samples of caribou muscle tissue at a mean lipid normalized concentration of  $0.40 \pm 0.16$  ng/g lw and in one of seven samples of wolf liver at  $0.06 \pm 0.033$  ng/g lw (Supporting Information of Morris et al. (2014)).

168 Chlorpyrifos was detected in seals and polar bears in the same region by Morris et al. (2016). Concentrations in seals blubber were not reported as the number of samples showing values above MDL were below 20%. Chlorpyrifos was measured in polar bear fat at all three sites. Geometric mean concentrations of 0.022 (0.013–0.035) ng/g lw, 0.032 (0.013–0.076) ng/g lw and 0.016 (0.0078–0.033) ng/g lw were measured (all values were recovery corrected and lipid normalized) (Supporting Information of Morris et al. (2016)).

169 Chlorpyrifos was detected in all samples of polar cod sampled in and outside Bessel Fjord (NE Greenland) (Spataro et al., 2021).

## Discussion on long-range-transport potential according to the criteria in Annex D

170 While modelling results do not predict long-range transport, chlorpyrifos is widely detected in remote areas far away from point sources and/ or agricultural use. Potential routes of transport include atmospheric transport in the gas or particulate phase, transport via water in rivers and/ or ocean currents.



171 Chlorpyrifos in the vapour phase is susceptible to reaction with OH radicals. As described by Muir et al. (Muir et al. 2004), atmospheric half-life is impacted by seasonal variations of OH radical concentration. Calculations indicate that a reduced OH radical concentration would result in a higher contribution of atmospheric transport.

172 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.

173 Based on physico-chemical properties and modelling results, transport in the water phase is expected to be relevant for chlorpyrifos. In the water compartment, the substance may also bind to suspended solids and sediment (Macalady & Wolfe, 1985), where it is persistent (see chapter on persistence). Chlorpyrifos bound to particles in the Arctic ocean has been measured by Bigot et al. (2017). Water-borne chlorpyrifos could be carried to remote regions by long range transport via oceanic currents (Ma et al., 2018).

174 The numerous detections of chlorpyrifos in water samples from remote areas as well as modelling results indicate that transport also occurs via water. A recent study of Sührling et al. (2020) found that the long-range transport of organophosphate esters is not adequately predicted by the OECD Tool. Uncertainty in gas-particle partitioning of non-chlorinated organophosphate esters and river-based transport in case of chlorinated organophosphate esters were discussed as potential reasons for the underestimation of long-range transport (Sührling et al., 2020). Chlorpyrifos is an organothiophosphate, but the respective modelling results could be subject to similar problems. Particularly transport in water might be underestimated by the OECD Tool.

175 There is no straightforward, model-supported explanation for a long-range transport of chlorpyrifos. However, the available data show that chlorpyrifos is present in ambient abiotic and biotic compartments in remote areas as the Arctic and Antarctic. It was detected in various studies, at different remote regions. Both modelling data and detection of chlorpyrifos in water indicate that transport via water is an important, but probably not the only route of transport.

## Conclusion on long-range transport potential according to the criteria in Annex D

176 Though long-range transport is not predicted by modelling results, the compound has been found far away from point sources, in various abiotic and biotic compartments of remote areas such as in caribou, seals and ice bears in the Arctic and sea-ice meltwater and air of Antarctica. Thus, chlorpyrifos is considered to meet the criterion of the Stockholm Convention on long-range environmental transport (SSC, 2018).

## 3.4 Exposure

177 Chlorpyrifos has been detected in air samples, both in regions close to application areas and in remote locations far from application areas, as it can be carried with the wind (Mackay et al., 2014). In a Norwegian screening programme from 2019, chlorpyrifos was found in the samples of house dust from private homes at levels ranging from < 3.0 to 1300 µg/kg dw (Henninge et al., 2020). Concentrations of Chlorpyrifos were found in the air in North America as reported in several studies. In Ontario, Canada, between 2003 and 2005, chlorpyrifos was found in passive air samples at concentrations of 0.0003 to 0.06 ng/m<sup>3</sup> with 73% frequency of detection (Kurt-Karakus et al., 2011). Between 2004 and 2005 in 8 sites in Canada, chlorpyrifos was found at concentrations 0.08 to 22 ng/m<sup>3</sup> in areas of application and distant areas (Yao et al., 2008). In Iowa, USA, chlorpyrifos was detected at an average concentration of 1 ng/m<sup>3</sup> with 19% frequency of detection (Peck and Hornbuckle, 2005). In the Chesapeake Bay, USA, in 2000, chlorpyrifos concentrations of 0.015 to 0.670 ng/m<sup>3</sup> were found with a 87% frequency of detection (Kuang et al., 2003). In the air (Nandhini et al., 2021; Das et al., 2020; Gebremariam et al., 2012).

178 In Canada, chlorpyrifos was detected at concentrations of 10 to 100 ng/m<sup>3</sup> with 3 concentrations exceeding 100 ng/m<sup>3</sup> and a maximum of 250 ng/m<sup>3</sup> in 2003, then a maximum of 1.38 ng/m<sup>3</sup> in 2005 at Bratt's Lake. In addition, concentrations of values less than 0.26 ng/m<sup>3</sup> were found in 2004 and 2005 in Abbotsford area, British Columbia (Raina et al., 2010). In 2003, Gouin et al. (2008) found chlorpyrifos air concentrations ranging between 3.2 and 2700 pg/m<sup>3</sup> at the agricultural sites, while it was reported to range from 0.3 and 7.6 to pg/m<sup>3</sup> in forested areas. Air concentrations of currently-used pesticides were measured at the Canadian High Arctic station of Alert (Nunavut) between 2006 and 2009 and chlorpyrifos was found at levels of 0.27 pg/m<sup>3</sup> (Hung et al., 2013; 2015). Average air concentrations of currently-use pesticides measured during oceanographic surveys in the western Arctic Ocean between 2007 and 2013 had an average chlorpyrifos concentration of 1.1 pg/m<sup>3</sup> (Jantinen et al., 2015). The concentration range of chlorpyrifos in Arctic air and seawater measured during an oceanographic cruise from the North Pacific to the Arctic Ocean in 2010 was 0.5 to 2 pg/m<sup>3</sup> in the air and 0.08 to 0.85 pg/L in seawater (Zhong et al., 2012).

179 Concentrations of chlorpyrifos have also been detected in precipitation and snow in North America. In Chesapeake Bay, USA, chlorpyrifos concentrations were detected in the rain with values ranging between 0.97 and 29



ng/L and an average of 4.8 ng/L, with 14% frequency of detection (Kuang et al., 2003). Between 2000 and 2003, chlorpyrifos concentration in the rain ranged between 1 and 29 ng/L with a 39% frequency of detection in the Delaware and Maryland areas, US (Goel et al, 2005). With regard to snow concentrations, in 2003, chlorpyrifos was found in Sequoia National Park, USA, with average values of 2.8 and 1.3 ng/L (Hageman et al., 2006). In Ontario, Canada, between 2003 and 2005, chlorpyrifos was detected in rain with concentrations ranging between <0.004 and 43 ng/L with 80% frequency of detection (Kurt-Karakus et al., 2011). Moreover, in the Arctic Beaufort Sea area in 2008, chlorpyrifos levels were measured in the air and sea water to predict the levels in the sea-ice melt water. The estimated total annual release of chlorpyrifos was 6 kg (Pucko et al., 2015).

180 Other studies detected chlorpyrifos in surface water in North America. In Sierra Nevada and Yosemite national park in California, USA, chlorpyrifos was found at concentrations less than 0.07 ng/L in surface water in 2004/2005 (Bradford et al., 2010). In Ontario, Canada, it was found at concentrations ranging from less than 0.002 to 0.5 ng/L with a frequency of detection of 77% (Kurt-Karakus et al., 2011). Chlorpyrifos was also detected in Chesapeake Bay, USA, in 2000, at concentrations ranging between 0.51 and 4.6 ng/L (Kuang et al., 2003). Moreover, in Australia, since 2006, Murrumbidgee Irrigation reported chlorpyrifos levels above the limit of detection but below the aquatic NOEC of 0.1 µg/L. An exception to this was reported in 2007 where one sample had a concentration level of 0.1 µg/L and in 2013 two samples had concentration levels of 0.138 and 0.250 µg/L. Likewise, Colleambally Irrigation reported levels below the limit of detection, with the exception of two samples in 2015 (<0.20 µg/L) and one sample in 2006 (30 µg/L) (The Australian Pesticides and Veterinary Medicines Authority, 2019). A monitoring programme in the Niagara fruit belt, Canada, detected chlorpyrifos in 12 of 76 surface water samples with concentrations up to 0.417 µg/L, during the period of chlorpyrifos application (Struger, 2000). The results from a 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 lies in Northern Norway (Schlabach et al., 2018).

181 In 2015, a study by Bigot et al. (2017) investigated the chlorpyrifos levels as dissolved and in particle state in arctic snow, sea ice, and seawater samples in Northeast Greenland. The study found concentration of dissolved/melt water chlorpyrifos to be 6.2-11.5 pg/L in the snow, 5.2-12 pg/L in sea ice, and 0.74 -1 pg/L in sea water. The particles concentrations were <0.66, <0.86 – 15.5, and <0.099 – 0.29 pg/L in the snow, sea ice, and sea water, respectively. In another study by Pucko et al. (2017) examining currently-use pesticides, concentrations in Resolute Passage of the Canadian Arctic, average chlorpyrifos concentrations were reported as  $0.10 \pm 0.04$  pg/m<sup>3</sup>,  $4.8 \pm 1.3$  pg/L,  $14.4 \pm 2.5$  pg/L,  $14.1 \pm 6.1$  pg/L, and  $10.5 \pm 1/7$  pg/L in air, snow, meltponds, seawater (at 0m depth), seawater (at 5m depth), respectively. In Canada, between 2001 and 2017, around 7796 samples were analysed; chlorpyrifos was detected in 841 samples with a maximum concentration of 44 µg a.i./L. This could be broken down to several regions (The Health Canada Pest Management Regulatory Agency, 2020):

- (a) Atlantic Region (2003, 2009, 2014–2015): 103 samples, detected in 3 with a maximum concentration of 0.09 µg a.i./L.
- (b) Quebec (2002–2017): 2819 samples, detected in 387, with a maximum concentration of 44 µg a.i./L.
- (c) Ontario (2002–2015): 1435 samples, detected in 289, with a maximum concentration of 0.52 µg a.i./L.
- (d) Manitoba (2001–2015): 928 samples, detected in 1, with a maximum concentration of 0.02 µg a.i./L.
- (e) Saskatchewan (2000–2011): 449 samples, detected in 1, with a maximum concentration of 0.96 µg a.i./L.
- (f) Alberta (2000–2005): 1701 samples, detected in 2, with a maximum concentration of 0.005 µg a.i./L.
- (g) British Columbia (2004–2014): 454 samples, detected in 161, with a maximum concentration of 1.1 µg a.i./L.

182 In Sweden, data from the Swedish national monitoring programme from 2002-2018 include 4114 measurements where chlorpyrifos has been analyzed. Including air, precipitation, surface water, ground water and sediments, the substance was detected 359 times. The monitoring programme for pesticides is focused on agricultural areas and includes surface water, groundwater and sediment sampling. Chlorpyrifos has almost exclusively been detected in precipitation and air samples but also in flow proportional surface water samples on four occasions, three of them at 0.0002 µg/l and one at 0.0001 µg/l. Chlorpyrifos' concentrations in precipitation are higher in the very south of Sweden, closer to continental Europe, than at the sampling point further north (Boström, 2020).

183 Chlorpyrifos was reported in the list of pesticides most frequently exceeding environmental quality standard (EQS) in surface water bodies in the 2nd River Basin Management Plans (RSMs) in European waters (EEA Report No 7/2018). The annual average EQS (AA-EQS) for surface water is 0.03 µg/l and the maximum allowable concentration (MAC-EQS) is 0.1 µg/l according to Directive 2013/39/EU. In particular, 8 EU Member States had incidences of exceedance, covering a total of 70 water bodies. In 2018, 7 EU Members States (Belgium, Spain, Italy, France, Czechia, Cyprus and Germany) failed to achieve good status for chlorpyrifos levels, covering a total of 66



surface water bodies. In regard to groundwater, only one country, Spain, (for two water bodies) exceeded EQS levels in the 2nd RBMPs. In Austria, in 2018, chlorpyrifos was found at concentrations of 0.018 µg/L in surface water.

## 4. Hazard assessment for endpoint of concern

184 As mentioned earlier in this dossier, chlorpyrifos is an organophosphorus insecticide with a broad-spectrum pest-control. Because chlorpyrifos induces irreversible inhibition of acetylcholinesterase in the central and peripheral nervous system (Colovic et al., 2013; Solomon et al., 2014; WHO, 1987), severe toxic effects in non-target organisms are also expected. This was confirmed by the US EPA Registration Review of chlorpyrifos from 2009 (US EPA, 2006), which identified concerns about acute and chronic risks to birds, mammals, fish, aquatic invertebrates and terrestrial invertebrates. Similar concerns to birds and mammals were identified by EFSA (2005) and EFSA (2014). Additionally, 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).

### Adverse effects on aquatic organisms

185 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 2005 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” (EFSA, 2014).

186 Standard 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 (2017b) reports a 96 h LC<sub>50</sub> value of 8 µg active substance per litre (a.s./L) for a test performed with “Dursban” (trade name of DOW, 99.9% purity). For fish, based on data available in Spain (2017b) 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 203 but performed under similar conditions, lower 96 h LC<sub>50</sub> values are reported. Accordingly, 96 h LC<sub>50</sub> values ranging from 0.53 to 520 µg a.s./L are reported in J. R. Clark et al. (1985). The authors identified the estuarine fishes *Menidia menidia*, *M. peninsulæ*, *M. beryllina* and *Leuresthes tenuis* as the most sensitive species, with 96 h LC<sub>50</sub> values ranging from 0.53 to 4.2 µg a.s./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 a.s./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<sub>5</sub>-LC<sub>50</sub>) of 0.812 µg a.s./L. This means that at the concentration of 0.812 µg a.s./L already 5% of the fish species included in the SSD reach their LC<sub>50</sub>, which clearly demonstrates the acute toxicity of Chlorpyrifos to fish.

187 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. (1985) reported NOEC values of 0.14 and 0.3 µg a.s./L for embryo weight and lethality respectively. Jarvinen and Tanner (1982) determined NOEC values of 1.6 and 3.2 µg a.s./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 a.s./L. This endpoint was assessed for embryo lethality in *Leuresthes tenuis* in a 35-days exposure design (Goodman et al., 1985).

188 Substantial quantity of data is available for aquatic exposure of amphibians to chlorpyrifos. Fryday and Thompson (2012) report 96-h LC<sub>50</sub> < 1 mg/L for the *Xenopus laevis* and *Bufo bufo* *Gargarizans* (0.564 from Richards and Kendall (2002) and 0.800 mg a.s./L from Yin et al. (2009), respectively).

189 Invertebrates, especially crustaceans and insects, are the most sensitive taxa among aquatic organisms. Considering only tests performed in an OECD 202 design, European Commission (2005) and Spain (2017b) identified *Daphnia magna* as the most sensitive species with an EC<sub>50</sub> of 0.1 µg a.s./L. This endpoint is in the same range as the EC<sub>50</sub> of 0.138 µg a.s./L determined for the macroinvertebrate *Hyaella azteca* (Brown et al., 1997). When referring to non-OECD tests with similar set ups, Giddings et al. (2014) identified *Daphnia ambigua* as the most sensitive species with an EC<sub>50</sub> of 0.035 µg a.s./L. Using an SSD approach, the authors calculate HC<sub>5</sub> values of 0.034 µg a.s./L for



crustacea and 0.087 µg a.s./L for insects, based on EC50 values collected for 23 and 17 species, respectively. These hazardous concentrations are a factor 10 below the HC5-LC50 calculated for the fish.

190 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 a.s./L. based on mortality and growth impairment occurring at concentrations of 10 ng a.s./L and above (Sved, 1993).

## Adverse effects on terrestrial organisms

191 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 RAR (Spain (2017b) to revise the LD50 of 13.3 mg a.s./kg bw initially recorded in a Peer Review study (Schafer et al., 1983) on the Japanese Quail (*Coturnix coturnix*) to the LD50 of 39.24 mg a.s./kg bw calculated according to the OECD 223 guideline for the Bobwhite quail (*Colinus virginianus*). Both tests were 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 (2017b) reports LD50 values of 19.92 and 17.5 mg a.s./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 LD50 of 71 mg a.s./kg bw (European Commission, 2005).

192 When the substance is administrated by gavage in mammals, European Commission (2005) reports acute oral LD50 ranging from 66 to 192 mg a.s./kg body weight (bw) in rats and from 64 to 71 mg a.s./kg bw in mice. The LD50 of 64 mg a.s./kg bw was confirmed by EFSA (2011) to assess the acute toxicity of chlorpyrifos for wild mammals.

193 Long-term reproduction toxicity studies identified various effects on nervous system, depression of erythrocyte (RBC) and acetylcholinesterase (AChE) in mammals. Considering a two-generation reproductive study in rats performed in an OECD 416 design, European Commission (2005) reported a parental and neonatal NOAEL of 1 mg a.s./kg bw/day based on brain cholinesterase depression, histopathologic alteration for parents and decreased growth and survival for offspring. However, lower NOAEL of 0.1 mg/kg bw/day due to a decreased body weight gains and brain cholinesterase depression was also observed in a 2-year dietary study in rats (European Commission, 2005).

194 For birds, no reproductive impairment (NOAEL) was reported in a study of DOW for 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 the equivalent of eight chlorpyrifos granules per day 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.

195 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 honey bee *Apis mellifera*. The highest toxicity is identified when the substance is administrated via contact. Bell (1994) measured an acute LD50 of 0.068 µg a.s./bee in a test performed with Dursban F (97.4% purity). For comparison, the lowest LD50 estimated for oral toxicity is 0.15 µg a.s./bee (Bell, 1993).

196 In addition to acute toxicity, Spain (2017b) 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 they follow the OECD 237 guideline to assess potential lethal or sublethal effects affecting the bee brood and development. Accordingly, for chlorpyrifos technical Nöel (2015) calculated a 10 d-LC50 of 0.002 µg a.s./bee/day. For bee brood development, Deslandes (2014) determined a NOED of 0.018 µg a.i./bee for larvae.

197 Chlorpyrifos has been extensively tested on non-target arthropods. Laboratory tests reported in Spain (2017b) 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-LR50 of the beneficial aphid parasite *Aphidius colemani* (Hymenoptera: Braconidae) was determined to be < 1ppm (Mead-Briggs, 1997). The high acute toxicity of Chlorpyrifos to Braconidae is confirmed by tests performed in a topical (i.e. contact) design (e.g. 24h-LR50 values of 3.21 and 3.62 ppm for *Bracon brevicornis* and *Chelonus*



*blackburni*, respectively). Acute LR50 values < 1 ppm were also reported for the beneficial aphids *Acyrtosiphon kondoi*, *A. Pisum* (Homoptera: Aphididae) as well as for the brown lacewings *Austromicromus tasmaniae* (Neuroptera: Hemerobiidae). Further acute LR50 values of 1 ppm or less are reported in Spain (2017b) for the damselflies *Enallagma spp.* and *Ischnura spp.* (Odonata: Coenagrionidae) and larvae of Trichopteran species *Hydropsyche* and *Chematopsyche spp.* (Trichoptera: Hydropsychidae).

198 Among Coleoptera, the lady beetle *Coccinella undecimpunctata* was the most sensitive species tested (LR50 = 1.9 ppm). A LR50 of 24 ppm is reported by Siegfried (1993) for the European corn borer pest *Ostrinia nubilalis* (Lepidoptera: Crambidae).

199 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 LC50 of 313 ppm corresponding to about 137 mg a.s./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 a.s./kg soil. Compared to the earthworms, chlorpyrifos is more chronically toxic 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 a.s./kg soil (Witte, 2014). When looking at sub-lethal effects, the NOEC is 0.024 mg a.s./kg soil for effects on reproduction of the animals. These effects observed at laboratory level were confirmed by field data.

## Adverse effects on human health

200 Chlorpyrifos can cause cholinesterase inhibition in humans at high enough doses that leads to an overstimulate of the nervous system causing nausea, dizziness, confusion, and at very high exposures (e.g. accidents or major spills), respiratory paralysis and death. Chlorpyrifos is listed in Annex VI of Regulation (EC) No 1272/2008 (CLP Regulation) as Acute Tox. 3, with the hazard phrase "H301-Toxic if swallowed". Prospective cohort studies in humans evaluated pre- and post-natal exposure to chlorpyrifos in mother-infant pairs and birth and developmental outcomes in neonates, infants, and children. The results from these studies have shown associations of 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.

201 It is acknowledged that there is no established uniform mode of action/adverse outcome pathway (MOA/AOP pathway), single epidemiological studies do not provide causal linkages, and the window(s) of susceptibility is currently unknown. However, these uncertainties do not undermine or reduce the confidence in the findings of the epidemiology studies.

202 Severe poisoning in humans causes neurotoxic effects such as slurred speech, tremors, ataxia, convulsions, depression of respiratory and circulatory centres. Coma and death may ensue as a direct result of respiratory failure due to the combination of bronchoconstriction, bronchorrhea, central respiratory depression, and weakness or paralysis of respiratory muscles. Together, these immediate symptoms are referred to as the cholinergic syndrome or the cholinergic toxidrome. At lower concentrations, there is no evidence of systemic repeated dose toxicity, apart from significant decrease of RBC cholinesterase activity in chronic studies in rats and dogs. No evidence for a carcinogenicity potential was found upon chlorpyrifos administration in guideline studies in rats or mice. In the public literature, induction of oxidative stress was suggested to result in tissue damage and point towards beginning of cancer incidence. There is no evidence of adverse effects on fertility or prenatal developmental toxicity, with the exception of developmental neurotoxicity (DNT). Developmental neurotoxicity has been observed in rats and mice at doses that elicit minimal or no fetal brain acetylcholinesterase (AChE) inhibition. The developmental neurotoxicity database for chlorpyrifos is evolving and contains several in vivo animal studies that permit the establishment of a critical oral NOEL. The neurodevelopmental effects in these studies were similar regardless of the exposure window or the duration of the exposure.

## Developmental neurotoxicity

### Human studies

203 Epidemiological evidence showing associations between chlorpyrifos exposure during neurodevelopment and adverse health effects is in particular derived from, three cohort studies conducted by the Columbia Center for Children's Environmental Health (CCCEH) study, the Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS) and Mt. Sinai study.

204 In 2011, researchers at CCCEH published the results of a study that reported an association between foetal cord blood levels of chlorpyrifos and neurodevelopmental outcomes (Rauh et al., 2011). A sample of pregnant non-



smoking women between 18-35 years old was enrolled. The cohort started in 1997 to evaluate effects of prenatal exposure to ambient and indoor pollutants on birth outcomes, neurocognitive development, and procarcinogenic damage among a cohort of mother and new-borns from minority communities in New York City. As a follow-up, the authors 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 high chlorpyrifos 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 use was allowed for indoor use, U.S. EPA subsequently cancelled all indoor uses of chlorpyrifos by the end of 2001 (US EPA, 2001).

205 In a follow up study, cohort children (n=271) were assessed again at age 11 (Rauh et al., 2015). The children underwent a full battery of neurodevelopmental measures, including a test of motor function. chlorpyrifos exposure was significantly associated with tremor in the dominant arm ( $p = 0.015$ ), tremor in either arm ( $p = 0.028$ ), and tremor in both arms ( $p = 0.027$ ), and marginally associated with tremor in the non-dominant arm ( $p = 0.055$ ) (Rauh et al., 2015). The authors state that morphologic changes appear to be related to lower IQs in these children and that the results support the notion that in utero exposure to chlorpyrifos is associated with general cognitive deficits (Rauh et al., 2012) and potential central or peripheral nervous system effects later in life (Rauh et al., 2015). Limitations of the study include the small sample size, and the extent of the cognitive assessment.

206 The Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS) project within the UC Berkeley Center for Children’s Environmental Health Research is a longitudinal birth cohort study of the effects of pesticides and other environmental exposures on the health of pregnant women and their children living in the Salinas Valley of California (Eskenazi et al., 2004). Eligible women were 18 or older and were less than 20 weeks pregnant at the time of enrollment (Oct 1999 – Oct 2000). (Bouchard et al., 2011) reported that children 7 years old in the highest quintile of prenatal Dialkyl phosphate (DAP) concentrations have an average deficit of 7.0 IQ points compared to the lowest quintile of prenatal urinary DAP. Prenatal DAP concentrations were also associated with poorer scores for Working Memory Processing Speed, Verbal Comprehension, and Perceptual Reasoning. Stein and colleagues published findings investigating early childhood adversities and the impact they may have on the association between prenatal OP pesticide exposures and the decrements in Full Scale IQ noted in the CHAMACOS cohort children. Overall, there were stronger associations between prenatal OP exposures (as measured by nonspecific urinary metabolites) and IQ scores among children who are experiencing certain adversities (Stein et al., 2016). PON1 genetic polymorphisms were studied in the CHAMACOS cohort, with allele frequencies for many polymorphisms differing between ethnic groups. The authors noted that functional effects of PON genetic variability related to susceptibility to organophosphates and oxidative stress varied by age, and variability should be considered in protecting certain subpopulations.

207 From 1998 to 2002, the Mount Sinai Children’s Environmental Health Study enrolled more than 400 pregnant women into a prospective study to investigate linkages between environmental exposures and impaired child cognitive development. All mothers gave birth at Mount Sinai Hospital in New York City between May 1998 and July 2001. The overall results support the association of prenatal OP exposure and the presence of specific PON1 genotypes associated with slower catalytic activities with negative effects on cognitive development. The authors note that reconciling estimated effects when using nonspecific urinary metabolites add uncertainty as those metabolites can derive from multiple parent compounds (Engel et al., 2011).

208 In 2015 US EPA updated a literature review (US EPA, 2016). In addition to the three main birth cohort studies (CCCEH, CHAMACOS, Mt. Sinai study), the update identified seven studies which were considered relevant (Bouchard et al., 2010; Fortenberry et al., 2014; Furlong et al., 2014; Guodong et al., 2012; Oulhote & Bouchard Maryse, 2013; Shelton et al., 2014; Zhang et al., 2014). Despite differences in study design, with the exception of two negative studies in the 2015 literature review (Guodong et al., 2012; Oulhote & Bouchard Maryse, 2013) and the results from the more recent (Engel et al., 2016) study, all other study authors have identified neurodevelopmental outcomes associated with OP exposure; these conclusions were across four cohorts and twelve study citations.

209 In July 2018, California EPA published their “Final Toxic Air Contaminant Evaluation of Chlorpyrifos” (CalEPA, 2018) Several additional epidemiological studies have been reviewed (Bielawski et al., 2005; Corrión et al., 2005; Fluegge et al., 2016; Enrique M. Ostrea, Jr. et al., 2012; E. M. Ostrea, Jr. et al., 2006; Posecion et al., 2006; Silver et al., 2015; Silver et al., 2017; Wickerham et al., 2012). CalEPA concluded 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.



210 In July 2019, the European Food Safety Authority (EFSA, 2019), published a statement on the available outcomes of the human health assessment in the context of the pesticides peer review of chlorpyrifos. The experts discussed the epidemiological evidence showing associations between chlorpyrifos exposure during neurodevelopment. In particular, the same three main birth cohort studies were considered: (CCCEH, CHAMACOS, and Mt. Sinai study). It was 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 discussed also 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 DNT effects in humans due to the exposure to chlorpyrifos and occurring at doses lower than that causing 20% inhibition of AChE.

211 In 2020 US EPA revised the human health risk assessment of chlorpyrifos. This assessment substantially relies on the previous documents developed for chlorpyrifos (US EPA 2016), an updated drinking water assessment, and animal toxicity literature review. Five new laboratory animal studies were reviewed, and it was concluded that 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 (US EPA 2020).

212 Additional 28 epidemiological studies have been identified subsequently to the CalEPA review since 2017. The studies add information related to exposure assessments and potential targets. The results are in line with the remaining body of evidence but do not provide significant new information. An exemption is the reevaluation of the statistics used in a 1972 Dow study by researchers at the Albany Medical College (report no #071392 as summarized in Spain (2019)). Sheppard et al. (2020) suggest that the statistical method for deriving a chronic no-observed-adverse-effect-level (NOAEL) of 0.03 mg/kg-day for chlorpyrifos in humans was not correct. In contrast, the authors suggest a lower NOAEL of 0.014 mg/kg-day, and that use of statistical methods first available in 1982 would have shown that even the lowest dose in the study had a significant treatment effect.

## Animal experiments

213 The developmental neurotoxicity database for chlorpyrifos is evolving and currently contains several in vivo animal studies that might permit the establishment of an oral NOEL below the reported threshold of 1 mg/kg/day established for RBC AChE inhibition. Silva et al. (2017) investigated the effects on complex behaviors (particularly anxiety and depression) in Wistar rats exposed to chlorpyrifos in utero. Pregnant dams (11-14/dose) received 7 consecutive daily doses (0.01, 0.1, 1 and 10 mg/kg/day) by oral gavage on gestation days 14–20. Behavioral parameters in male offspring were evaluated during the infant-juvenile period (postnatal day [PND] 21) and in adulthood (PND70). Male pups were separated into 4 groups (8-10 pups/group) comprised of those tested on PND 21 or PND70. The elevated plus-maze test was used to assess anxiety levels. The open field test was used to evaluate locomotor activity. The modified forced swimming test was used to assess depressive behavior. Neither RBC nor brain AChE levels were determined in dams or pups. The authors concluded that chlorpyrifos treatment during pregnancy induced anxiogenic behavior in pups at the end of lactation (PND21). It should be emphasised that the use of maze-based behaviours as the method for discerning cognitive deficits may not cover the more complex neurological functions in humans. Therefore, its direct relevancy is unknown. As a result, the authors set the LOEL for neurodevelopmental effects at 0.1 mg/kg/day. The lowest tested dose 0.01 mg/kg/day was the NOEL. The apparent absence of a dose-related exacerbation of this response above 0.1 mg/kg/day was unexplained but was considered plausibly due to saturation of one or more of the neural pathways involved in regulation of complex behaviors such as these. The data were presented without reporting individual data, means, or standard deviations.

214 Gómez-Giménez et al. (2017) conducted a study to determine if spatial learning was affected in either sex after developmental exposure and if hippocampal inflammation was associated with effects on spatial learning. Pregnant Wistar rats (6/dose) were fed chlorpyrifos mixed in sweet jelly at GD 7-GD20 (0, 0.1, 0.3 and 1.0 mg/kg/d). Pups were weaned PND 21 and were tested for Cognitive Impairment in the Morris water maze (Escape latency, Reference errors, Working memory). Escape latency in males increased at 0.1 mg/kg/day and above. Time spent in right quadrant on day 3 of testing was decreased in males at 1.0 mg/kg/day and unaffected in females. Spatial reference errors (first visits to unbaited arms) on testing day 4 were increased in males at >0.3 mg/kg/day. Working errors (visits to arms already visited in the same trial when seeking the baited arm) over the 5 days of testing increased in males at 0.3 mg/kg/day; females were not statistically significantly affected. Learning index at day 4 decreased in males at >0.3 mg/kg. There was no apparent dose response in any of the effects. The authors conclude that chlorpyrifos impaired learning in males but not in females. The LOEL for decreased spatial learning in males was 0.1 mg/kg/day. After the behavioral tests, rats were terminated, and the hippocampus was for proteins indicative of neuroinflammation. Neuroinflammation was also equivocal since only one parameter (IL10) was positive out of 13



tested in both sexes. Effects to IL10 in females at 0.3 mg/kg/d lead to a LOEL for neuroinflammation was 0.1 mg/kg/d for both males and females.

215 In 2018, Gómez-Giménez et al. (2018) tested for potential gender-related effects of chlorpyrifos on spontaneous motor activity and motor coordination. As in the previous study, pregnant Wistar rats were fed chlorpyrifos mixed in sweet jelly at 0, 0.1, 0.3 and 1.0 mg/kg/day at GD 7 through PND 21. The pups, weaned on PND 21, were tested at age 2-3 months for impacts on motor activity. Spontaneous motor activity was measured in an open-field activity chamber (novel environment) using an actimeter (infrared motion detection). Motor coordination was measured by rotarod. Females at 0.3 mg/kg/day exhibited decreased motor coordination on the rotarod. There was a statistically significant increase in spontaneous motor activity in males and females at 0.1 mg/kg/day, but not at 0.3 or 1 mg/kg/day. The LOEL was established at 0.1 mg/kg/d based on increased spontaneous motor activity in both sexes at that dose.

216 Similar motor effects were observed by Lee et al. (2015) in PND 60 mouse pups both at doses of 0.1 mg/kg. Male NMRI mice were treated by gavage with chlorpyrifos during rapid brain growth and maturation to investigate whether an acute perinatal exposure could be associated with behavioral effects in adulthood. Testing included motor activity assessment, brain AChE inhibition analysis and neuroprotein analysis. Results indicated 8-12% brain AChE inhibition at 5.0 mg/kg (only dose tested: inhibition peaked at 3 h post-dose) which was reversed by 6 hours post-dose. The spontaneous motor behavior tests at 2 or 4 months after exposure showed statistically significant decreases in locomotion, rearing and total activity at 5.0 mg/kg. Total activity was statistically significantly increased at 0.1 and 1 mg/kg/day at 2 months and remained increased for the rats at 1 mg/kg/day at 4 months. The LOEL for increased total activity was 0.1 mg/kg/day. The authors suggested that homeostatic disturbances during BGS of CaMKII may lead to irreversible behavioral effects lasting into adulthood.

217 Mohammed et al. (2015) showed that male and female rat pups treated by oral gavage with chlorpyrifos at 0.5 mg/kg/day during PND 10-16 exhibited behavioral anomalies when tested on PND 25. Decreased anxiety was evident through increases in number and percent of open arm entries, time and percent time spent in open arm of a plus maze, occurrences of crawling over/under, motor activity, play-fighting and time spent playing. 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 high dose, setting the LOEL for brain AChE inhibition at 1.0 mg/kg/day. Behavioral testing showed decreased times to emergence from a dark container into a novel environment at 0.5 mg/kg/day in both sexes. This behavior was associated with decreased anxiety. The data confirm earlier findings from this group showing that chlorpyrifos treatment generated behavioral effects at doses lower than those inhibiting brain AChE. The LOEL for decreased anxiety in PND 25 pups was 0.5 mg/kg/day.

218 Effect on developmental neurotoxicity (DNT) was examined 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/d (Hoberman, 1998). Evident maternal effects were observed at 5 mg/kg bw/day, with decreased bodyweight 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 same dose, such as decreased viability index (day 1-5), bodyweight and food consumption. Developmental landmarks were also delayed. On the contrary, brain AChE was not altered. 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. As high dose male brain weights were 11.5% lower than concurrent controls, a chlorpyrifos-mediated impact on cerebellar growth in these males was considered to be possible. Similar morphometric measurements were conducted in PND 66-71 adults, revealing statistically reduced parietal cortex dimensions in 1 and 5 mg/kg females (4% and 5%, respectively;  $p < 0.05$ ). Because control and 1 mg/kg/day female brain weights were unaffected, these changes were consistent with the possibility of a chlorpyrifos-mediated effect. A developmental lowest observed effect level (LOEL) of 1 mg/kg/day was suggested based on reduced parietal cortex and hippocampal dimensions in PND 66-71. Morphometric observations were not made at 0.3 mg/kg/day; consequently, a discrete no-observed effect level (NOEL) could not be determined.

219 In October 2000, Hoberman et al. provided a Report Supplement to Hoberman 1998 (# supplement: 304-001) (Hoberman, 2000). Brain morphometric data from the original report were re-tabulated alongside historical control data from 4 or 5 studies per parameter. Only one measurement having a high dose value statistically significantly different from concurrent controls was outside the range of the historical controls: the cerebellar anterior/posterior dimension in 5 mg/kg/d male 12-day pups was significantly below concurrent control dimension, and also outside the range of the available historical controls. Females did not suggest such a relationship at 12 days, and neither sex



showed altered cerebellar anterior/posterior distance after 66 days. In the context of the demonstrated high maternal and neonatal toxicity of this dose, the supplemental data reinforce the conclusion that study findings are not of sufficient magnitude or persistence to be considered as “adverse” even at gestational / postnatal doses as high as 5 mg/kg/day. This was surprising in light of the observations in later studies of effects at 0.1 mg/kg.

220 Both anxiogenic and anti-anxiogenic responses were observed in the DNT studies (Carr et al., 2017; Silva et al., 2017), highlighting the possibility that the effects were mutable and possibly toxicologically insignificant. However, CalEPA notes that the anxiogenic behavior observed by Silva et al. (2017) resulted from gestational exposure, while the anti-anxiogenic behavior observed by Carr et al. (2017) resulted from postnatal exposure (CalEPA, 2018). As the developmental status of the very young organism changes with time, the precise staging of chlorpyrifos exposures likely affects the nature of the response.

221 Several in vitro studies have observed negative 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). These in vitro effects occurred at concentrations orders of magnitude less than what would result in AChE inhibition and add to the body of evidence, that effects other than AChE inhibition might trigger the risk assessment of chlorpyrifos.

## Human epidemiology

222 In a birth cohort study prenatal chlorpyrifos exposure associated with H3K4me3 and DNA methylation levels of the PPAR $\gamma$  gene in the placenta and related effects on birth outcomes and neurodevelopment was investigated. Chlorpyrifos was measured among 425 mother-infant pairs from the Taiwan Birth Panel Study. Association was found for prenatal chlorpyrifos exposure with poor performance in the cognitive and language domains at two years old. Each unit increase in the natural log-transformed prenatal chlorpyrifos exposure level was associated with an increase in the PPAR $\gamma$  DNA methylation level ( $p = 0.032$ ) and poorer performance in the cognitive ( $p = 0.016$ ) and language domains ( $p = 0.023$ ), especially in boys (Chiu et al., 2021).

223 It is acknowledged that single epidemiological studies cannot determine causation. There is also the lack of established MOA/AOP pathway and uncertainty about the window(s) of susceptibility. Genetic polymorphisms have been shown to influence the rates of organophosphate metabolism in humans (Bouchard et al., 2011; Engel et al., 2011). Genotype data is not available for most epidemiological study. However, these uncertainties do not undermine confidence in the results of the majority of epidemiological studies.

## Conclusion:

224 Laboratory studies clearly demonstrate that chlorpyrifos is highly toxic to aquatic communities at concentrations around 0.1  $\mu\text{g a.s./L}$  and below for aquatic invertebrates. Chlorpyrifos also shows high acute toxicity to terrestrial vertebrates, especially to birds, with an LD50 value of 13.3 mg a.s./kg bw for Japanese quail. For mammals, LD50 values from 64 to 71 mg a.s./kg bw in mice are reported. Values for chronic toxicity are lower, with e.g. a NOAEL of 0.1 mg/kg bw/day observed in a 2-year dietary study in rats. Based on these studies, the available data on ecotoxicity of chlorpyrifos indicates the potential for damage to the environment.

225 In vivo animal studies provide evidence of developmental neurotoxicity (DNT) at chlorpyrifos doses below those causing cholinesterase inhibition. Effects on the developing nervous system include altered cognition, motor control, and behaviour in rats and mice. Based on these studies, along with epidemiological evidence, chlorpyrifos is considered toxic to the developing nervous system.

## 5. Synthesis of information

226 The POPs Review Committee at its seventeenth meeting concluded that chlorpyrifos fulfilled the screening criteria in Annex D (decision POPRC-17/4) and to prepare a risk profile in accordance with Annex E to the Convention.

227 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. In 2008 chlorpyrifos products were authorised for use in more than 88 countries. Usage as a biocide was phased-out in the European Union by Commission Decision (2007/565/EC) by 2008 (European Union, 2007). A decision on phasing out most non-agricultural applications was adopted by the EPA in 2000 (US EPA, 2006). However, usage as a biocide, e.g., for termite control in buildings, is



still practiced in other countries. For example, use for termite control is still recommended by the Indian authorities (India, 2020).

228 Chlorpyrifos was first produced commercially in 1965 by Dow Chemical Company. While a number of methods for the commercial preparation of chlorpyrifos have been reported, a common method is the by reaction of 3,5,6-trichloro-2-pyridinol with diethyl phosphorochloridothioate under basic conditions e.g. in the presence of sodium carbonate (ATSDR, 1997). While data are not available on total global production volumes, data from the CCPIA (2022) indicated that, in terms of volume of use, prior to 2007, global use was about 10,000 tonnes/year. It is indicated that, following the prohibition of five highly toxic organophosphorus pesticides in China, chlorpyrifos has become the dominant insecticide used in the country (Chen et al., 2012), with the global use now estimated to be 50,000 tonnes/year (CCPAA, 2022). It is understood that China and India are currently two of the biggest producers of chlorpyrifos globally.

229 Environmental degradation half-lives of chlorpyrifos range from a few days to several years, depending on application rate, ecosystem type, soil or sediment characteristics, and other environmental factors, including temperature. 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. In addition, chlorpyrifos is found in dated sediment cores in Arctic and sub-Arctic lakes (Landers, 2008). Thus, chlorpyrifos can be considered persistent in some environments according to the definition of the Stockholm Convention.

230 The log  $K_{ow}$  for chlorpyrifos indicates potential bioaccumulation. The combination of a log  $K_{ow} > 2$  and a log  $K_{oa} > 5$  indicates potential bioaccumulation in air-breathing organisms. Chlorpyrifos has been found in biota at different trophic levels in the remote regions, globally in apex predators and in human breast milk at levels concerning for offspring. Based on current data available, a BCF of  $> 5000$  cannot be concluded. Fish studies show moderate bioaccumulation with BCF in the range of 1000 to 2000 at concentrations showing toxic effects. BCF above 2000 are observed in early life stages. In combination with high toxicity, even moderate bioaccumulation can lead to body concentrations that elicit adverse effects, thus it is a serious concern. Based on high toxicity in fish and other species such as invertebrates, amphibians, birds and mammals including humans, in combination with a moderate BCF and a BSAF above 6 for soil organisms, chlorpyrifos meets the second criteria (ii) for bioaccumulation in other species, high toxicity and ecotoxicity of Annex D. Based on the reasons stated above, we conclude that chlorpyrifos fulfils the criteria for bioaccumulation.

231 While modelling results do not predict long-range transport, chlorpyrifos is widely detected in remote areas far away from point sources and/ or agricultural use. Potential routes of transport include atmospheric transport in the gas or particulate phase, transport via water in rivers and/ or ocean currents. Chlorpyrifos has been found far away from point sources, in various abiotic and biotic compartments of remote areas such as in caribou, seals and ice bears in the Arctic and sea-ice meltwater and air of Antarctica. Thus, chlorpyrifos is considered to meet the criterion of the Stockholm Convention on long-range environmental transport.

232 Chlorpyrifos has been detected in air samples, both in regions close to application areas and in remote locations far from application areas, as it can be carried with the wind (Mackay et al., 2014).

233 Laboratory studies clearly demonstrate that chlorpyrifos is highly toxic to aquatic communities at concentrations around  $0.1 \mu\text{g a.s./L}$  and below for aquatic invertebrates. Chlorpyrifos also shows high acute toxicity to terrestrial vertebrates, especially to birds, with an LD50 value of  $13.3 \text{ mg a.s./kg bw}$  for Japanese quail. For mammals, LD50 values from 64 to  $71 \text{ mg a.s./kg bw}$  in mice are reported. Values for chronic toxicity are lower, with e.g. a NOAEL of  $0.1 \text{ mg/kg bw/day}$  observed in a 2-year dietary study in rats. Based on these studies, the available data on ecotoxicity of chlorpyrifos indicates the potential for damage to the environment.

234 In vivo animal studies provide evidence of developmental neurotoxicity (DNT) at chlorpyrifos doses below those causing cholinesterase inhibition. Effects on the developing nervous system include altered cognition, motor control, and behaviour in rats and mice. Based on these studies, along with epidemiological evidence, chlorpyrifos is considered toxic to the developing nervous system.



## 6. Concluding statement

235 Environmental degradation half-lives of chlorpyrifos range from a few days to several years, depending on application rate, ecosystem type, soil or sediment characteristics, and other environmental factors (Gebremariam et al., 2012). Chlorpyrifos can be persistent in marine water, in some soils and 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. 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 (Landers, 2008). Thus, it can be concluded that chlorpyrifos is sufficiently persistent to justify its consideration within the Convention.

236 Although numerous studies show moderate bioconcentration, this in combination with high toxicity gives reason for serious concern. As chlorpyrifos has been found in biota at different trophic levels in the Arctic regions, globally in apex predators and in human breast milk at levels concerning for offspring, we conclude that the bioaccumulation potential of chlorpyrifos is sufficient to justify its consideration within the Convention.

237 The predicted half-lives of chlorpyrifos in air ranging from 1.4 to 14 hours are relatively low, but it has been found in various abiotic compartments of remote areas in the Arctic and Antarctic, as well as 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, transport via water in rivers and/ or ocean currents.

238 Epidemiological evidence in combination with animal studies are evidence for developmental neurotoxicity (DNT) of chlorpyrifos in humans. Additionally, chlorpyrifos exhibits acute and chronic effects at very low and environmentally relevant concentrations. It is highly toxic to aquatic communities, early life stages of fish and aquatic invertebrates, bees, birds and mammals. The ecotoxicological and toxic properties of chlorpyrifos lead to adverse effects for human health and the environment

239 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 the use of chlorpyrifos is likely to lead to significant adverse human health and environmental effects such that global action is warranted.

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