Chlorpyrifos

Draft risk profile

April 2022

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Executive summary

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

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 United States Environmental Protection Agency (US EPA) in 2000 (US EPA, 2006). However, usage as a biocide, e.g., for termite control in buildings, is still practiced in other countries.

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 China Crop Protection Industry Association (CCPIA) (Annex E, 2022) indicated that 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 (CCPIA, 2022). It is understood that China and India are currently two of the biggest producers of chlorpyrifos globally since Corteva (formerly Dow Chemical) announced the end of chlorpyrifos production by the end of 2021.

4 Environmental degradation half-lives of chlorpyrifos range from a few days to several years (in the case of termite control), depending on application rate, ecosystem type, soil or sediment characteristics, and other environmental factors, including temperature. Monitoring data from the Arctic and Antarctica demonstrate that chlorpyrifos 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, 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 could lead to body concentrations that elicit adverse effects, thus may be 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 Annex D criteria (ii) for bioaccumulation in other species, high toxicity and ecotoxicity. Hence, we conclude that chlorpyrifos fulfils the criteria for bioaccumulation.

6 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).

7 While modelling results do not predict long-range environmental 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 and 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 polar bears in the Arctic and in sea-ice meltwater and air of Antarctica. Thus, chlorpyrifos is considered to meet the criterion of the Stockholm Convention on long-range environmental transport.

8 Developmental neurotoxicity (DNT) of chlorpyrifos in humans has been demonstrated through eEpidemiological evidence in combination with animal studies. Additionally, chlorpyrifos exhibits acute and chronic toxic effects at very low and environmentally relevant concentrations. It is highly toxic to aquatic communities at concentrations around 0.1 µg a.s./L and below for aquatic invertebrates, early life stages of fish and 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. The ecotoxicological and toxic properties of chlorpyrifos lead to adverse effects for human health and the environment.

9 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.

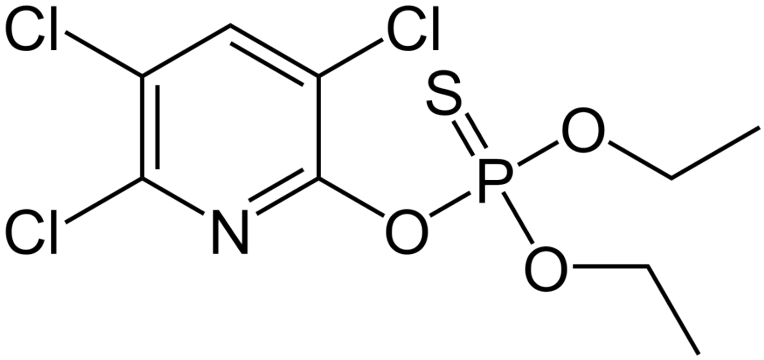
10 Some of the text included in this version for the second commenting round may have to be moved to the INF-document due to space limitations.

1. Introduction

1.1 Chemical identity

11 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.

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

Physical and chemical properties

12 Table 2 reports the main physicochemical properties of chlorpyrifos. 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 * 10-3 25°C (purity 99.8%) 1.43 * 10-3 20°C (purity 99.8%) 1.0 * 10-3 Experimental, 25°C (purity 98%) 2.3 * 10-3	European Commission (2005) European Commission (2005) WHO (2009) Compiled by Mackay et al. (2014)
Water solubility [mg/L]	1.05 at 20°C, in unbuffered solution, no pH dependency reported 0.39 at 19.5°C, pH not cited (98 % purity) 0.73 0.941 (20°C, pH unknown, guideline EEC Method A6/OECD 105) Dow 0.588 (20°C, pH not stated, guideline OECD 105 flask method) Makhteshim, as cited in WHO (2009)	European Commission (2005) WHO (2009) Mackay et al. (2014) WHO (2009) WHO (2009)
n-Octanol/water partition coefficient, K_{ow} (log value)	4.7 at 20°C, neutral pH. 5.0 at 24.5°C (purity 98%). 4.96 – 5.11 at 20°C 5.2 – 5.27 at 25°C	European Commission (2005) WHO (2009) Gebremariam et al. (2012) Gebremariam et al. (2012)
n-Octanol-air partition coefficient K_{oa} (log value)	8.88 (estimated) 8.34	US EPA (2012) Mackay et al. (2014)
Air/water partition coefficient (log K_{AW})	-3.92 Experimental database	US EPA (2012)
Organic carbon/water partition coefficient (K_{OC})	8,500 (US EPA gives 5,860, 4,960, 7,300) Log Koc is 3.93	Mackay et al. (2014)

Transformation products

13 Transformation products of chlorpyrifos are 3,5,6-trichloro-2-pyridinol (TCP), chlorpyrifos-oxon, des-ethyl chlorpyrifos, 3,6-dichloro-2-pyridinol (3,6-DCP) and 2,3,5-trichloro-6-methoxypyridine (TMP). 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 POPRC regarding Annex D information

14 In June 2021, the European Union and its Member States submitted a proposal to list chlorpyrifos in Annex A, B and/or C of the Stockholm Convention (UNEP/POPs/POPRC.17/5), 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 screening criteria set-out under Annex D of the Stockholm Convention, warranting that chlorpyrifos move to the next stage of the review process.

15 The POPRC evaluated the proposal regarding chlorpyrifos (UNEP/POPS/POPRC.17/5) according to the requirements in Annex D of the Stockholm Convention at its seventeenth meeting. In Decision 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

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

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

18 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, the Netherlands, Norway, Republic of Korea, Sweden, Thailand, The United Kindom, Uzbekistan, United States of America, China Crop Protection Industry Association (CCPIA), International Pollutants Elimination Network and Alaska Community Action on Toxics (IPEN/ACAT) and Pesticide Action Network (PAN), Pesticides Manufacturers & Formulators Association of India (PMFAI).

19 Reports and other grey literature, as well as peer-reviewed scientific journals.

1.4 Status of the chemical under national regulations and international forums

20 The US EPA has performed numerous human health risk assessments over the years, as well as an 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 residential uses (except for ant and roach baits in child resistant packaging and fire ant mound drenches for public health purposes), all indoor non-residential non-agricultural uses (with exemptions), and most outdoor non-residential uses were eliminated (US EPA, 2006). All chlorpyrifos tolerances expired on 28 February 2022 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-food uses will remain registered as chlorpyrifos undergoes registration review, a program that re-evaluates all pesticides on a 15-year cycle. Non-food uses of chlorpyrifos in the US include nursery/greenhouse, turf farms, golf courses, and wide area treatments such as mosquito control and recreational areas, among others. Use of chlorpyrifos on exported food crops can still take place as long as it is not in conflict with the laws of the country to which it is intended for export ((21 USC 381 (e)(1) (USA, 2022; US EPA, 2022).

21 The Canadian re-evaluation of chlorpyrifos was completed in phases, with the health and environmental assessments completed in 2007 and 2020, respectively, following public consultations (Health Canada Pest Management Regulatory Agency, 2020).. 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 a 2007 health re-evaluation. Health Canada's Pest Management Regulatory Agency requested these additional health data from chlorpyrifos registrants. As the registrants of chlorpyrifos products were unable to fulfil 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 of all chlorpyrifos products by 10 December 2023 (Health Canada Pest Management Regulatory Agency, 2021).

22 In the European Union chlorpyrifos has been prohibited to be marketed for use as an active substance in plant protection products since 2020 and in biocidal products since 2008 (Regulation (EC) No 1107/2009, Regulation (EU) No 528/2012)[1].

23 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).

24 In Norway, chlorpyrifos has never been authorised for use as a plant protection product. For use as a biocide, it was phased out in 2008.

25 In the Netherlands chlorpyrifos has been authorised since 1971. In 2003 it was 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). In 2022, there are no uses of chlorpyrifos as active ingredient in plant protection products or biocides authorised, as required by EU regulations (EC) No. 1107/2009 and 528/2012, respectively.

26 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)

27 In Egypt, chlorpyrifos will be banned at the end of 2022 with an exemption for the use in cotton and against termites and locusts. (Egypt, 2022)

28 The New Zealand Environment Protection Agency (EPA) has assigned the following GHS hazard classifications to chlorpyrifos[2]: Acute toxicity cat.2 (H310), acute toxicity cat.3 (H301), acute toxicity cat.4 (H332),

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[1] https://ec.europa.eu/food/plants/pesticides/approval-active-substances/renewal-approval/chlorpyrifos-chlorpyrifos-methyl_en

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

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 powder, 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. After reassessement (re-registration) of plant protection products by the EPA in 2013 approvals were retained with additional controls/restrictions added[3]. Currently, chlorpyrifos and chlorpyrifos-methyl are being reassessed as plant protection products by the EPA. Non-plant protection uses, such as veterinary medicines and use in urban pest management, were reassessed in 2016 and the approvals were revoked (New Zealand, 2022).

29 Australia is currently reviewing chlorpyrifos 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[4]. Proposed regulatory action is expected to be published in mid-2022 (Australia, 2022).

30 In China, the Ministry of Agriculture and Rural Affairs has issued measures to restrict the use of chlorpyrifos: it was prohibited from being used on vegetables since December 31, 2016 (Comment CCPIA on 1st draft)..

31 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 Food and Drug Administration), 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).

32 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 locus control on crops, acacia and other trees in concentrations of 240 grams active substances per hectar.

33 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, defoliants 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)

34 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).

35 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). Furthermore, the National Food Health and Quality Service (Senasa) highlighted that by resolution 414/2021 the commercialisation and import of chlorpyrifos or products containing chlorpyrifos is prohibited with a 1-year phase-out. Meaning use should cease by November 2022.

36 In Vietnam, the Ministry of Agriculture and Rural Development issued a decision in 2019 removing the approval for chlorpyrifos within products sold and used within the country. The decision included a phase-out period which meant all remaining use of chlorpyrifos should have ceased by 2021 (Eurofins, 2019). Furthermore, chlorpyrifos is banned in Morocco (ONSSA, 2020), Saudi Arabia, Sri Lanka (PIC Database, 2021), Indonesia (Indonesia, 2019), Switzerland (Switzerland, 2019)), Palestine, Thailand (Thailand, 2022) and Turkey (PIC Database, 2022).

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[3] APP201045-APP201045-Decision-Amended-with-s67As-and-APP202142-2015.07.28.pdf (epa.govt.nz)

[4] 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

2. Summary information relevant to the risk profile

2.1 Sources

Production, trade, stockpiles

37 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 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).

38 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 (CCPIA, 2022).

39 It is understood that China and India are currently two of the biggest producers of chlorpyrifos globally. Total production of chlorpyrifos in India in 2021 was reported to be 24,000 tonnes, of which 11,000 tonnes was used domestically, 12,000 tonnes was exported and 1,000 tonnes was in 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 China the total domestic consumption of the substance applied on several crops (mainly rice, vegetables, fruits and cotton) in 2017 was reportedly ~18,000 tonnes ((CCPIA, 2022).

40 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.

41 In Canada, no production is reported. All chlorpyrifos active ingredient and most chlorpyrifos end-use products were imported into Canada prior to its cancellation in 2021. Annual sales of chlorpyrifos in Canada, expressed as volume of active ingredient sold were 133 t in 2020. Australia (2022) reported importing 2131 t of chlorpyrifos (product/active).

42 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.

43 As presented in European Commission (2017), according to the FAO, chlorpyrifos has been imported during the period 2008 2015 by 12 developing countries and economies in transition representing 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

44 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 & Shaike, 2015). Pesticide products containing chlorpyrifos are registered for use on many agricultural crops, including corn, soybeans, alfalfa, oranges, apples, bananas, wheat, and walnuts (US EPA, 2020; Foong et al, 2020). Additionally, chlorpyrifos products are registered for use on non-food sites such as ornamental plants in nurseries, golf course turf, as a wood treatment, and as an ear tag

for cattle. There are also public health uses including aerial and ground-based mosquito adulticide fogger treatments, use as fire ant control and for some tick species that may transmit diseases such as Lyme disease (US EPA, 2020).

45 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), although based on estimates from the US EPA pesticide program as of 2007 it was still the highest volume insecticide in use within the USA (Alavanja, 2013). Between 2014-2018 use had fallen to 2,300 t of chlorpyrifos, with primary use on soybeans, alfalfa and corn, which made up nearly 50% of the total volume used. Within these estimates soybeans accounted for nearly 25% of total volume applied (US EPA, 2020). In August 2021 the US EPA ended the use of chlorpyrifos products on all food products nationwide. US EPA will next proceed with registration review for the remaining non-food uses[5].

46 In January 2020, the European Commission adopted implementing Regulation EU 2020/18[6], 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 was widely used from 1971, however, following the EU level ban use has ceased and alternative insecticides are being developed. In Sweden, chlorpyrifos was never authorised as a plant protection product (Sweden, 2022). In Norway, chlorpyrifos has never been authorised for use as a plant protection product (Norway, 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).

47 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 in table 2 of the Annex[7].

48 Other chlorpyriphos 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[8].

49 The use of chlorpyrifos as a termiticide was phased-out in the USA in 2000. Although several other countries also have phased out the use of chlorpyrifos in termite control, 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, 2020). However, in Australia a review process for chlorpyrifos usage as termiticide is in progress (Australia, 2019).

50 As noted above, use of chlorpyriphos 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

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

52 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.

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

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

[7] 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)

[8] 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)

3. Environmental fate

3.1 Persistence

53 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. All half-lives mentioned in the following chapters are listed in tables 2-7 in the INF-document.

54 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_2 and to non-extractable residues.

Environmental distribution

55 Chlorpyrifos' vapour pressure and Henry's Law constant (for values see the table 1) indicate that the chemical is volatile, and it is concluded that volatilisation plays a role in the overall dissipation process in the field. In the US, chlorpyrifos has been detected in the air regularly at various sites by the California Department of Pesticide Regulation's Air Monitoring Network, which has conducted both seasonal air monitoring in certain counties and weekly random ambient air sampling throughout the year at sites located in major California agricultural regions, starting in 2011 (California Department of Pesticide Regulation).

Soil photolysis

56 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 (r2=0.94) and 28.5 h (r2=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 d in light, and could not be calculated in the dark since levels increased throughout the study period.

57 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 h of sunlight exposure, the half-life was calculated to be 14.1 d ($R^2 = 0.820$). The major photoproduct of TCP was CO_2 (40% AR at 30 days), 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_2.

Hydrolytic degradation

58 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 d. At alkaline pH, hydrolysis is dependent on pH with a measured half-life for chlorpyrifos of 16 d at pH 9, 25ºC 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. For an overview of pH dependant degradation of chlorpyrifos see the INF-document table 2.

59 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 d, respectively. A comparable aqueous hydrolysis half-life at 35 °C and pH 4.7 of 15.75 d has been reported.

60 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.

61 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.

62 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).

63 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.m3/mole (Mackay, 2014) is high enough that volatilisation from water should occur. Early laboratory half-lives of 8-24 h 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 h. 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

64 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 d for mid-summer at 20ºN

65 Adam (2015) concluded that chlorpyrifos is degraded by direct and indirect photolysis with net half-lives of 7.2 and 2.9 d 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 d 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 d (corrected for hydrolysis) and 7.8 to 11.0 d (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.

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

67 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

68 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 a follow-up test conducted to investigate the reasons for the low recovery in the main test, on day 40 up to 95.7 % of the radioactivity were found in the foam plugs of the volatile organic carbon trap. this was shown to be 100 % unchanged chlorpyrifos. 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 d of incubation, and to a lesser extent by biodegradation. Similarly, in another study on degradation in three static marine water systems by 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^3mol-1 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 h 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 h. 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 4of the INF-document.

69 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.

70 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 open sea water, at 8°C. 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

71 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

72 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)[9]. 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 d). 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.

73 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.

74 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).

75 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 (t½ 53.3 - 77.0 d), compared to dry (t½ 49.5 - 120 d) and wet soils (t½ 63.0 - 124 d). 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.

76 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

77 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

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[9] FOCUS is a tool for the estimation of half-lives used for the evaluation of pesticides in the EU

soils (see INF-document table 6), and Old (2002a, 2002b, 2002c) investigated four soils. Dissipation half-lives were in the range 5 to 89 d. In India, various field studies were conducted, both proprietary and published studies, with dissipation half-lives ranging from 0.44 - 16 d (Menon et al., 2004; Vijyalakshmi et al., 1996; Balasubriam et al., 1995 and 1996, Sardar et al., 2005 and Upendra Kumar et al., 2017). Following application, volatilisation is expected to contribute significantly to early losses of chlorpyrifos from soil surfaces (up to 25 % within 24 – 48 h) and plant surfaces (80 % within 24 – 48 h) (Australia 2022).

Degradation of chlorpyrifos at application rates used for termite control

78 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 in the test, to replicate application rates used for control of termites). The application rates are given as 392 kg/ha in soil trench applications, as opposed to 0.28 - 2.24 kg/ha for agricultural applications. 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 drespectively.

79 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.

80 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).

81 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 the primary transformation product (detected after 3 d, maximum level after 30 d). At all application levels TCP concentrations decreased afterwards and could no longer detected after 120 d. TMP as secondary transformation product was detected during the study course, but also not after 120 d.

82 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.

83 The reduced degradation of chlorpyrifos at high application rates may be an effect of toxicity to microorganisms.

Anaerobic degradation

84 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

85 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 d in the sandy loam and clay loam systems respectively (DT90 values 72 and 168 d). Dissipation was more rapid in the water layer, with DT50 values of 3 and 6 d 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 14CO2, < 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 d, and only minimal mineralization to 14CO2 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 (36 d). 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 d under aerobic conditions with associated overlying waters at a sediment/water ratio of 1:3 in the dark at 20 ± 2 C. [14C] 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.

86 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 dand under anaerobic conditions of 223 and 57.6 drespectively. 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.

87 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.

88 In a study on the persistence of chlorpyrifos in seawater relative to fresh water, Bondarenko et al (2004) determined that it was approximately 3 times more persistent in seawater (half-life of 49.4 vs 18.7 at 10oC). The half-life in seawater was 15.2 at 21oC; and 49.4 at 10oC, so half-life trebled as the temperatures halved. It could be expected to behave similarly with a halving of temperature to 5oC leading to an expected half-life in the order of 148 day in Arctic seawater.

89 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 d in anaerobic pond sediments.

90 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.

91 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

92 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.

93 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.

94 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).

95 Chlorpyrifos was found in surface sediments in the tropical western Pacific Ocean at three sample sites (samples were 0-2 cm deep and obtained at depths ranging from 2,169 m to 5,666 m). Of the other pesticides monitored for, hexachlorocyclohexane isomers were the dominant organic pesticides and were detected at all 23 of the study sites. Chlorpyrifos concentrations detected ranged from 362.6 pg/g dry weight to 1,700 pg/g dry weight. DDTs and chlordanes were not found at levels at or above the method detection limits in this study (Ge et al. 2021).

96 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, and has been found to do so (Ruggirello et al. (2010). 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

97 In the water degradation studies evaluated here, DT50 values range from 3.55 d in Indian basic water (temperature not reported) to 75 d at 8°C. Chlorpyrifos fulfils the criterion for persistence with half-lives in water greater than two months.

98 In soil, highest half-lives for the chlorpyrifos degradation were found at high application rates (100 - 1000 mg/kg, or at 0.28 - 2.24 kg/ha (Racke, 1993)). 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 be a result of toxicity to microorganisms that might otherwise degrade it. 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 d at 20°C to 224 d at 15°C. Normalised to 12°C, as suggested in the guidance document used for the evaluation of chemicals in the EU, the Endpoint specific guidance R.7b (ECHA, 2017) for comparability and to illustrate degradation in temperate regions, these values range from 12.7 to 483 d, and would be greater at 5°C normal to Arctic conditions. 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. Chlorpyrifos fulfils the criterion for persistence with half-lives in soil greater than 6 months under some circumstances.

99 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.

100 Environmental degradation half-lives of chlorpyrifos range from a few days to several years (in the case of termite control), depending on application rate, ecosystem type, soil or sediment characteristics, and other environmental factors, including temperature (Gebremariam et al., 2012). Monitoring data from the Arctic

demonstrate that chlorpyrifos can be transported over long distances to remote regions (see section 3.3). Since degradation of chlorpyrifos is temperature dependent, it is expected to persist in these regions for a considerable length of time. Frequent findings of chlorpyrifos in all media in the Arctic support this. 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

101 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.

102 Bioaccumulation of chlorpyrifos in fish has been studied for many species, developmental stages and exposure scenarios. The available BCF values cover a broad range, but in many studies, toxicity occurred at low doses, thus they cannot be considered fully valid. For an overview of all bioconcentration studies assessed for this dossier, please see the INF-document table 8.

103 Regulatory assessments conducted by the USA, 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 occurred during these experiments at very low doses. Toxicity is also observed for other aquatic organisms, birds and mammals and especially for humans, see chapter 4.

104 The key BCF considered for the Renewal Assessment Report for EU approval is 1374 ± 321 in rainbow trout (*Onchorhynchus mykiss*) (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 some underestimation of the BCF.

105 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).

106 Deneer (1994), compared lab and mesocosm BCF for three-spined stickleback (*Gasterosteus aculeatus*) to investigate the feasibility of predicting the concentration of 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 actually found in fish from the outdoor mesocosms.

107 Other fish studies have produced BCF in a wide range, most studies however show toxic effects even at low concentrations. Generally speaking for BCF studies, no toxic effects should be observed in the study since these could affect the resulting BCF. Jarvinen et al. (1983) calculated a BCF of 1673 ± 423 for the fathead minnow (*Pimephales promelas*) in a chronic toxicity study, not stating for which concentration this value was calculated. 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. (1985a) exposed early life stages of two silverside species to chlorpyrifos and determined a maximum BCF of 580 at 0.38 µg/L. At 0.093 µg/L, no toxic effects were found, the corresponding BCF was 410. Significant mortality occurred at 1 µg/L and 2 µg/L. Following the same experimental set-up Goodman et al. (1985b) produced a maximum BCF of 1000 using the california grunion (*Leuresthes tenuis*) at 0.25 µg/l. Here significant mortality and decreased body weight occurred at concentrations of 0.63 ± 0.11 µg/L to 2.8 ± 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.

108 As demonstrated in the studies described above, toxicity to fish occurs at very low concentrations. These finding are supported by data from the EU RAR (Spain 2017b) 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. (1985b) 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 moderate bioaccumulation is that the likelihood of body concentrations being reached that lead to toxic effects, increase either with high bioaccumulation or with high toxicity. Chlorpyrifos' high toxicity means that even moderate bioaccumulation will have a similar effect as high bioaccumulation of less toxic chemicals, reflected in criterion [c][ii] of Annex D.

109 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.

110 Robles-Menoza (2011) found a BCF of 3632 in axolotl (*Ambystoma mexicanum*) in spite of a decrease in chlorpyrifos concentration in the water of 50%. Also, behavioural effects were seen.

111 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 lipid weight 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 stems from the high surface to volume ratio. Adsorption may occur and could skew bioaccumulation values upward.

112 A study in 2016, by Bonansea et al., investigated the accumulation of chlorpyrifos in the fish *Jenynsia multidentata* when exposed for 96 h to different mixtures, namely: a mixture with chlorpyrifos individually of a 0.4 µg/L concentration, a technical mixture of concentrations 0.04 µg/L of cypermethrin þ 0.4 µg/L of chlorpyrifos, and a mixture of commercial products with concentrations 0.04 µg/L of cypermethrin þ 0.4 µg/L of chlorpyrifos. The LOD level set for chlorpyrifos was 3 µg/kg. The mixture with only chlorpyrifos showed concentration <LOD in the muscles and brain, 67 ± 49 µg/kg in intestines, 58 ± 25 µg/kg in liver, and 42 ± 31 µg/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 ± 5 µg/kg in muscles, 50 ± 29 µg/kg in intestine, 323 ± 187 µg/kg in liver, and 11 ± 6 µg/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 limited capacity to bioconcentrate in *J. multidentata*, however the BCF calculated in these organs were low.

113 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 lipid weight 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 stems from the high surface to volume ratio. Adsorption may occur and could skew bioaccumulation values upward.

114 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 Dursban (Bell (1994). A LD50 of 39.24 mg a.s./kg body weight (bw) was set for the Bobwhite quail (Spain 2017b). 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 chapter4 of this document.

115 The biomagnification of chlorpyrifos was investigated in the vegetation-caribou-wolf food chain in the Bathurst region (Nunavut) in Canada by Morris et al. (2014). The analytical recovery of chlorpyrifos from biota was low at 52 ± 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 ± standard errors (ng/g lw). For lichen the concentrations were 0.25 ± 0.21 ng/g lw, for green plants including willow, mosses and grasses the concentrations were 0.24 ± 0.088 ng/g lw and for mushrooms the concentrations were 0.85 ± 0.52 ng/g lw. Chlorpyrifos was found in five caribou samples at 0.40 ± 0.16 ng/g lw specifically in muscle but not in the liver and in one wolf liver below the MDL. The lichen-caribou-wolf food chain leads to a trophic magnification factor (TMF) of <1 for muscle, liver and total body burden.

116 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 d 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 the soil and chlorpyrifos concentration. This BSAF value indicates high bioaccumulation (ECHA, 2017).

117 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−1 soil dry weight to represent worst case scenarios. BAF under steady state were calculated as 6.34 ± 1.30 and 4.51 ± 0.76 for the different soils.

Conclusion on bioaccumulation according to the criteria in Annex D

118 The log Kow for chlorpyrifos, with some values > 5, indicates potential bioaccumulation. Chlorpyrifos has been found in biota at different trophic levels in 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 could lead to body concentrations that elicit adverse effects, thus may be a 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 and the evidence of widespread biotic contamination, it is concluded that chlorpyrifos fulfils the criteria for bioaccumulation.

3.3 Potential for long-range transport

119 The predicted atmospheric half-life of chlorpyrifos is mainly determined by the reaction rate with OH radicals. Measured and predicted values do not exceed a half-life of two days. Modelling results indicate air and water as the main media for chlorpyrifos transport. Chlorpyrifos has been measured in abiotic and biotic compartments of remote regions, indicating that LRET has occurred.

Environmental fate properties and model results

120 The vapour pressure for chlorpyrifos has been estimated between 1.0 x 10^{-3} and 3.35 x 10^{-3} Pa (see Table 1 and 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.

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

122 Using the Atmospheric Oxidation Program (AOPWIN; ver.1.89; (US EPA)), Simon (2001) calculated an OH radical reaction rate of 9.16 x 10^{-12} cm^3/molecule-sec for chlorpyrifos. When applying atmospheric OH radical concentrations of 0.5 x 10^6 molecules/cm^3 (European standard value) and 1.5 x 10^6 molecules/cm^3 (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 x 10^6 molecules/cm^3, the corresponding half-life is 4.1 h For an OH radical concentration of 1.5 x 10^6 molecules/cm^3 as used in AOPWIN, the corresponding half-life is 1.4 h.

123 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 x 10^6 molecules/cm^3 the predicted half-life of chlorpyrifos amounted to 1.4 h while an OH concentration of 1.5 x 10^5 molecules/cm^3 resulted in a half-life of 14 h. 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.

124 Modelling results are corroborrated 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^3 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 ± 2.1) × 10^{-11} cm^3/ molecules-sec at 29 ± 5 °C. The atmospheric half-life of chlorpyrifos was approximately 2 h.

125 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 heterogenous OH radical reaction rate of 5.8 × 10^{-12} cm^3/ molecules-sec at 25°C. For an OH radical concentration of 0.5 x 10^6 molecules/cm^3, the corresponding half-life of particulate chlorpyrifos is 66.4 h. For an OH radical concentration of 1.5 x 10^6 molecules/cm^3, the corresponding half-life is 22.1 h.

126 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.

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

128 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).

129 As described in the section on persistence, chlorpyrifos binds strongly to soil and sediment. 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).

130 In summary, particulate chlorpyrifos appears to be more recalcitrant to atmospheric degradation and may thus be transported over longer distances. These attributes are relevant as per Annex D (d) (iii). However, the percentage of particulate chlorpyrifos is below 10% in observed scenarios.

131 Once in the water compartment, chlorpyrifos bound to suspended solids and sediment is persistent and can 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).

132 The OECD Pov and LRTP Screening tool[10] 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[11]. However, the publications cited above show that transport of particulate chlorpyrifos via water and air are relevant.

Presence in remote areas

133 von Waldow et al. (2010) proposed an index to characterize the remoteness of regions. The resulting remoteness index is based on calculations with a global atmospheric transport model, with two different emission scenarios for industrial chemicals and plant protection products, respectively. For the crop emission scenario, regions with farmland were used as source regions. It should be noted that this remoteness index was derived based on atmospheric transport modelling and does not consider transport through water. A map generated by von Waldow et al. (2010) showing the resulting remoteness indices 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

134 According to an AMAP report on Arctic Pollution (Nilsson & Huntington, 2009) chlorpyrifos has been found 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 paragraphs below results of monitoring studies published in scientific literature are compiled.

135 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/m³ in the vapour phase and 0.08 pg/m³ bound to particles, while the level in the water phase of a corresponding fog sample was 0.08 ng/L ((Rice & Chernyak, 1997).

136 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.

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[10] OECD POV and LRTP Screening Tool, Version 2.2, 2009

[11] Input physico-chemical properties: log K_{ow} 5.2, log Kaw -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 = $7.86 \cdot 10^{-2}$%.
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 = $7.69 \cdot 10^{-3}$%.

137 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, and 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.

138 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^2/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^2/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 from over-populated and agricultural regions in northern Eurasia might be the source of greater burdens of some pesticides used there.

139 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. Chlorpyrofos was detected at the highest concentrations of any of the analyzed substances at both sites (Hermanson et al., 2021).

140 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)

141 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 Artic 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.

142 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^2 (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)

143 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^3.

144 During a cruise in 2008 across the Beaufort Sea chlorpyrifos was measured in the air at 3.1 ± 1.9 pg/m^3 and in the sea water at 31 ± 19 pg/L (Pućko et al., 2015). These values were used to model the input of chlorpyrifos and other chemicals to the Beauford 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 Beauford Sea region. Authors hypothesized that this phenomenon would increase with climate change.

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

146 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^3 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.

147 In 2012 Pućko 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 ± SD with 4.8 ± 1.3 pg/L in snow, 14.4 ± 2.5 pg/L in melt-pond water, 14.1 ± 6.0 pg/L at surface level sea water, 10.5 ± 1.7 pg/L at sea water of five-meter depth and 0.10 ± 0.04 pg/m^3 for air.

148 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 ± SD of 13 ± 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 ± 20 pg/L, 0.82 ± 0.53 pg/L and 3.1 ± 1.9 pg/L respectively. For air the detection frequency was 85% with a mean value of 1.1 ± 1.3 pg/m^3. 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% reduction in air concentration was reached in 1.5 years.

149 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^3 (Supporting Information of Bigot et al. (2017)).

150 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^3. 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.

151 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

152 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).

153 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 trouts (*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.

154 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 more detail in section 3.2.

155 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 ± 27.31 ng/g feather in male and 49.56 ± 18.45 ng/g in female Albatross and 84.88 ± 50.57 ng/g for male petrels and 75.98 ± 47.97 ng/g for female petrels.

156 Morris et al (2014) detected chlorpyrifos in the Canadian Arctic Archipelago in vegetation and mushrooms up to 0.85 ± 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 ± 0.16 ng/g lw and in one of seven samples of wolf liver at 0.06 ± 0.033 ng/g lw (Supporting Information of Morris et al. (2014)).

157 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)).

158 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

159 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.

160 Chlorpyrifos in the vapour phase is susceptible to reaction with OH radicals. As described by 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.

161 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.

162 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, and to microplastics (Camacho et al 2019). 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).

163 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 Sühring et al. (2020) found that the long-range transport of organophosphate esters and, potentially, other substances, is not adequately predicted by the OECD Pov and LRTP Screening Tool. Uncertainty in gas-particle partitioning of non-chlorinated organophosphate esters and river-based transport in the case of chlorinated organophosphate esters were discussed as potential reasons for the

underestimation of long-range transport (Sühring et al., 2020). The authors suggest modifications to the OECD Pov and LRTP Screening Tool to account for transport mechanisms like episodic air and riverine transport. Chlorpyrifos is an organothiophosphate, and hence structurally related. The respective modelling results could be subject to similar problems. Particularly transport in water might be underestimated by the OECD Pov and LRTP Screening Tool.

164 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

165 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 polar 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

166 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^3 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^3 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^3 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^3 were found with an 87% frequency of detection (Kuang et al., 2003) in the air (Nandhini et al., 2021; Das et al., 2020; Gebremariam et al., 2012). Chlorpyrifos was detected in particulate matter in air at a remote alpine site in the Southern Alps, New Zealand in 2009, with the Canterbury Plains as the likely source region. Chlorpyrifos was one of the most commonly detected pesticides, together with dieldrin, transchlordane and endosulfan, all listed POPS with known LRET (Lavan et al., 2012). This reported movement of chlorpyrifos from the agricultural area indicates the potential for chlorpyrifos originating in New Zealand to be contributing to that found in Antarctica.

167 In Canada, chlorpyrifos was detected at concentrations of 10 to 100 ng/m^3 with 3 concentrations exceeding 100 ng/m^3 and a maximum of 250 ng/m^3 in 2003, then a maximum of 1.38 ng/m^3 in 2005 at Bratt's Lake. In addition, concentrations of values less than 0.26 ng/m^3 were found in 2004 and 2005 in Abbotsford area, British Colombia (Raina et al., 2010). In 2003, Gouin et al. (2008) found chlorpyrifos air concentrations ranging between 3.2 and 2700 pg/m^3 at the agricultural sites, while it was reported to range from 0.3 and 7.6 to pg/m^3 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^3 (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^3 (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^3 in the air and 0.08 to 0.85 pg/L in seawater (Zhong et al., 2012).

168 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).

169 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). 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). Chlorpyrifos was found in waterways in New Zealand at a maximum concentration of 189 ng/L, higher than any other pesticide. At 2 sites levels were above the NOEC values for fish, and in several other cases close to the New Zealand Environmental Exposure Limits (Hageman et al., 2019).

170 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 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 ± 0.04 pg/m^3, 4.8 ± 1.3 pg/L, 14.4 ± 2.5 pg/L, 14.1 ± 6.1 pg/L, and 10.5 ± 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 water 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 (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.

171 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).

172 The results from the Norwegian pesticide residues monitoring programme have shown maximum residue level (MRL) exceedances for chlorpyrifos in various food commodities. For 2020 residues of chlorpyrifos were found above the MRL (0.01 mg/kg) in dried beans at 0.1 mg/kg and 0.14 mg/kg, from Madagascar and Turkey, respectively. For 2019 residues of chlorpyrifos were found above the MRL (0.02 mg/kg) in coriander leaves from Laos at 0.29 mg/kg, while for 2018 they were found above the MRL (0.01 mg/kg) in pears from China at 0.033 mg/kg and in table grapes from Chile at 0.029 mg/kg. Furthermore, it has been reported in 2018 that one sample of organic lime from Colombia contained chlorpyrifos. The report for 2021 is expected to be published in summer 2022 (Overvåkingsresultater for plantevernmidler i næringsmidler 2020, Overvåkingsresultater for plantevernmidler i næringsmidler 2019, Overvåkingsresultater for plantevernmidler i næringsmidler 2018).

173 In the Norwegian screening programme from 2019, chlorpyrifos was found in the samples of house dust from private homes at the levels ranging from < 3.0 to 1300 µg/kg dw (Screening programme 2019 – Suspected PBT compounds). In the Norwegian screening programme from 2017, the highest level of chlorpyrifos detected in the rat liver samples from Oslo city was 12.0 ng/g dw (Screening programme 2017 – Suspected PBT compounds). The results from another Norwegian screening programme from 2017 have shown that chlorpyrifos was detected with an average concentration of 0.30 ng/L and detection frequency of 83% in the effluent samples from one of the wastewater treatment plants in Tromsø, which lies in Northern Norway (Screening Programme 2017 – AMAP Assessment Compounds). In the Norwegian screening programme from 2016, chlorpyrifos was found in the liver

samples of large perch from Lake Mjøsa at the levels ranging from < 0.5 to 2.3 µg/kg dw (Screening programme 2016 – Suspected PBT compounds).

174 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 (RSMPs) in European waters (EEA Report No 7/2018). The annual average EQS (AA-EQS) for surface water is 0.03 µg/l and the maximun 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.

175 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).

176 In 1997 and 1998 blood samples from sea otters (*Enhydra lutris ssp.*) in California and Alaska, USA were analysed for POPs and other chemicals of concern (Jessup et al., 2010). Recovery rates were > 90% and the detection limit was 4 ng/g lw with capillary gas chromatography. The lipid percentage of serum ranged from 0.6 to 1%. No chlorpyrifos contamination was reported for Alaskan sea otters. For Californian sea otters, a range from below LOD to 342.6 ng/g lw chlorpyrifos was reported. 40 individuals were sampled. Significant differences were found at the three sampling locations.

177 In 2005 the liver of river otters (*Lontra canadensis*) from New Jersey, USA were sampled for POPs 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.

178 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 POPs 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 ± 27.31 ng/g feather in male Albatross and 84.88 ± 50.57 for male petrels.

179 Chlorpyrifos was detected in songbird spp. feet, in animals collected from Toronto in the spring. The birds sampled were most likely to have overwintered in Mexican or Central American crops (cacao, citrus, and coffee). The overall recovery was 80% for chlorpyrifos, with a limit of detection of 0.1 pg/mg feet weight. In the collection year 2011, chlorpyrifos ranged in feet samples from nondetectable to 1.2 pg/g feet weight. With sufficient duration of low-dose exposure, chlorpyrifos might persist and bioaccumulate (Alharbi et al. 2016). Owl carcasses were sampled for tissues (heart, liver, and kidney) Chlorpyrifos-ethyl was detected in the livers of two of the *Megascops* spp. (n=5), collected in 2018-2019 in Brazil, in an area with mixed agriculture and forests (Dal Pizzol et al. 2017).

180 Sixty wild boar (*Sus scrofa*) from northwestern Spain were sampled for POPs, and organophosphate pesticides including chlorpyrifos. Hair and liver samples were taken, and chlorpyrifos was detected in 98% of hair samples and 90% of liver samples. Hair sample concentrations ranged from nondetectable (n.d.) to 1.7 ng/g, and in liver, concentrations ranged from n.d. to 29 ng/g l.w. or n.d. to 3.2 ng/g (Gonzalez-Gomez et al. 2021).

181 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 ± 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 tree 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.

182 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.

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

184 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. Chen et al (2014) found chlorpryrifos in 100% of 10 samples each of breast milk, cow's milk and infant formula in the USA.

185 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 ADI/PTDI of 0 – 0.001 mg/kg bw set by FAO/WHO, which equals the acceptable daily intake for infants set by EFSA (2014) at 0.001 mg/kg bw.

186 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 ± SE of 0.230 ± 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.

187 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 ± 0.6 µg/L. The mean concentration of chlorpyrifos metabolite in mothers' and infants' urine was found to be 2.1 ± 1.4 and 1.4 ± 0.7 µg/L, respectively.

188 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 m/L for chlorpyrifos. The concentration levels in the plasma samples had a range of <LOD to 0.66 ng m/L, while the concentration levels in milk samples had a range of <LOD to 0.46 ng m/L.

189 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 ± 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 ± 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 ± 0.111 ppb, and when above LOD, the range was 0.20 to 0.395 ppb.

190 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 rage of 3.5 to 34.4 pg/g and a median of value 3.7 pg/g.

191 Chlorpyrifos exposure during pregnancy has been linked to severe adverse effects on neurodevelopment in children. As discussed in chapter 4 of this dossier, animal studies and epidemiological analyses suggest that chlorpyrifos has the potential to affect the developing nervous system even at very low levels.

192 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 ± 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 ± 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 by 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.

4. Hazard assessment for endpoint of concern

193 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

194 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).

195 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_{50} 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_{50} values are reported. Accordingly, 96 h LC_{50} 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. peninsulae, M. beryllina* and *Leuresthes tenuis* as the most sensitive species, with 96 h LC_{50} values ranging from 0.53 to 4.2 µg 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_5-LC_{50}) 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_{50}, which clearly demonstrates the high acute toxicity of chlorpyrifos to fish.

196 Studies looking at chronic toxicity usually expose animals to sub-lethal concentrations. However, in the case of chlorpyrifos, because of its high toxicity, lethality often remains the most sensitive endpoint recorded in chronic tests, despite the low concentrations tested in such studies. Only few studies performed in laboratory conditions similar to those of the OECD 210 guideline, i.e. focusing on sub-lethal effects and on the early life stages of the species tested, record effects at concentrations slightly lower but still in the same range as lethality. For the estuarine fish *Leuresthes tenuis*, Goodman, Hansen, Cripe, et al. (1985b) reported 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., 1985b).

197 A substantial quantity of data is available for aquatic exposure of amphibians to chlorpyrifos. Fryday and Thompson (2012) report 96-h LC50 < 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).

198 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 EC50 of 0.1 µg a.s./L. This endpoint is in the same range as the

EC50 of 0.138 µg a.s./L determined for the macroinvertebrate *Hyalella 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 EC50 of 0.035 µg a.s./L. Using an SSD approach, the authors calculate HC5 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. The HC5 for invertebrates are based on EC50s while fish was based on LC50s which also increased the factor difference when comparing both trophic levels.

199 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

200 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 oral studies performed with chlorpyrifos as technical grade. When tested as product, chlorpyrifos indicates a slightly higher toxicity for Emulsified Concentrate (EC) or Capsule Suspension (CS) formulations. Spain (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).

201 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.

202 Long-term and reproductive toxicity studies identified various effects on nervous system, depression of erythrocyte (RBC) and acetylcholinesterase (AChE) in mammals. Considering a two-generation reproductive toxicity study in rats performed in an OECD 416 design, European Commission (2005) reported a parental NOAEL of 0.1 mg a.s./kg bw/day based on red blood cell (RBC) (EFSA, 2017) reported that brain AChE was decreased and histopathological alterations of the adrenal gland occurred at the next dose level (5 mg/kg bw/day). An offspring NOAEL of 1 mg/kg bw/day was noted based on decreased growth and survival for offspring. A NOAEL of 0.1 mg/kg bw/day was also observed in a 2-year dietary study in rats which was based on decreased body weight gains and RBC acetylcholinesterase activity observed at 1 mg/kg bw/day. (European Commission, 2005). Oppositely, the decreased brain AChE was only observed at 10 mg/kg bw/day in the 2-year dietary rat toxicity study reported by EFSA (EFSA, 2017).

203 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.

204 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 millefera*. 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).

205 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.

206 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 < 1ppm were also reported for the beneficial aphids *Acyrthosiphon kondoi, A. Pisum* (Homoptera: Aphididae) as well as for the brown lacewings *Austromicromus tasmaniae* (Neuroptera: Hemerobiidae). Further acute LR50 values of 1 ppm or less are reported in Spain (2017b) for the damselflies *Enallagma spp.* and *Ischmura spp.* (Odonata: Coenagrionidae) and larvae of Trichopteran species *Hydropsyche* and *Chematopsyche spp*. (Trichoptera: Hydropsychidae).

207 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).

208 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 has a higher chronic toxicity to soil macro-organisms such as collembola and mites. A test on the springtail *Folsomia candida* (Collembola) conducted with technical chlorpyrifos following an OECD 232 design reports a 28-d NOEC mortality of 0.075 mg 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

209 Chlorpyrifos can cause cholinesterase inhibition in humans at high enough doses that leads to an overstimulation 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 classified based on UN GHS criteria 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 suggest an association of exposure to chlorpyrifos during pregnancy with adverse neurodevelopmental outcomes in children, including changes in brain morphology, delays in cognitive and motor functions, and problems with attention, and tremors.

210 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.

211 At lower concentrations, in longer-term toxicity studies with rats and dogs, the most sensitive effect was inhibition of cholinesterase activity. No evidence for carcinogenic potential was found upon chlorpyrifos administration in guideline studies in rats or mice. It has been discussed in the public literature that chlorpyrifos could induce oxidative stress leading to tissue damage and DNA damage. However, the studies supporting this hypothesis were not considered sufficient to draw a clear conclusion. 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 rat and mouse studies, 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 explore effects on the developing nervous sytem in rodents; however, uncertainty remains with respect to several aspects, including the dose level, timing, and duration of exposure required to produce adverse effects in the developing nervous system, as well as the mode of action underlying these effects.

Developmental neurotoxicity

Animal experiments

212 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 established for RBC AChE inhibition. Silva et al. (2017) investigated the effects on complex behaviours (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. Behavioural 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 behaviour. Neither RBC nor brain AChE levels were

determined in dams or pups. The authors concluded that chlorpyrifos treatment during pregnancy induced anxiogenic behaviour 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 behaviours such as these. The data were presented without reporting individual data, means, or standard deviations.

213 The US EPA (2020a) and APVMA (2019) evaluated the study of Silva et al. (2017) and regarded it as of unacceptable quality due to a number of deficiencies. Following deficiencies were identified in the study design: lacking information regarding measures taken to control for confounding factors (lighting, noise, transport/room acclimation and handling stress), information on thigmotaxis is missing, only male offspring were evaluated, inadequacies of the statistical methods used, insufficiently detailed published study report (US EPA, 2020b).

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 The publications by Gómez-Giménez et al. (2017 and 2018) were also considered not to be of regulatory quality by the US EPA (2020a) and APVMA (2019) due to numerous deficiencies in the studies design. For the study Gómez-Giménez et al. (2017) following limitation were identified such as misrepresentation of the sample size, inadequate description of test conditions, inadequate control/assessment of confounding factors, inappropriate duration of test interval in the 8-arm radial maze, and/or interpretation of the data. Additionally, the inadequate sample size, inadequacies of the statistical methods used, and insufficiently detailed study report were noted by the US EPA (2020b) and APVMA (2019) for Gómez-Giménez et al. (2018).

217 Similar motor effects were observed by Lee et al. (2015) in PND 60 mouse pups at doses of 5.0 mg/kg bw. 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 (brain growth spurt) of CaMKII (calcium calmodulin-dependent protein kinase 11) may lead to irreversible behavioral effects lasting into adulthood.

218 The study of Lee et al. (2015) was considered acceptable by US EPA but only for use qualitatively due to the several major deficiencies which were identified in the conduct and interpretation of this study. The number of litters, sample size were not identified in the study, information about assessment of the sacrificed female pups for BChE inhibition was unclear, inadequate sample size was used for motor activity assessments, and finally not appropriate statistical analysis was used in the study.

219 Mohammed et al. (2015), Buntyn et al. (2017); Carr et al. (2017) 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 (Mohammed et al., 2015). In a subsequent study, pups were treated by gavage on PND 10-15 with 0, 0.5, 0.75 or 1 mg/kg/day chlorpyrifos (6-8/sex/dose) (Carr et al., 2017). Forebrain AChE inhibition was noted at the 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 (1.0 mg/kg bw/day). The LOEL for decreased anxiety in PND 25 pups was 0.5 mg/kg/day.

220 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). The study was performed according to the US EPA guideline OPPTS 870.6300 and the OECD guideline 426; however, some limitations or guideline deviations have been noted, including a shortened exposure period (gestation day 6 to lactation day 11, rather than lactation day 21), and a lower number of pups included for neuropathology, learning and memory, and behavioural ontogeny assessments. 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 (5 mg/kg bw/day), 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 (Hoberman, 1998). Morphometric observations were not made at 0.3 mg/kg/day; consequently, a discrete no-observed effect level (NOEL) could not be determined.

221 The DNT study (Hoberman, 1998) was re-evaluated by Mie et al. (2018) based on the full study report, including the raw data. Mie et al. (2018) expressed each brain regional measure relative to brain weight in order to properly demonstrate the absence of a sensitive target region. Based on the re-analysis of row data was found that low- and mid-dose effects (cerebellum height in PND 11 pups relative to brain weight) are statistically highly significant, consistent in both sexes, and observed in the absence of general maternal toxicity. In the high dose group, however, the reduction of absolute cerebellum height coincides with a significant decrease in brain weight (observed at the high-dose only). Therefore, it was concluded that indication of the presence of DNT were observed at all dose levels tested in the study.

222 The re-evaluation of the study by Mie et al. (2018) was taken into account by EFSA’s statement on human health assessment of chlorpyrifos (2019). Moreover, in the statement was mentioned that the decrease in cerebellum height corrected by brain weight was considered an adverse effect indicating a damage of the architecture of the developing brain. The structural changes in the developing rat brain found in regulatory studies are consistent with human data (as cited in EFSA, 2019).

223 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). It is necessary to mention that the study Silva et al. (2017) was assessed by regulatory authorities, and it was concluded that it is not regulatory quality due to inadequacies of the statistical methods used, lack of blinding of the observer and/or other techniques to reduce observer bias, lack of assay validation by incorporation of appropriate control groups and lack of historical control data (APVMA 2019). 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.

224 Several *in vitro* studies have observed effects of chlorpyrifos and chlorpyrifos-oxon on neuronal growth in tissue culture, including decreased axonal length and inhibition of neurite outgrowth (D. L. Eaton et al., 2008).Based on the weight of evidence from animal studies and in vitro mechanistic studies it could be concluded that many of the neurodevelopmental effects of chlorpyrifos are secondary to inhibition of AChE in target tissues and alternative

mechanism suspected based on the in vitro studies. At present, many challenges still exist with respect to in vitro to in vivo extrapolation (IVIVE) in the context of DNT, including consideration of internal dosimetry at various life-stages, and physiological changes during pregnancy and lactation.

Human studies

225 Epidemiological evidence suggesting 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.

226 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, US EPA subsequently cancelled all indoor uses of chlorpyrifos by the end of 2001 (US EPA, 2001).

227 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 studies include the small sample size, the extent of the cognitive assessment, chlorpyrifos exposure was measured at a single timepoint rather than longitudinal testing, the lack of information regarding qualifications of researchers administering certain questionnaires, methodological issues with brain MRI data analysis and methods used for comparing brain images, and small sample size (APVMA 2017).

228 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. Limitations of the study were noted by regulatory authorities - the lack of exposure data specific to chlorpyrifos (and reliance on DAP measurements, which is a non-specific metabolite of OP pesticides), limits the regulatory utility of the CHAMACOS studies, authors did not discuss the passage of OP across the placental barrier, or how measurement of OP metabolites in the mother's urine relate to in utero exposure, the lack of detail provided regarding the techniques used for statistical analyses (USEPA, 2014, APVMA, 2017).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 related to their home environments (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.

229 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).

230 In 2015 US EPA updated a literature review (summarized in 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. The US EPA concluded that the 3 US cohort studies (CCCEH, CHAMACOS, and Mt. Sinai) provide the most robust available epidemiological evidence (US EPA, 2016).

231 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; Corrion 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 that results from the 3 US cohort studies have shown 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.

232 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.

233 In 2020 US EPA revised the human health risk assessment of chlorpyrifos. This assessment substantially relied on the previous documents developed for chlorpyrifos (US EPA 2014), an updated drinking water assessment, and animal toxicity literature review. Five new laboratory animal studies were reviewed, and it was concluded that 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 not robust enough for deriving a POD (point of departure) (US EPA 2020).

234 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. Sheppard et al. (2020) reanalysed the human study (Coulston, 1972) using the original statistical method and modern computational tools and considering limitation of the study. It was suggested that the statistical method for deriving a chronic no-observed-adverse-effect-level (NOAEL) of 0.03 mg/kg-day for chlorpyrifos in humans (Coulston, 1972) 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.

235 Moreover, the study of Coulston et al. (1972) was evaluated by Australian Pesticides and Veterinary Medicines Authority (APVMA, 2019). It was concluded that the study has numerous deficiencies and therefore is regarded as not reliable. Basad on the NOEL this study was considered not sufficiently reliable as a point of departure for the determination of health-based guidance values for chlorpyrifos (as cited in APVMA, 2019).

236 In a birth cohort study prenatal chlorpyrifos exposure associated with H3K4me3 and DNA methylation levels of the PPARγ 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 PPARγ 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). But the authors also acknowledged that the participants included in the analyses had higher cord blood chlorpyrifos levels than studies in the United States and in China (chlorpyrifos is still widely used in Taiwan), therefore results may not be applicable to populations with lower exposure levels. Also, they acknowledge that they cannot rule out the possibility of other pesticide exposures which may confound the results.

237 In a cohort of male adolescents from Spain, chlorpyrifos exposure measured by urinary TCPy was associated with significant decreases in E2, follicle-stimulating hormone, anti-Mullerian hormone, and an increase in dehydroepiandrosterone sulfate (DHEAS). Carriers of the PON1 genotype 55MM, had significantly higher increases of free T4 for detected TCPy (Suarez et al. 2021).

238 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:

239 Laboratory studies clearly demonstrate that chlorpyrifos is highly toxic to aquatic communities at concentrations around 0.1 µg 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.

240 The results of epidemiological studies suggested an association between neurodevelopmental effects and exposure to chlorpyrifos

241 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.

242 These studies, along with epidemiological analyses, suggest that chlorpyrifos has the potential to affect the developing nervous system. The structural changes in the developing rat brain found in regulatory studies are consistent with human data (EFSA, 2019). However, US EPA concluded, that despite several years of study, peer review, and public process, the science addressing neurodevelopmental effects remains unresolved (US EPA, 2020a)

5. Synthesis of information

243 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.

244 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 US EPA in 2000 (US EPA, 2006). However, usage as a biocide, e.g., for termite control in buildings, is still practiced in other countries.

245 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 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 (CCPIA, 2022). It is understood that China and India are currently two of the biggest producers of chlorpyrifos globally.

246 Environmental degradation half-lives of chlorpyrifos range from a few days to several years (in the case of termite control), depending on application rate, ecosystem type, soil or sediment characteristics, and other environmental factors, including temperature. A DT50 of 75 d at 8°C was determined in a water degradation studies, and as such chlorpyrifos fulfils the criterion for persistence in water with half-lives greater than two months. Monitoring data from the Arctic and Antartica 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, chlorpyrifos can be considered persistent in some environments according to the definition of the Stockholm Convention.

247 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 could lead to body concentrations that elicit adverse effects, thus it may be 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.

248 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 polar 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.

249 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).

250 Laboratory studies clearly demonstrate that chlorpyrifos is highly toxic to aquatic communities at concentrations around 0.1 µg 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.

251 *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. These studies, along with epidemiological evidence, suggest that chlorpyrifos has the potential to affect the developing nervous system.

6. Concluding statement

252 Environmental degradation half-lives of chlorpyrifos range from a few days to several years (in the case of termite control), depending on application rate, ecosystem type, soil or sediment characteristics, and other environmental factors (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.

253 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.

254 The predicted half-lives of chlorpyrifos in air ranging from 1.4 to 14 hours are relatively low, however, chlorpyrifos has been detected frequently in various abiotic compartments of remote areas in the Arctic and Antarctic, as well as in in apex predators of the Arctic including polar bears, demonstrating its ability to undergo long-range transboundary transport. Potential routes of transport include atmospheric transport in the gas and/or particulate phase, transport via water in rivers and/ or ocean currents.

255 Epidemiological analyses, in combination with animal studies, suggest that chlorpyrifos has the potential to affect the developing nervous system. 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 may lead to adverse effects for human health and the environment at certain exposure levels.

256 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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