CHLORPYRIFOS

Draft proposal for listing chlorpyrifos in Annex A to the Stockholm Convention on Persistent Organic Pollutants

October 2020

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1 Introduction

1. 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 (EC, 2007). A decision on phasing out most non-agricultural applications was adopted by the EPA in 2000 (US-EPA, 2006). However, usage as a biocide, e.g. for termite control in buildings, is still practiced in other countries. For example, termite control is still recommended by Indian authorities (GOI, 2020).

2. In 2014 the human health risk assessment on chlorpyrifos was revised by the US-EPA (2014). Risks were identified for workers; potential risks were found for drinking water. According to the US-EPA (2017) exposure to chlorpyrifos is also linked to the delay of mental development of young children.

3. In 2019, the renewal of the approval of chlorpyrifos for use as active substance in plant protection products has been denied in the European Union (EC, 2020), following the risk assessment carried out by the European Food Safety Authority (EFSA, 2019). EFSA had concluded that the approval criteria, which are applicable to human health as laid down in Article 4 of Regulation (EC) No 1107/2009 are not met. The data presented in this dossier is considered relevant, unless noted otherwise. All other information, as well as most tables, can be found in the INF-document.

2 Identification of the chemical

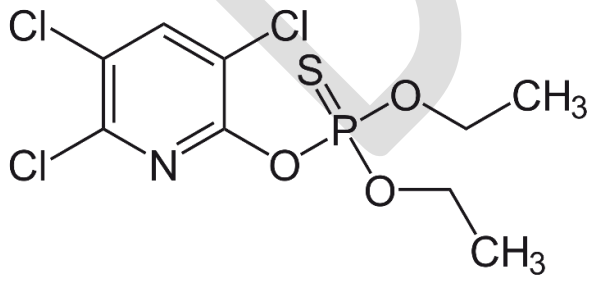
2.1 Names and identities

Table 1 Chemical identity of chlorpyrifos

CAS number:	2921-88-2
CAS chemical name:	O,O-diethyl O-(3,5,6-trichloro-2-pyridyl) phosphorothioate
IUPAC name:	O,O-Diethyl O-3,5,6-trichloro-2-pyridinyl phosphorothioate
EC number:	220-864-4
Smiles code	CCOP(=S)(OCC)Oc1nc(Cl)c(Cl)cc1Cl
Molecular formula:	$C_9H_{11}Cl_3NO_3PS$
Molecular weight:	350.59 g/mol
Synonyms:	chlorpyriphos; chlorpyrifos-ethyl; 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

4. A table of physico-chemical properties of chlorpyrifos is included in the document Chlorpyrifos-AnnexD-INF table 1.

2.2 Structure



Source: https://commons.wikimedia.org/wiki/File:Chlorpyrifos.svg, Public Domain

2.3 Transformation products

5. To be further developed – the transformation products of chlorpyrifos are not considered to fulfil the POP criteria.

3 Information on chlorpyrifos and how it fulfils the Annex D screening criteria

3.1 Persistence

6. According to the US-EPA (2006), the major route of dissipation of chlorpyrifos appears to be aerobic and anaerobic biodegradation. Based on available data, chlorpyrifos appears to degrade slowly in soil under both aerobic and anaerobic conditions. It possesses a low water solubility and a high soil binding capacity. Information on leaching and adsorption/desorption indicate that parent chlorpyrifos is largely immobile. The pesticide agent can contaminate surface water via spray drift at the time of application or as runoff up to several months after application. Available data indicate that most chlorpyrifos runoff is generally via adsorption to eroding soil rather than by dissolution in runoff water. However, under some conditions, dissolution in runoff water may be significant. All half-lives mentioned in the following chapters are listed in Chlorpyrifos-AnnexD-INF document for transparency.

Route of degradation and transformation products

7. Various studies examining the route of degradation have been assessed in the European DAR (Spain, 2017). A new study by B. Clark (2013) on the route of degradation in soil was submitted for the purpose of renewal of the EU approval of chlorpyrifos. The study was conducted according to OECD TG 307. 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. Additional minor metabolites were not fully characterised or identified in the report.

8. 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 unextractable residues.

3.1.1 Abiotic degradation

9. It is reported by the US-EPA (2006) that abiotic hydrolysis, photodegradation and volatilisation do not seem to play significant roles in the dissipation process. However, according to UNEP (2012) the substance may be volatile with regard to its vapour pressure and its Henry's Law constant (for values see Chlorpyrifos-AnnexD-INF document table 1). It is concluded that volatilisation might play a role in the overall dissipation process in the field, but to which quantities remains unknown.

Soil photolysis

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

11. Racke et al. (1994) determined the photodegradation rate and identified the photodegradates of the main metabolite (TCP) of both chlorpyrifos and chlopyrifos-methyl on soil surface. Approximately 50% of the applied TCP degraded during the first 8 hours of sunlight exposure, the half-life was calculated to be 14.1 days (R^2 = 0.820). The major photoproduct of TCP was CO_2 (40% AR at 30 days) and small amounts of polar and non-extractable residues were also formed. The study author suggests that these polar residues may represent transient intermediates to CO_2.

Water: Hydrolytic degradation

12. The European Union DAR for chlorpyrifos (Spain, 2017) lists five studies on hydrolysis. The hydrolysis of chlorpyrifos has been found by P.J. McCall (1986) to be independent of pH below pH 7 with a half-life of approximately 72 days. At alkaline pH, hydrolysis is dependent on pH with a measured half-life for chlorpyrifos of 16 days at pH 9, 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 of the chemical. For an overview of pH dependant degradation of chlorpyrifos please see Chlorpyrifos-AnnexD-INF document table 2.

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

14. 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.

15. 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.

16. 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).

17. 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. 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).

Water: Direct and indirect photochemical degradation

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

19. Adam (2015) concluded that [14C] chlorpyrifos is degraded by direct and indirect photolysis with net half-lives of 7.2 and 2.9 days natural summer sunlight at latitudes 30 to 50°N. For irradiated samples, it was not possible to completely avoid volatilisation of the test item from the water phase. The review by Racke (1993) cites the study by P.J. McCall (1986) who investigated photolytic degradation (0.35 - 0.38 ppm) in an aqueous buffer (pH 5) and reported a photolysis half-life of 52 days upon exposure to an artificial light source (general Electric Chroma lamps). The RMS used this information only as additional information. In the study of Meikle et al. (1983), photolysis half-lives observed ranged from 9.4 to 15.6 days (corrected for hydrolysis) and 7.8 to 11.0 days (uncorrected for hydrolysis). This study

also was used 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. The studies by Kralj et al. (2007) and Hossain et al. (2013) do not fulfil the OECD 116 test guideline and are thus not suitable to establish a reliable rate of photodegradation.

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

3.1.2 Biotic degradation

Water

21. The European Union DAR for chlorpyrifos (Spain, 2017) reports one study on ready degradability according to OECD test guideline 301 (Douglas & Pell, 1985). The percentage of biodegradation after 28 days was 22%, which implies that chlorpyrifos is not readily biodegradable. In a study by (Gassen, 2015) on aerobic mineralisation in surface water, conducted according to OECD TG 309, DT50 values of 21 and 46 d at 22°C were estimated. In all systems, up to 28.5% of unchanged parent was progressively lost from the test systems due to evaporation from the aqueous layer during the incubation period, thus the DT50 values do not refer to degradation alone, but rather to dissipation: loss through volatilisation as well as degradation. In Caviezel (2015) dissipation of chlorpyrifos was mainly caused by volatilisation from the surface water, reaching between 58.6% and 64.4% AR after 61 days of incubation, and to a lesser extent by biodegradation. Similarly, in another study on degradation in three static marine water systems Swales (2003) DT50s of 45 d in estuarine (15°C), 35 d in coastal (12°C) and 75 d in open sea water (8°C), respectively, were estimated, again with a rapidly declining ^{14}Cmass balance which points to substantial volatilisation. With a Henry's law constant of 0.478 Pa m³mol^{-1} at 20°C, these observations are plausible. All half-lives mentioned here are listed in Chlorpyrifos-AnnexD-INF document table 3 for transparency.

22. 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 ^{14}C-chlorpyrifos in estuarine outdoor microcosms in Vietnam was 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 Since degradation cannot be differentiated from volatilisation the results of these outdoor microcosm studies are considered less relevant.

23. 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, the criterion of a half-life >2 months mentioned in Annex D, chlorpyrifos can be considered persistent in water, especially at lower temperatures.

Soil

24. 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 DAR, which are written by the RMS, and published by the European Commission (Spain, 2017).

Laboratory studies – rate of degradation

25. 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) which is the current standard guidance for kinetic evaluations. Degradation half-lives range from 5.96 d – 110.3 d at 20°C. Although the soil used by Bidlack (1979) was stored for several months, the DegT50 values are in the same range as other studies (11 – 141 days). All half-lives mentioned here are listed in Chlorpyrifos-AnnexD-INF document table 4 for transparency.

26. 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).

27. 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).

28. 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 days), compared to dry (t½ 49.5 - 120 days) and wet soils (t1/2 63.0 - 124 days). Degradation increased markedly with temperature and decreased with higher chlorpyrifos dosages (5-fold) which are often applied in the tropics due to severe insects' infestations. Degradation and mineralization rates decreased 2-fold.

Laboratory studies - route of degradation

29. Various studies examining the route of degradation have been assessed in the European DAR (Spain, 2017). A new study by B. Clark (2013) on the route of degradation was submitted for the purpose of renewal of the EU approval of chlorpyrifos. The study was conducted according to OECD TG 307 and was considered valid by the RMS. A total of five metabolites were identified. The major transformation product detected was TCP, with maximum mean concentrations of 16.6%, 59.7%, 43.3% and 14.8% AR, for Boone, Raymondville, MSL-PF and Tehama soils, respectively. Other minor metabolites, 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. Additional minor metabolites were not fully characterised or identified in the report.

30. 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 unextractable residues.

Field studies

31. 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). Dissipation half-lives were in the range < 2 - 120 d, with a mean of 32 d and geometric mean of 22 d. However, according to EC (2012) field dissipation studies are not relevant for the persistence assessment of chlorpyrifos because of expected high losses due to volatilisation of the compound (vapour pressure of chlorpyrifos ≥ 1 * 10^{-3} Pa at 20°C and Henry's Law constant > 0.5 Pa m^3/mol; Chlorpyrifos-AnnexD-INF document table 1).

32. The overall rate of decline in field studies is influenced by factors such as volatilization, soil surface photolysis, leaching out of the sampled soil layers and uptake into plants, which can significantly influence the disappearance of the applied substance from the sampled soil layers in addition to degradation within the soil matrix. As a result, in many cases the initial decline of applied substance can be more rapid followed by a slower rate of decline. In addition, the influence of soil photolysis could affect the apparent formation and decline profile of any metabolites/degradation products

formed, particularly if the depth of sampling is limited. Since chlorpyrifos can be classified as semi-volatile according to its vapour pressure (1.43 mPa), the potential for volatilization of chlorpyrifos in field conditions cannot be ruled out.

33. Various studies examining field degradation have been assessed in the European RAR. Fontaine (1987) investigated three soils (see Chlorpyrifos-AnnexD-INF document table 5), and Old (2002a, 2002b, 2002c) investigated four soils. All of these studies belong to legacy studies which were not tailored to obtain the $DegT50_{matrix}$ and therefore it is reasonable to assume that the effects of volatilization may influence the degradation rates obtained from these studies. Thus, the DT50 values obtained in these studies were recalculated by the RMS and are in the range of 5 to 89 days.

Use of chlorpyrifos for termite control

34. The use of chlorpyrifos as a termiticide was phased-out in the USA in the year 2000. Although several other countries also have phased out the use of chlorpyrifos in termite control, this is not the case everywhere. Chlorpyrifos is still used as a termiticide in India (GOI, 2020) and Australia (APVMA, 2000), as well as in a number of African states such as Zambia and Zimbabwe (Rother). However, in Australia a review process for chlorpyrifos usage as termiticide is in progress (APVMA, 2019).

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

36. 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.

37. 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. Chlorpyrifos dissipated at a rate of 68.9% for each doubling of time. 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).

38. Sardar and Kole (2005) conducted a laboratory experiment to study the dissipation of chlorpyrifos in an Indian alluvial soil. Test concentration corresponded to 1 kg, 10 kg and 100 kg per ha. The dissipation followed first order kinetics and the calculated half-lives ranged from 20 to 37 d at 28 °C. TCP was identified as primary transformation product (detected after 3 d, maximum level after 30 d).

At all application levels TCP concentrations decreased afterwards and could no longer detected after 120 d. TMP as secondary transformation product was detected during the study course, but also not after 120 d.

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

Anaerobic degradation:

40. In EEC (1999) an unpublished laboratory study is cited which covered a comparison between the 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

41. 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.

42. Reeves and Mackie (1993) in (Spain, 2017) have conducted a water-sediment study according to BBA Part IV Section 5-1, which was used before adoption of the OECD guideline 308. They used a sandy loam from Brown Carrick Sediment and a clay loam from Auchingilsie Sediment. Due to low recoveries, the study cannot be considered fully valid, but it does give an indication: Chlorpyrifos degraded under aerobic aquatic conditions with DegT50 values in the total system of 22 and 51 days in the sandy loam and clay loam systems respectively (DT90 values 72 and 168 days). Dissipation was more rapid in the water layer, with DT50 values of 3 and 6 days respectively, this may be due either to adsorption to sediment, to volatilisation or to degradation. Significant levels of radioactivity were lost from the system. It was only partially retained by the connecting PVC tubing. This radioactivity was identified as volatile chlorpyrifos. Low levels of $^{14}CO_2$, < 1% AR, were formed during the incubation period. The principal degradation product was TCP, accounting at a maximum of 16.86% AR at 0 h in Sandy loam Total system and 9.89% AR at 100 d in Clay Loam Total system. In the study by Kennard (1996), chlorpyrifos was applied to the sediment (silty clay loam), not to the water. Here, too, significant amounts of radioactivity were lost. The half-life for chlorpyrifos in the test system (sediment and water) was 30.5 days, and only minimal mineralization to $^{14}CO_2$ was observed. The major degradation product formed was TCP, which accounted for a maximum of 44% applied radioactivity in the total system at the end of the incubation period (36d). Another study was conducted by Kang (2015), with two sediment/water test systems. One was collected from Calwich Abbey Lake, the other from Swiss Lake, both in the UK. Samples were incubated for up to 150 days under aerobic conditions with associated overlying waters at a sediment/water ratio of 1:3 in the dark at 20 ± 2 C. [^{14}C]chlorpyrifos was applied at a nominal concentration of 0.50 mg/L. The raw data of this study was re-evaluated by Abu, 2015, who estimated DegT50 values of 30.7 and 58.3 d for the total system.

43. Bondarenko and Gan (2004) investigated the degradation of chlorpyrifos in urban sediments from two creeks in southern California, USA. Under aerobic conditions, chlorpyrifos showed half-lives of 20.3 and 23.7 d, and under anaerobic conditions of 223 and 57.6 d, respectively. Half-lives were calculated for first-order degradation kinetics and based on measured concentrations at several time

points. In this study, natural sediment was not topped up with original water but deionised water, no mass balance was reported and potential losses by volatilisation were not considered.

44. A shake-flask screening test with chlorpyrifos was performed by Walker (1984). The test was designed to rapidly evaluate the relative degradation rates under diverse regimes of, e.g., salinity, pH, and microbial biomass. The experimental design for the screening test covered four treatments. For chlorpyrifos, the half-lives (n = 2) were 18 and 25 d in active sediment, 17 and 39 d in sterile sediment, 16 and 27 d in active water, and 24 and 29 d in sterile water, respectively. The experiments with sterilized samples showed mostly longer half-lives which may be interpreted as degradation of chlorpyrifos being increased in the presence of micro-organisms (biodegradation).

45. 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.

46. Budd et al. (2011) studied the fate of chlorpyrifos in a ditch and a constructed wetland in California (USA). The DT50 for chlorpyrifos in the ditch sediment under anaerobic (flooded) conditions was 144 d and in the constructed wetland sediment 44 d. Under aerobic conditions the DT50 was 58 d in the ditch. Due to low concentrations it was not determined for the constructed wetland. The test set-up is not comparable to laboratory studies conducted according to OECD TG 308, as the studies in aerobic sediment were conducted *in situ*, with changing environmental conditions, the water samples are not directly associated with the sediment samples and losses due to volatilisation are not accounted for.

47. 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.

48. 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, K_{OC}, were 8,163 and 7,227 L/kg for soils and 13,439 and 15,500 L/kg for sediments (Gebremariam et al., 2012).

49.

3.1.3 Other evidence of persistence

50. For chlorpyrifos data from several monitoring studies are available: According to US-EPA (2006) monitoring data indicated a widespread and persistent occurrence of chlorpyrifos in aquatic areas in the USA from the early 1990s on. In a 1992 EPA fish monitoring study, approximately 23 % of the fish nationwide had measurable levels of chlorpyrifos residues (US-EPA, 1992). The study revealed that few sites with relatively high concentrations (above 50 ng/g) were scattered throughout the East and Midwest USA and in California. Highest concentrations were detected at sites near agricultural areas. This reflects high usage of chlorpyrifos, not so much persistence.

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

52. 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 has been identified as a site where potential toxic conditions could arise.

53. 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).

54. Monitoring data from the Arctic demonstrate that chlorpyrifos can be transported over long distances to remote regions (see section 3.3). Since degradation of chlorpyrifos is temperature dependent, it is expected to persist in these regions for a considerable length of time. Frequent findings of chlorpyrifos in all media in the Arctic support this. In addition, chlorpyrifos is found in dated sediment cores in arctic and sub-arctic lakes (Landers, 2008). Although the concentrations in these sediments are low, they do not derive from local use of chlorpyrifos and can be dated back several decades. This also demonstrates the persistence of chlorpyrifos in sediments.

3.1.4 Conclusion on persistence

55. **I**n the water degradation studies evaluated here, DT50 values range from 21 to 75 days at varying temperatures. Normalised to 12°C to reflect environmental conditions in temperate areas, these values range from 6.8 to 124 d. Chlorpyrifos fulfils the criterion for persistence with half-lives in water greater than two months.

56. In soil, highest half-lives for the chlorpyrifos degradation were found at high application rates (100 - 1000 mg/kg). These are used for termite control, which is still an approved use in a number of countries. The reduced degradation of chlorpyrifos at high application rates may not be a result of persistence as such but rather an effect of toxicity to microorganisms. At application rates for agricultural uses (below 100 mg/kg), the half-lives found in literature and study summaries of proprietary studies span a wide range from 6 to 224 d, at varying temperatures. Normalised to 12°C, these values range from 12.7 to 483 days. Of the 38 soil studies evaluated here, 22 DT50 values exceed the criterion for persistence in soil with half-lives greater than 6 months.

57. 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 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.

58. Environmental degradation half-lives of chlorpyrifos range from a few days to several years, depending on application rate, ecosystem type, soil or sediment characteristics, and other environmental factors (Gebremariam et al., 2012). 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

59. Log K_{ow} values for chlorpyrifos have been reported between 4.7 and 5.2 (see Chlorpyrifos-AnnexD-INF document table 1).

3.2.1 Bioaccumulation in laboratory and mesocosm studies

60. According to a review by (Giesy et al., 2014) relevant and reliable BCF values for aquatic plants range from 72 to 5700.

61. The highest BCF value of 5700 was measured for duckweed (*Lemna minor*) (Prasertsup & Ariyakanon, 2011). In a seven-day static experiment plants were exposed to a nominal concentration of 100 µg/L chlorpyrifos. Samples of plants and water were taken daily and analysed for chlorpyrifos content by gas chromatography at recovery rates of 98 ± 2%. With the same experimental set up, a BCF of 3000 was calculated for water lettuce (*Pistia stratiotes*).

62. Rubach et al. (2010) conducted exposure experiments of 15 invertebrate species with C^{14} labelled chlorpyrifos. This resulted in highest BCF value for the diptera *Culex pipens* of 13 930. This value should be evaluated with caution as the C^{14} label was placed at the di-ethyl-phosphorothiol branch of the chlorpyrifos molecule. Accordingly radioactivity measured was not limited to chlorpyrifos but included phosphorylated proteins Mackay et al. (2014) and could result in an overestimated BCF.

63. The BCF for the axolotl (*Ambystoma mexicanum*) was determined in a 48 h static test (Robles-Mendoza et al., 2011). The nominal concentrations were 50 µg/L and 100 µg/L. Ten animals per concentration were tested. Chemical analysis of water and tissue samples were conducted with gas chromatography with a recovery rate of > 95%. Water samples were taken to determine chlorpyrifos concentration at 0 h, 24 h and 48 h. Chlorpyrifos concentration had declined up to 50% at the end of the experiment. The calculated BCF was 3632 at 100 µg/L. This value has some level of uncertainty as chlorpyrifos level were not stable. Additionally, toxicity test showed significant acetylcholinesterase inhibition, reduced motor activity and reduced hunting at 50 µg/L.

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

on soil and chlorpyrifos concentration. A BSAF value above 0.5 is an indicator for high bioaccumulation (ECHA, 2017).

65. Bioaccumulation of chlorpyrifos in fish has been studied for many species, developmental stages and exposure scenarios. Accordingly, BCFs cover a broad range, many studies however do not meet the validity criteria of the OECD 305 test. For an overview of all studies on bioconcentration assessed in this report, please see Chlorpyrifos-AnnexD-INF document table 7.

66. An extensive review on bioaccumulation was conducted by Giesy et al. (2014) with BCFs ranging from 0.6 to 6760 in fish. The highest valid study as assessed by the authors was Hansen et al 1986 with a BCF of 5100 for the gulf toad fish.

67. Hansen et al. (1986) conducted a 49-day early life stage toxicity test with the marine gulf toadfish (*Opsanus beta*). Embryos were exposed to chlorpyrifos concentrations ranging from 1.2 to 150 µg/L in a flow through system. The authors reported a range of BCFs from 100 to 5100. The results of this study must be interpreted with caution as toxic effects occurred at all concentrations higher than 3.7 µg/L. Effects included mortality, reduced size, retarded development and behavioural effects such as hyperactivity and hyperventilation. Mortality was significantly increased at the concentration 150 µg/L which produced the BCF of 5100.

68. In a 28-day field experiment, artificial ponds were dosed with a mosquito larvicide application of granular chlorpyrifos resulting in mean water concentrations between 0.6 µg/L and 0.1 µg/L, exposing four fish species (Mulla et al., 1973). Concentrations in the water declined as concentrations in the upper sediment layer increased to a maximum of 180 µg/kg. Sediment associated species such as channel catfish (*Ictalurus punctatus*) and black crappie (*Pomoxis nigromaculatus*) accumulated mean maximum residues of 0.8 mg/kg and 0.6 mg/kg, resulting in BCFs of 4667 and 3333 respectively. Free swimming species such as largemouth bass *(Micropterus salmoides)* and bluegill *(Lepomis microchirus)* accumulated 0.2 mg/kg and 0.1 mg/kg, resulting in BCF of 1333 and 1200. This study may underestimate chlorpyrifos bioaccumulation, as the viscera was removed from fish before analysis. Results should be interpreted with caution as chlorpyrifos concentrations varied above the 20% mark throughout the experiment.

69. The key BCF considered for the Draft Assessment Report for EU approval is 1374 ± 321 in rainbow trout (*Onchorhynchus mykiss*) (report no ES-928 (J42) as summarized in Spain (2017)). 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. Values were not normalized for lipid content or growth dilution. As the study was conducted with juvenile trout growth dilution can lead to underestimation of the BCF.

70. In many studies, the test organisms show toxic effects accompanied by BCFs lower than 2000 (see Chlorpyrifos-AnnexD-INF document table 7). These effects include reduced growth (J. Eaton et al., 1985; Hansen et al., 1986; Jarvinen et al., 1983) and behavioural abnormalities (J. Eaton et al., 1985; Hansen et al., 1986; Macek et al., 1972). This is published data and with respect to current-day information requirements, insufficient information is given. The studies have not been conducted according to the current OECD test guideline 305, due to their age. The toxic effects shown in these studies violate the validity criteria of the test guideline. What BCF would have been reached at concentrations below toxic effects, is highly speculative. So although in general a BCF exceeding the trigger value of 5000 as given in Annex D of the Stockholm Convention (SSC, 2018) is not reached in adult fish, the toxic effects occurring at much lower bioconcentration in combination with the extremely high toxicity at low exposure levels give rise to serious concern.

71. Eleuthero embryos are freshly hatched larvae, free from the egg membrane and still reliant on the attached yolk for sustenance (Balon, 1975). El-Amrani et al. (2012) exposed zebrafish (*Danio rerio*) eleuthero embryos to chlorpyrifos following the OECD 305 validity criteria. 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. LOD for chlorpyrifos in water samples was 0.5 µg/L for exposure medium and 3 ng/g for eleuthero embryos. The kinetic BCF was calculated, as steady state was not reached. A kinetic BCF of 3548 was calculated at exposure concentration of 1 µg/L. For 10 µg/L the kinetic BCF was 6918.

72. An experiment following the same setup was conducted for medaka (*Oryzias latipes*) at 10 µg/L chlorpyrifos (Alharbi et al., 2017). The LOD for chlorpyrifos was 0.19 ng/g. Steady state was not reached, therefore the kinetic BCF was calculated at 2187. In a separate experiment instead of exposure medium, processed water from surface level mining, containing chlorpyrifos, was used. This resulted in a kinetic BCF of 8912.

73. 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). The high lipid content does not impair the relevance of the study as Eleuthero embryos are a naturally occurring stage of the fish life cycle which portrays a realistic exposure scenario. A normalization of the BCF to 5% lipid content would grossly underestimate the bioaccumulation for this sensitive life stage.

74. Eleuthero embryos have shown higher vulnerability to pesticides than other life stages (Cao et al., 2016; Mu et al., 2013; Velisek et al., 2012) including to chlorpyrifos (Mhadhbi & Beiras, 2012; Wang et al., 2017). As eleuthero embryos show the highest bioconcentration factors and are most readily affected by chlorpyrifos toxicity they are at high risk from chlorpyrifos exposure.

3.2.2 Monitoring data concerning bioaccumulation

75. Chlorpyrifos has been detected in various biota samples from around the world, including the Arctic.

76. 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).

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

78. In the years 1997 and 1998 blood samples from sea otters (*Enhydra lutris* ssp.) in California and Alaska, USA was 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 based on the three sampling locations.

79. 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.

80. 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.

81. The bioaccumulation of chlorpyrifos was investigated in the vegetation-caribou-wolf food chain in the Bathurst region (Nunavut) in Canada by Morris et al. (2014). Trophic levels of species were determined by stable isotope analysis. The authors report for chlorpyrifos so-called volumetric bioconcentration factors (BCF_v)[1] for uptake from the atmosphere into the vegetation (mushrooms, lichen and green plants) amounting to 8.0 - 8.7 referring to lw. The detection for chlorpyrifos in samples was 50% in lichens, willow, and grasses, 67% in moss, and 80% in mushrooms, respectively. Concentrations of chlorpyrifos were as follows: 0.85 ± 0.52 ng/g lw in mushrooms, 0.25 ± 0.21 ng/g lw in lichen, 0.24 ± 0.088 ng/g lw in green plants and 0.18 ± 0.068 ng/g lw in willows. The biomagnification factor (BMF) of chlorpyrifos in caribou and their spring diet was 1.6 ± 0.31. For summer diet the BMF was 1.4 ± 0.43 and 2.1 ± 0.64 for the fall/winter diet. The wolf:caribou BMFs for total body burden of both species amounted to 0.078 ± 0.019. Total body burden was calculated with information from Müller et al. (2011), allowing to extrapolate concentration from samples to the whole carcass. The BMF was greater than 1 in $wolf_{liver}$:$caribou_{liver}$ comparison (1.7 ± 0.52), but the result was not significant due to the high standard deviation (Pearson correlation > 0.05). The trophic magnification factor (TMF) for the assessed food-chain was less than 1 (0.47 - 0.79), indicating chlorpyrifos exhibits trophic dilution in this terrestrial food chain. All values were lipid normalized. The value of the study is limited because analytical recoveries of chlorpyrifos were only low (52 ± 17%) and data thus has a high degree of uncertainty.

82. 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. Current-use pesticides were analysed by gas chromatography, negative chemical ionization, low-resolution mass spectrometry. Chlorpyrifos showed the highest concentrations in plankton of all substances analysed. A BAF ± Standard Error (SE) for plankton of 7 943 282 ± 5 011 872 mL/g was calculated. Mean concentrations with 95% standard deviation for chlorpyrifos were reported for the three sites in ng/g lw in polar bear fat 0.022 (0.013–0.035), 0.032 (0.013–0.076), 0.016 (0.0078–0.033). Concentrations in muscle tissue of arctic char (*Salvelinus alpinus*) and capelin (*Mallotus villosus*) were only measured at one sampling site with 0.11 (0.013–0.93) and 0.31 (0.017–5.5) ng/g lw respectively. A BCF for these fish species cannot be calculated as the water samples for 2007 were non-detect for chlorpyrifos and the samples for 2008 and 2010 were corrupted. BMFs for ice bear fat:seal blubber are given for two sampling sites with 1.3 ± 0.22 and 0.90 ± 0.27. All values were lipid normalized. These values should be considered with caution as the concentration of chlorpyrifos in seal blubber was not reported. TMF values for the three locations were 0.27, 0.57 and 0.18 based on seal blubber. The results should be interpreted with caution, as the recovery of chlorpyrifos from biota was only 52 ± 17%. Additionally, substances were considered non-detectable and not reported if they were found in less than 20% of the samples of one subset, e.g. chlorpyrifos in seal blubber.

83. 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

[1] The volumetric bioconcentration factor (BCFv) is defined as the ratio of the volumetric concentration in vegetation tissues (unit: pg/m^{-3} lw) to the gaseous-phase air concentration (unit: pg/m^{-3}) of a chemical (Morris et al. 2014).

to levels of lindan. For other species chlorpyrifos levels in blood were measured at 80 ppb in chicken, 70 ppb for goat and 40 ppb for men. These levels were comparable to the level of aldrin found in the blood of these species.

84. 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.

85. 53 breast milk samples were analysed from women of the agricultural area of Punjab, India (Bedi et al., 2013). Samples were collected during November and December of 2011. Chlorpyrifos was found in 5.7% of samples at a median of 1664.2 ng/g lw. Authors stated this to be the first finding of chlorpyrifos in human breast milk in the area of Punjab, which could be explained by the current shift towards the extensive use of this pesticide in India. Three samples exceeded the acceptable daily intake for infants set by EFSA (2014) at 0.001 mg/kg body weight.

86. Similar observations have been made for the region Bhopal (India), where the breast milk of 12 women could be 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 the factor 41.

3.2.3 Conclusion on bioaccumulation according to the criteria in Annex D

87. The BCF of 5000 is exceeded for plants and early life stages of fish. Additionally, the log kow for chlorpyrifos is greater than five. We therefore conclude that chlorpyrifos meets the annex D c I criteria for bioaccumulation.

88. Although numerous BCF, being below 2000, show moderate bioconcentration, this in combination with high toxicity especially to sensitive life stages gives reason for serious concern. A BSAF of up to 99 suggest a high bioaccumulation in sediment dwelling organisms. We therefore conclude that chlorpyrifos meets the annex D c II criteria for high toxicity and ecotoxicity.

89. 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 chlorpyrifos meets the annex D c III criteria for bioaccumulation potential.

3.3 Long-range transport potential

3.3.1 Environmental fate properties and model results

90. The vapour pressure for chlorpyrifos has been estimated between 1.0×10^{-3} and 3.35×10^{-3} Pa (see Chlorpyrifos-AnnexD-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.

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

92. Using the Atmospheric Oxidation Program (AOPWIN; ver.1.89; (Corporation)), Simon (2001) calculated an atmospheric half-life of 1.4 hours for chlorpyrifos. The estimated reaction pathways were hydrogen abstraction with 38.63×10^{-12} cm^3/molecule-sec and the reaction with N, S and OH at 53.0×10^{-12} cm^3/molecule-sec at 25°C.

93. Muir et al. (2004) replicated these results using AOPWIN (Corporation) to calculate the half-life of chlorpyrifos. Applying an OH radical concentration of 1.5×10^6 molecules/cm^3 the predicted half-life of chlorpyrifos amounted to 1.4 hours while an OH concentration of 1.5×10^5 molecules/cm^3 resulted

in a half-life of 14 hours. The authors noted, that the later scenario was realistic for spring in the northern hemisphere when chlorpyrifos may be applied early in the growing season. Since the used modelling program version and the applied parameters are comprehensible documented the study is considered as reliable without restriction.

94. Modelling results are confirmed by degradation experiments. In Muñoz et al. (2012) the atmospheric degradation of gas phase chlorpyrifos was observed in the European Photoreactor (EUPHORE). EUPHORE is a reaction chamber with about 200 m^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 hours.

95. Based on results described above the long-range transport potential of chlorpyrifos seems unlikely. The methodology however refers to chlorpyrifos in the vapour phase which is susceptible to reaction with OH radicals. In the particulate phase this reaction is greatly reduced (ATSDR, 1997). The atmospheric half-life of particulate phase chlorpyrifos could therefore be much longer and exceed values relevant for long range transport as has been shown for other pesticides (Socorro et al., 2016).

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

97. 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 latter phase in oceanic air (see Zhong et al. (2012), supporting information).

98. As described earlier, chlorpyrifos binds strongly to soil and sediment (see chapter on persistence). Coscollà et al. (2014) hypothesize that chlorpyrifos adsorbed to soil particles could be transported by wind erosion as has been shown for other pesticides (Larney et al., 1999). Additionally, the volatilization of chlorpyrifos from soil can continue for days after an application (Voutsas et al., 2005). Once in the water compartment, chlorpyrifos bound to suspended solids and sediment is persistent (see chapter on persistence) and could be carried to remote regions in long range transport via oceanic currents (Ma et al., 2018). Chlorpyrifos bound to particles in the arctic ocean have been measured by Bigot et al. (2017).

99. The sum of these processes could explain the presence of chlorpyrifos in ambient abiotic and biotic compartments in remote areas as the Arctic, despite its relatively low atmospheric half-life based on the reaction with OH radicals.

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

3.3.2 Monitoring in abiotic compartments of remote regions

101. 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 was one of the most frequently identified contaminants in sea water with levels ranging up to 67 pg/L. The highest concentration amounting to 170 pg/L was measured in melting ice. 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 its 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) as cited in (Watts, 2012)).

102. 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.

103. 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. Chlorpyrifos first appears at Austfonna in 1972. 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.

104. 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/cm²/year), and a decreasing trend until 1995 - 2005. During the latter period the flux peaked at 808 pg/cm²/year. The chlorpyrifos burden of the entire ice core accumulated between 1953 and 2005 amounted to 776 ng. Chlorpyrifos and the current use pesticide methyl parathion made up 44 % 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 very short atmospheric half-life of the substance predicted for mid-latitude environments. Instead, results suggested that it is persistent in some Arctic conditions. The results of this study were compared with the results found by Hermanson et al. (2005). For this purpose, the concentration data determined at Austfonna were converted to core burdens. The comparative data showed that the chlorpyrifos as well as the alpha-endosulfan burden at Austfonna were much higher than that at Holtedahlfonna. The chlorpyrifos burdens differed by a factor of about 13. It was assumed that the general sources of these pesticides are different at least part of the time, and that Austfonna generally receives the greater input. Ten-year cumulative 5-day air mass trajectories confirmed the assumption that Austfonna had received more atmospheric flow from Eurasia than Holtedahlfonna. The greater Eurasian flow to Austfonna suggested that airflows over populated and agricultural regions in northern Eurasia might be the source of greater burdens of some pesticides used there.

105. 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.

106. 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 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/m². On average concentrations found in blanks were 3% of the concentration in snowpacks and the concentration in blanks was subtracted from concentrations found in snow samples (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).

107. L. M. 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/m³.

108. During a cruise in 2008 across the Beaufort Sea chlorpyrifos was measured in the air at 3.1 ± 1.9 pg/m³ 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. 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.

109. 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/m³ (Hung et al. as cited in Balmer et al. (2019)).

110. 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/m³ 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.

111. 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/m³ for air.

112. L. M. 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. 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% change in air concentration was reached in 1.5 years.

113. 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.

114. 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.

3.3.3 Monitoring in biotic compartments of remote regions

115. 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 South-east 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).

116. 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.

117. 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.

118. For more data on chlorpyrifos monitoring in arctic biota please see chapter on monitoring data concerning bioaccumulation.

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

119. Predicted half-lives of chlorpyrifos in air ranging from 1.4 to 14 hours are relatively low and significantly below the threshold for LRTP of two days set by the Stockholm Convention. Despite these modelling results the compound has been found in various abiotic and biotic compartments of remote areas in the Arctic, as demonstrated above. Thus, chlorpyrifos is considered to meet the criterion of the Stockholm Convention on long-range environmental transport (SSC, 2018).

3.4 Adverse effects

3.4.1 Human health effects

120. Chlorpyrifos can cause cholinesterase inhibition in humans at high enough doses that leads to an overstimulate of the nervous system causing nausea, dizziness, confusion, and at very high exposures (e.g. accidents or major spills), respiratory paralysis and death. Prospective cohort studies in humans evaluated pre- and post-natal exposure to chlorpyrifos in mother-infant pairs and birth and developmental outcomes in neonates, infants, and children. The results from these studies have shown associations of exposure to chlorpyrifos during pregnancy with adverse neurodevelopmental outcomes in children, including changes in brain morphology, delays in cognitive and motor functions, and problems with attention, and tremors.

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

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

Developmental Neurotoxicity

Human studies

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

124. 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

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

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

127. 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).

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

129. 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 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.

130. 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.

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

132. 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.

Animal experiments

133. The developmental neurotoxicity database for chlorpyrifos is evolving and currently contains several in vivo animal studies that might permit the establishment of an oral NOEL below the reported threshold of 1 mg/kg/day established for RBC AChE inhibition:

Silva et al. (2017) investigated the effects on complex behaviors (particularly anxiety and depression) in Wistar rats exposed to chlorpyrifos in utero. Pregnant dams (11-14/dose) received 7 consecutive daily doses (0.01, 0.1, 1 and 10 mg/kg/day) by oral gavage on gestation days 14–20. Behavioral parameters in male offspring were evaluated during the infant-juvenile period (postnatal day [PND] 21) and in adulthood (PND70). Male pups were separated into 4 groups (8-10 pups/group) comprised of those tested on PND 21 or PND70. The elevated plus-maze test was used to assess anxiety levels. The open field test was used to evaluate locomotor activity. The modified forced swimming test was used to assess depressive behavior. Neither RBC nor brain AChE levels were determined in dams or pups. The authors concluded that chlorpyrifos treatment during pregnancy induced anxiogenic behavior in pups at the end of lactation (PND21). It should be emphasised that the use of maze-based behaviours as the method for discerning cognitive deficits may not cover the more complex neurological functions in humans. Therefore, its direct relevancy is unknown. As a result, the authors set the **LOEL for neurodevelopmental effects at 0.1 mg/kg/day.** The lowest tested dose 0.01 mg/kg/day was the

NOEL. The apparent absence of a dose-related exacerbation of this response above 0.1 mg/kg/day was unexplained but was considered plausibly due to saturation of one or more of the neural pathways involved in regulation of complex behaviors such as these. The data were presented without reporting individual data, means, or standard deviations.

134. 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 **an LOEL for neuroinflammation was 0.1 mg/kg/d** for both males and females.

135. 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.

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

137. Mohammed et al. (2015) showed that male and female rat pups treated by oral gavage with chlorpyrifos at 0 and 0.5 mg/kg/day during PND 10-16 exhibited behavioral anomalies when tested on PND 25. Decreased anxiety was evident through increases in number and percent of open arm entries, time and percent time spent in open arm of a plus maze, occurrences of crawling over/under, motor activity, play-fighting and time spent playing. In a subsequent study, pups were treated by gavage on PND 10-15 with 0, 0.5, 0.75 or 1 mg/kg/day chlorpyrifos (6-8/sex/dose) (Carr et al., 2017).

Forebrain AChE inhibition was noted at the high dose, setting the LOEL for brain AChE inhibition at 1.0 mg/kg/day. Behavioral testing showed decreased times to emergence from a dark container into a novel environment at 0.5 mg/kg/day in both sexes. This behavior was associated with decreased anxiety. The data confirm earlier findings from this group showing that chlorpyrifos treatment generated behavioral effects at doses lower than those inhibiting brain AChE. The **LOEL for decreased anxiety in PND 25 pups was 0.5 mg/kg/day**.

138. Effect on developmental neurotoxicity (DNT) was examined by daily oral gavage of chlorpyrifos in pregnant rats (25/dose) during gestation and the perinatal period (GD 6 - PND 11) at doses of 0, 0.3, 1, and 5 mg/kg/d (Hoberman, 1998). Evident maternal effects were observed at 5 mg/kg bw/day, with decreased bodyweight gain, food consumption, brain, RBC and plasma cholinesterase inhibition, and manifestation of clinical signs (fasciculations, hyperpnea and hyperactivity). The critical maternal effect was a decrease in the RBC Cholinesterase at all dose levels (maternal LOAEL: 0.3 mg/kg bw/day). The offspring showed signs of toxicity at the same dose, such as decreased viability index (day 1-5), bodyweight and food consumption. Developmental landmarks were also delayed. On the contrary, brain AChE was not altered. Developmental neurotoxicity was transiently manifested with changes in the brain weight, decreased layer thickness in brain areas (PND 12), and increased latency of the auditory startle response at PND 23. All effects were resolved in the adult period (PND 60-71). Morphometric measurements for nine brain regions in PND 12 pups revealed statistically reduced cerebellar dimensions in high dose males. As high dose male brain weights were 11.5% lower than concurrent controls, a chlorpyrifos-mediated impact on cerebellar growth in these males was considered to be possible. Similar morphometric measurements were conducted in PND 66-71 adults, revealing statistically reduced parietal cortex dimensions in 1 and 5 mg/kg females (4% and 5%, respectively; $p<0.05$). Because control and 1 mg/kg/day female brain weights were unaffected, these changes were consistent with the possibility of a chlorpyrifos-mediated effect. A developmental lowest observed effect level (LOEL) of 1 mg/kg/day was suggested based on reduced parietal cortex and hippocampal dimensions in PND 66-71. Morphometric observations were not made at 0.3 mg/kg/day; consequently, a discrete no-observed effect level (NOEL) could not be determined.

139. In October 2000, Hoberman et al. provided a Report Supplement to Hoberman 1998 (# supplement: 304-001) (Hoberman, 2000). Brain morphometric data from the original report were re-tabulated alongside historical control data from 4 or 5 studies per parameter. Only one measurement having a high dose value statistically significantly different from concurrent controls was outside the range of the historical controls: the cerebellar anterior/posterior dimension in 5 mg/kg/d male 12-day pups was significantly below concurrent control dimension, and also outside the range of the available historical controls. Females did not suggest such a relationship at 12 days, and neither sex showed altered cerebellar anterior/posterior distance after 66 days. In the context of the demonstrated high maternal and neonatal toxicity of this dose, the supplemental data reinforce the conclusion that study findings are not of sufficient magnitude or persistence to be considered as “adverse” even at gestational / postnatal doses as high as 5 mg/kg/day. This was surprising in light of the observations in later studies of effects at 0.1 mg/kg.

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

141. Several *in vitro* studies have observed negative effects of chlorpyrifos and chlorpyrifos-oxon on neuronal growth in tissue culture, including decreased axonal length and inhibition of neurite outgrowth (D. L. Eaton et al., 2008) These *in vitro* effects occurred at concentrations orders of

magnitude less than what would result in AChE inhibition and add to the body of evidence, that effects other than AChE inhibition might trigger the risk assessment of chlorpyrifos.

3.4.2 Conclusion on human health effects according to the criteria in Annex D

142. *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 behavior in rats and mice. Based on these studies, along with epidemiological evidence, chlorpyrifos is considered toxic to the developing nervous system.

3.4.3 Ecotoxicological effects

143. 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; K. R. 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, 2009), 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

144. 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).

145. Standard laboratory studies performed with the active ingredient chlorpyrifos according to the OECD 203 guideline for acute effects (i.e. letahlity) identify *Oncorhynchus mykiss* as the most sensitive species tested. Spain (2017) 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 (2017) there is no evidence for higher toxicity of the active ingredient when formulated, although no test with EC formulations (Emulsified Concentrate), the most common formulations in agriculture, are available. When considering studies from the literature not strictly following the OECD 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 acute toxicity of Chlorpyrifos to fish.

146. Studies looking at chronic toxicity usually expose animals to sub-lethal concentrations. However, in the case of Chlorpyrifos, because of its high toxicity, lethality often remains the most sensitive endpoint recorded in chronic tests, despite the low concentrations tested in such studies. Only few studies performed in laboratory conditions similar to those of the OECD 210 guideline, i.e. focusing on sub-lethal effects and on the early life stages of the species tested, record effects at concentrations slightly lower but still in the same range as lethality. For the estuarine fish *Leuresthes tenuis,* Goodman et al. (1985) reported NOEC values of 0.14 and 0.3 µg a.s./L for embryo weight and lethality

respectively. Jarvinen and Tanner (1982) determined NOEC values of 1.6 and 3.2 µg a.s./L for weight and lethality of *Pimephales promelas* fry exposed to Dursban technical grade for 35 days. The lowest NOEC estimated for chronic mortality is 0.3 µg a.s./L. This endpoint was assessed for embryo lethality in *Leuresthes tenuis* in a 35-days exposure design (Goodman et al., 1985).

147. 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).

148. Invertebrates, especially crustaceans and insects, are the most sensitive taxa among aquatic organisms. Considering only tests performed in an OECD 202 design, EC (2005b) and Spain (2017) identified *Daphnia magna* as the most sensitive species with an EC_{50} of 0.1 µg a.s./L. This endpoint is in the same range as the EC_{50} 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 EC_{50} 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 EC_{50} values collected for 23 and 17 species, respectively. These hazardous concentrations are a factor 10 below the HC_5-LC_{50} calculated for the fish.

149. 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 & Ruiter, 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

150. 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 Spain (2017) to revise the LD_{50} 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 LD_{50} of 39.24 mg a.s./kg bw calculated according to the OECD 223 guideline for the Bobwhite quail (*Colinus virginianus*). Both tests were performed with Chlorpyrifos as technical grade. When tested as product, Chlorpyrifos indicates a slightly higher toxicity for Emulsified Concentrate (EC) or Capsule Suspension (CS) formulations. Spain (2017) reports LD_{50} 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 LD_{50} of 71 mg a.s./kg bw (EC, 2005a).

151. When the substance is administrated by gavage in mammals, EC (2005a) reports acute oral LD_{50} 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 mouse. The LD_{50} of 64 mg a.s./kg bw was confirmed by EFSA (2011) to assess the acute toxicity of chlorpyrifos for wild mammals.

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

153. 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 (EC, 2005a). 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.

154. 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. G. Bell (1994) measured an acute LD_{50} of 0.068 µg a.s./bee in a test performed with Dursban F (97.4% purity). For comparison, the lowest LD_{50} estimated for oral toxicity is 0.15 µg a.s./bee (G. Bell, 1993).

155. In addition to acute toxicity, Spain (2017) reports recent studies on chronic toxicity of chlorpyrifos for bees and bee brood. These tests follow the recommendations of Decourtye et al. (2005) and EFSA (2013) to evaluate among others the chronic mortality following a 10-day exposure at very low concentrations, or 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-LC_{50} of 0.002 µg a.s./bee/day. For bee brood development, Deslandes (2014) Deslandes (2014) determined a NOED of 0.0018 µg a.i./bee for larvae.

156. Chlorpyrifos has been extensively tested on non-target arthropods. Laboratory tests reported in Spain (2017) indicate that Chlorpyrifos is very harmful for beneficial arthropods. When exposed to fresh dry residues of an EC formulation (EF-1042) on glass plates, the 24h-LR_{50} 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-LR_{50} values of 3.21 and 3.62 ppm for *Bracon brevicornis* and *Chelonus blackburni*, respectively). Acute LR_{50} 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 LR_{50} values of 1 ppm or less are reported in Spain (2017) for the damselflies *Enallagma* spp. and *Ischmura spp*. (Odonata: Coenagrionidae) and larvae of Trichopteran species *Hydropsyche* and *Chematopsyche spp*. (Trichoptera: Hydropsychidae).

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

158. The acute toxicity of chlorpyrifos tested as EC formulation (EF 1042 = Dursban 480) on the redworm *Eisenia foetida* in an artificial soil (OECD 207) delivers a 7-days LC_{50} of 313 ppm corresponding to about 137 mg a.s./kg soil (Johnson, A.J. (1993) in EC (2005a)). However, additionally to acute effects, chlorpyrifos appears to be highly chronically toxic to earthworms. In a 56 days study following the OECD 222 design (earthworm reproduction test), De Silva et al. (2009) detected effects of the technical chlorpyrifos on the reproduction of *E. foetida* at concentration around and lower than 1 mg a.s./kg soil. Compared to the earthworms, chlorpyrifos is more chronically toxic to soil macro-organisms such as collembola and mites. A test on the springtail *Folsomia candida* (Collembola) conducted with technical chlorpyrifos following an OECD 232 design reports a 28-d NOEC mortality of 0.075 mg a.s./kg soil (Witte, 2014). When looking at sub-lethal effects, the NOEC is 0.024 mg a.s./kg soil for effects on reproduction of the animals. These effects observed at laboratory level were confirmed by field data.

3.4.4 Conclusion on ecotoxicolotical effects according to the criteria in Annex D

159. Chlorpyrifos exhibits acute and chronic effects at very low and environmentally relevant concentrations. Overall, laboratory studies clearly demonstrate that chlorpyrifos is highly toxic for

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 LD_{50} value of 13.3 mg a.s./kg bw for Bobwhite quail. For mammals, LD_{50} values from 64 to 71 mg a.s./kg bw in mouse 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.

4 Statement of the reasons for concern and need for global action

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

161. Although numerous BCF show moderate bioconcentration below 2000, some BCF values exceed the threshold, especially for vulnerable life stages. This in combination with high toxicity especially to sensitive life stages 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

162. The predicted half-lives of chlorpyrifos in air ranging from 1.4 to 14 hours are relatively low, but it has been found in various abiotic and biotic compartments of remote areas in the Arctic, demonstrating its ability to undergo long-range transboundary transport.

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

164. Chlorpyrifos exhibits acute and chronic effects at very low and environmentally relevant concentrations. Overall, laboratory studies clearly demonstrate that chlorpyrifos is highly toxic for 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 LD_{50} value of 13.3 mg a.s./kg bw for Bobwhite quail. For mammals, LD_{50} values from 64 to 71 mg a.s./kg bw in mouse 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. Based on the persistence, potential for bioaccumulation, toxicity to aquatic organisms and in 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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