Methoxychlor

Draft risk profile

Prepared by the intersessional working group of the
Persistent Organic Pollutants Review Committee

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Executive summary

1. The POPs Review Committee at its fifteenth meeting concluded that methoxychlor fulfilled the screening criteria in Annex D (decision POPRC-15/3) and to prepare a risk profile in accordance with Annex E to the Convention.

2. Methoxychlor is an organochlorine pesticide (OCP) which has been used as a replacement for DDT. It has been restricted/banned in several countries for over 15 years. In response to the call for information (Annex E information submission (2019)), no Parties have indicated current use of methoxychlor. However, a literature search made for the purpose of drafting the risk profile suggests that ongoing, or recent use of methoxychlor may still be occurring in certain regions. In 1975, three U.S. companies produced 2500 tonnes of methoxychlor. The production decreased to 1361 tonnes in 1982. After 1992, production of methoxychlor in the U.S. was significantly reduced until its ban in 2000. No information on the current level of production or use of methoxychlor is publicly available. Methoxychlor does not occur naturally in the environment. It is released to the environment mainly as a result of its application to crops and livestock as a pesticide. Smaller amounts of methoxychlor may be released to the environment during its production, formulation, storage, shipment and disposal. Based on the maximum 8,000 t/y of methoxychlor produced worldwide, atmospheric release during production may be estimated to be 800 kg/y at the maximum.

3. Methoxychlor is very persistent in the environment. Numerous studies have reported detections and/or quantifications of methoxychlor in sediment, water, seawater, groundwater, drinking water and in a variety of biota. Contamination with methoxychlor is especially apparent in the vicinity of intensive agricultural activities as a result of the historical and ongoing use of methoxychlor as pesticide. A half-life of 208 days was derived for methoxychlor from first-order rate constants in water-only systems presented in Walker *et al.* (1988), suggesting that methoxychlor may be persistent in water (degradation half-life > 2 months). Measured data in surface waterbodies from Europe and Canada provide that methoxychlor continued to be detected in European and Canadian surface waters years after it has been phased out, thus supporting the evidence that the substance is very persistent in water. Data from surface seawater in the Arctic Ocean and Chukchi Sea in 2016-2017 (concentrations <MDL[1]-0.38 ng/L (mean 0.15±0.11 ng/L)) support the evidence that the substance is also persistent in marine water. The substance is very persistent in sediment based on laboratory data (degradation half-life in sediment of 206±186.8 days for lake under aerobic conditions (half-life > 6 months)) and concentrations found in sediment samples from Portugal, Australia and Canada a long time after methoxychlor was banned in these countries.

4. Methoxychlor is a strongly hydrophobic substance with an experimental octanol-water partition coefficient (log K_{ow} value) of 5.08. Laboratory studies indicate that methoxychlor has a high bioaccumulation potential in fish species with Biocentration Factor (BCF) values > 5,000 (BCFs in the range 2,358-8,300). Supporting information in a bivalve (BCF of 12,000) and in snails (BCF in the range 5,000 to 8,570) also indicate a high bioaccumulation potential in aquatic organisms with BCF values > 5,000.

5. Based on measured data, methoxychlor is ubiquitous in the environment including in urban cities, rural areas and in regions that use methoxychlor as a pesticide in agricultural activities. It is also found in Arctic (in air, snow, ice core, lake waters, Arctic Ocean and sea, in plants and in biota samples (terrestrial, avian and marine)) and Antarctic (in marine biota samples) regions far away from any sources of release thus suggesting that atmospheric transport and transport via ocean currents are occurring.

6. Based on measured data, exposure of the general population takes place by consumption of contaminated food and drinking water, and by respiratory and oral uptake of dust and aerosols containing methoxychlor and by contaminated herbal drug materials. Small children may play close to the ground and are therefore more likely than adults to come in contact with dirt and dust. Children may also intentionally or unintentionally ingest soil that contains low levels of methoxychlor. Methoxychlor has been detected in human serum, adipose tissues, umbilical cord blood and human breast milk. Based on measured data, children can be exposed to methoxychlor *in utero* via the placenta and after birth via lactation and infant formula.

7. Due to its high persistence, methoxychlor is still found in drinking water, waterbodies and sediments, in regions where regulations and phase-outs have been implemented. Environmental trend data are not available, and the available measured data are insufficient to draw a clear conclusion on trends. However, over the last 15 years, it was observed that the concentrations of methoxychlor in Southern elephant seals in Antarctica have increased. No data are available on exposure trends of methoxychlor in humans.

8. Concerns exist regarding methoxychlor's toxicity to aquatic organisms in addition to health hazards including a potential endocrine disrupting property with toxic effects to reproduction. Toxicity testing indicates that methoxychlor has clear toxic effects on reproduction. In addition, studies in mice indicate methoxychlor exposure induced immune dysfunction. Furthermore, observations in rats indicate that methoxychlor has the potential to promote the epigenetic transgenerational inheritance of disease and associated sperm epimutations. Methoxychlor has

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[1] Method detection limit (MDL).

been demonstrated to be a neurotoxicant. Finally, the simultaneous exposure to multiple environmental chemicals increases the immunotoxic effects, the endocrine disrupting effects, the hepatic effects, the risk of neurotoxicity and the additive action of methoxychlor compared to individual exposure when mixed with certain other pesticides.

9. Methoxychlor is detected in environmental compartments such as surface water, seawater, groundwater, drinking water, sediment, atmosphere, plants as well as biota (including wildlife) and humans globally. Methoxychlor is persistent, bioaccumulative, toxic to aquatic organisms and to animals (including humans) and transported to locations far from its production and use. Therefore, it is concluded that methoxychlor is likely, as a result of its long-range environmental transport, to lead to adverse human health and/or environmental effects such that global action is warranted.

1. Introduction

10. In May 2019, the European Union and its Member States submitted a proposal to list methoxychlor in Annex A to the Stockholm Convention. The proposal (UNEP/POPS/POPRC.15/4) was submitted in accordance with Article 8 of the Convention and it was reviewed by the Persistent Organic Pollutants Review Committee (POPRC) at its fifteenth meeting held in October 2019.

1.1 Chemical identity of the proposed substance

11. Pure methoxychlor is a pale-yellow powder that has a slightly fruity or musty odour (ATSDR, 2002).

Table 1: Names and registry numbers

Common name	Methoxychlor*
IUPAC	1,1'-(2,2,2-trichloroethane-1,1-diyl)bis(4-methoxybenzene) 1-methoxy-2-[2,2,2-trichloro-1-(4-methoxyphenyl)ethyl]benzene 1,1'-(2,2,2-trichloroethane-1,1-diyl)bis(2-methoxybenzene)
CAS registry number (non exhaustive list)	72-43-5 30667-99-3 76733-77-2 255065-25-9 255065-26-0 59424-81-6 1348358-72-4
EINECs number	200-779-9
Synonyms and Trade name	1,1-Bis(para-methoxyphenyl)-2,2,2-trichloroethane 2,2-Bis(para-methoxyphenyl)-1,1,1-trichloroethane 2,2-Di-para-anisyl-1,1,1-trichloroethane para,para'-Dimethoxydiphenyltrichloroethane Dimethoxy-DDT Dimethoxy-DT Di(para-methoxyphenyl)trichloromethyl methane DMDT para,para'-DMDT ENT1716 Higalmetox Methoxychlore Maralate Marlate OMS 466 para,para'-Methoxychlor Metox Methoxy-DDT Prentox 1,1,1-Trichloro-2,2-bis(para-methoxyphenyl)ethane 1,1,1-Trichloro-2,2-di(4-methoxyphenyl)ethane 1,10-(2,2,2-Trichloroethylidene)bis(4-methoxy-benzene) Ethane, 1,1,1-trichloro-2-(o-methoxyphenyl)-2-(p-methoxyphenyl)- 2,4'-Methoxychlor o,p-Methoxychlor o,p'-Methoxychlor Benzene, 1,1'-(2,2,2-trichloroethylidene)bis[2-methoxy- Benzene, 1-methoxy-3-[2,2,2-trichloro-1-(4-methoxyphenyl)ethyl]- Benzene, 1,1'-(2,2,2-trichloroethylidene)bis[3-methoxy-
Abbreviations	MXC

*methoxychlor refers to any possible isomer of dimethoxydiphenyltrichloroethane or any combination thereof.

Table 2: Structure

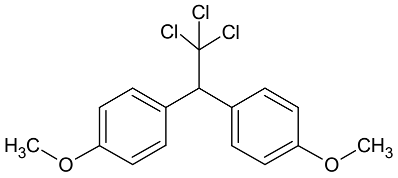
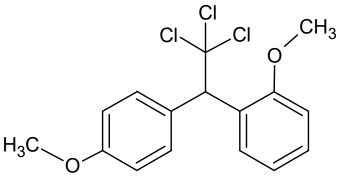
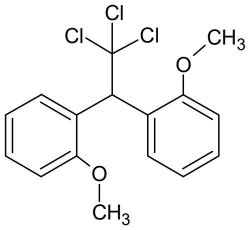
Formula	$C_{16}H_{15}Cl_3O_2$
Molecular mass	345.65 g/mol
Structural forms examples	  

Table 3: Overview of relevant physicochemical properties of methoxychlor

Property	Value	References
Physical state at 20°C and 101.3 kPa	Solid (pale-yellow powder)	ATSDR, 2002
Melting/freezing point (MP)	87°C *(experimental)* 129.34°C *(EPI Suite, MPBPVP v1.43 estimate, Mean or weighted MP) (within applicability domain (parametric))*	Lide, 2007 US EPA, 2012
Boiling point (BP)	346°C *(experimental)* 377.87°C *(EPI Suite, MPBPVP v1.43 estimate, Adapted Stein & Brown method) (within applicability domain (parametric))*	US EPA, 2012 US EPA, 2012
Vapour pressure	5.56×10^{-3} Pa at 25°C *(EPI Suite, MPBPVP v1.43 estimate, modified grain method; input experimental MP and BP, temp 25°C) (within applicability domain)*	US EPA, 2012
Henry's Law constant	2.03×10^{-7} atm.m^3/mol *(experimental)* (or 2.06×10^{-2} Pa m3/mol) 9.75×10^{-8} atm.m^3/mol (or 9.88×10^{-3} Pa m3/mol) (*EPI Suite HENRYWIN v3.20 estimate, Bond method)(within applicability domain)*	Altschuh *et al.*, 1999 US EPA, 2012
Water solubility	0.040 mg/L at 24°C (*experimental, 99% purity*) 0.10 mg/L at 25-45°C *(experimental, shake flask-UV)* 0.12 mg/L at 25°C *(experimental, in WSKOW training set)* 0.302 mg/L at 25°C *(EPI Suite, WSKOW v1.42 estimate) (within applicability domain)*	Verschueren, 1996 Richardson and Miller, 1960 Zepp *et al.*, 1976 US EPA, 2012
Organic carbon normalized adsorption coefficient (log K_{oc})	4.9 *(experimental, in KOCWIN training set)* 4.43 *(EPI Suite, KOCWIN v2.00 estimate, MCI method) (within applicability domain)*	Schüürmann *et al.*, 2006 US EPA, 2012
Octanol/water partition coefficient (log K_{ow})	5.08 *(experimental, in KOWWIN training set)* 5.67 *(EPI Suite, KOWWIN v1.68 estimate) (within applicability domain)*	Karickhoff *et al.*, 1979 US EPA, 2012
Octanol/air partition coefficient (log K_{oa})	10.48 (*experimental, GC retention time method*) 10.161 *(EPI Suite, KOAWIN v1.10 estimate; log Kow and Henry's Law constant experimental values as input) (within applicability domain (parametric))*	Odabasi and Cetin, 2012 US EPA, 2012

Property	Value	References
Air/water partition coefficient (log K_{aw})	-5.081 *(experimental)*	US EPA, 2012

1.2 Conclusion of the Review Committee regarding Annex D information

12. The Persistent Organic Pollutants (POPs) Review Committee evaluated the proposal by the European Union to list methoxychlor under the Stockholm Convention at its fifteenth meeting. The Committee concluded that methoxychlor met the screening criteria specified in Annex D (decision POPRC-15/3).

1.3 Data sources

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

(a) Proposal submitted by the European Union and its Member States that are Parties to the Convention (UNEP/POPS/POPRC.15/4), 2019;

(b) Information submitted by Parties and observers according to Annex E of the Convention (Annex E, 2019 and 2020): Austria, Canada, Costa Rica, Egypt, Hungary, Monaco, the Netherlands, New Zealand, State of Palestine, Thailand, Qatar, Republic of Belarus, Republic of Korea, Romania, IPEN and Alaska Community Action on Toxics (ACAT);

(c) Peer-reviewed scientific journals, as well as information from reports such as: Toxicological Profile for Methoxychlor (ATSDR, 2002); Methoxychlor in Drinking-water, Background document for development of WHO Guidelines for Drinking-water Quality (WHO, 2004); and the Protection of the Marine Environment of the North-East Atlantic (OSPAR) Background Document on Methoxychlor (OSPAR, 2004).

1.4 Status of the chemical under International Conventions

14. Methoxychlor is subject to a limited number of international actions and Conventions, as follows:

(a) The OSPAR Commission included methoxychlor in the List of Chemicals for Priority Action in 2000 (OSPAR, 2004);

(b) The UNECE Working Group on Environmental Monitoring and Assessment (WGEMA) added methoxychlor as a new parameter for measurement under diffuse soil contamination monitoring[2]. This was done in support of Shared Environmental Information System (SEIS);

(c) Methoxychlor has a water-quality objective of 0.04 ppb for the Great Lakes[3]. The water-quality objectives related to persistent organic substances have been established under the responsibility of the International Joint Commission according to the provisions of the 1978 Great Lakes Water Quality Agreement;

(d) According to the State of Palestine (Annex E, 2019), methoxychlor is subject to the terms and conditions of the Basel Convention in accordance with Annex I (category of wastes to be controlled) category Y3 (waste pharmaceuticals, drugs and medicines).

2. Summary information relevant to the risk profile

2.1 Sources

2.1.1 Production, trade, stockpiles

15. According to ATSDR (2002), methoxychlor was first synthesised in 1893 by the reaction of chloral hydrate with anisole in the presence of acetic acid and sulfuric acid. It is produced commercially by the condensation of anisole with chloral in the presence of an acidic condensing agent (IARC, 1979; Sittig, 1980 as cited in ATSDR, 2002). Commercial production of methoxychlor in the United States (U.S.) was first reported in 1946. In 1975, three U.S. companies produced methoxychlor (IARC, 1979 as cited in ATSDR, 2002). Very few data on the levels of production of methoxychlor are readily available. According to Götz *et al.* (2008), the peak production of methoxychlor in the U.S. was in the late 1970s to early 1980s. After that period, production of methoxychlor continuously decreased over time. U.S. production in 1975 was 2500 tonnes (IARC 1979, as referenced by ASTDR 2002), decreasing to 1361 tonnes in 1982 (EPA 1988c, as referenced by ASTDR 2002). After 1992, production of methoxychlor in the U.S. was significantly reduced until its ban in 2000 (US EPA, 2004).

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[2] This information is available on the UNECE website at the following link: https://www.unece.org/fileadmin/DAM/env/europe/monitoring/15thMeeting/Official/Questionnaire_2014_Eng_final_Serbia.pdf

[3] This information is available on the UNECE website at the following link: http://www.unece.org/fileadmin/DAM/env/water/publications/documents/Reco_E/Reco_waterquality_crit_obj_WS1.pdf

16. Methoxychlor is not approved as a protection plant product (PPP) in the European Union (Commission Regulation (EC) No 2076/2002) and the uses as PPP were withdrawn by 25 July 2003. Some EU Member States had imposed a ban of the use prior to 2003. Based on the WWF (2001) report for OSPAR (as cited in OSPAR, 2004), no existing producers or importers of methoxychlor have been reported in Europe since it has been phased out in 2002. Methoxychlor is not approved as an active substance in the EU under the Regulation 528/2012 concerning the market and use of biocidal products. Methoxychlor is not approved for use as a veterinary medicinal product in the EU according to Regulation 726/2004 on the procedures for the authorisation and supervision of medicinal products for human and veterinary use.

17. Monaco, Qatar, Republic of Korea and State of Palestine do not currently produce methoxychlor (Annex E (2019) submission information). Canada and Thailand do not currently produce, import or export methoxychlor (Annex E, 2019). Furthermore, methoxychlor has never been manufactured in Belarus (Annex E, 2019). No stockpiles of methoxychlor have been registered in Costa Rica (Annex E (2020) submission information). Egypt does not currently produce or import methoxychlor (it has been banned in Egypt since 1996 by ministerial decree no. 55/1996 (Annex E, 2019)).

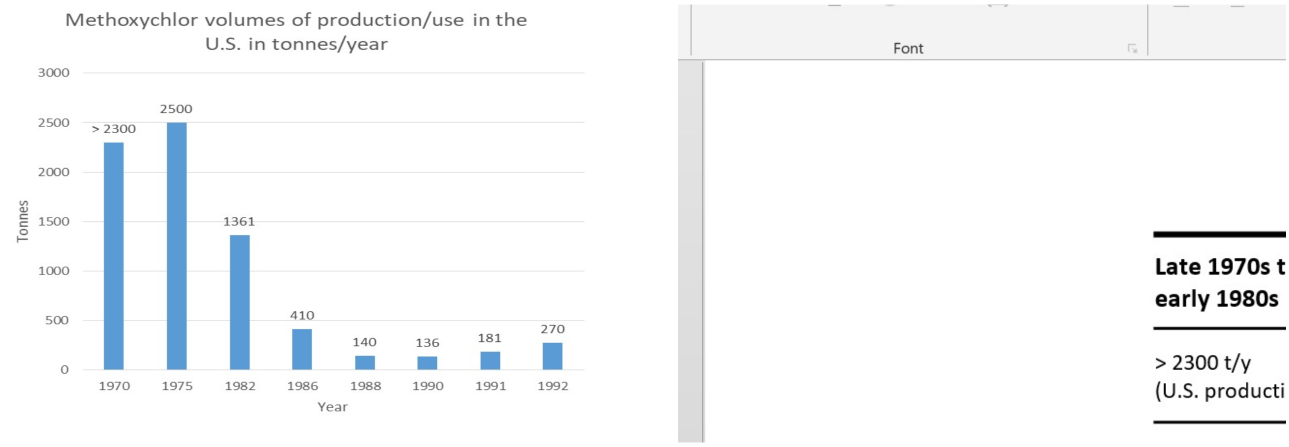

Figure 1: Methoxychlor production/use/import volumes in tonnes per year in the U.S. (Götz *et al.,* 2008; ATSDR, 2002; Minister of Indian Affairs and Northern Development Ottawa, 2003)

18. No further data on the current levels of production, import or use of methoxychlor are publicly available.

2.1.2 Uses

19. Methoxychlor is an organochlorine pesticide (OCP) and it has been used as a replacement for DDT which is a structural analogue. In veterinary practices, methoxychlor was used as an ectoparasiticide[4] (US EPA, 2000). Methoxychlor was also used against the elm bark-beetle vectors of Dutch elm disease (US EPA, 2000). Methoxychlor has been used as an insecticide combating a wide range of pests, including biting flies, houseflies and mosquito larvae, cockroaches, chiggers, and various arthropods commonly found on field crops, vegetables, fruits, stored grain, livestock, and domestic pets (EPA, 1988b and Verschueren, 1983 as cited in ATSDR, 2002). Methoxychlor can be applied to large areas such as beaches, estuaries, lakes, and marshes for control of fly and mosquito larvae by aerial application (EPA, 1988b as cited in ATSDR, 2002). Other uses include the spray treatment of barns, grain bins, mushroom houses, and other agricultural premises and the spraying or fogging of garbage containers, sewer manholes, and sewage disposal areas (EPA, 1988b as cited in ATSDR, 2002). In the U.S., approximately 28% of methoxychlor was used for home and garden purposes, 15% for industrial and commercial purposes, and 57% for agricultural purposes (Kincaid Enterprises, 1992 as cited in ATSDR, 2002). Pesticide workers usually dissolve methoxychlor in a petroleum-based liquid and apply it as a spray, or they mix it with other chemicals and apply it as a dust (ATSDR, 2002). Methoxychlor has been formulated as wettable powders, dusts, emulsifiable concentrates, ready-to-use products (liquids), and pressurised liquids (US EPA, 2004).

20. According to Götz *et al.* (2008), Methoxychlor was used extensively from 1974–1985 as a replacement product for DDT. Between 1986 and 1992, the usage of methoxychlor in the U.S. continuously decreased. After 1992, the use of methoxychlor was heavily reduced. For modelling purposes, Götz *et al.* (2008) estimated the worldwide use of methoxychlor to be three times higher than the use in the U.S. (i.e. worldwide maximum of 8,000 t/y). Based on extrapolation factors used for other pesticides, such as trifluralin or DDT. Information on the use of methoxychlor in the U.S. from early 1970s to 1999 is reported in Figure 1. Pesticide uses of methoxychlor in the U.S. were suspended in 2000, and all products were expected to have been voluntarily discontinued by 2004 (US EPA, 2004).

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[4] A medicine used to kill parasites that live on the exterior of their host.

21. It is reported that the use of methoxychlor as a pesticide ceased in most EU countries between the 1970s and 2000 (OSPAR, 2004). In Austria, the volume of methoxychlor used in agriculture was 1 kg/y in 1991-1992 with no use since 1993 (Annex E, 2019). Methoxychlor has been phased out in the European Union since 25 July 2003, with some Member States having put bans in place prior to this (e.g. the substance is no longer used in Hungary since 1972, in the Netherlands since 1990 and in Austria since 1993 (Annex E, 2019)). The European Agency for the Evaluation of Medicinal Products (EMEA) reported that methoxychlor was not used in veterinary medicines in EU Member States (OSPAR, 2004). According to Langford *et al.* (2012), methoxychlor is no longer registered for use in Norway. The registration of methoxychlor in Canada was withdrawn in 2002, with a phase out period of three years (Annex E, 2019). Consequently, the use of methoxychlor pesticides in Canada ended in December 2005[5]. In Australia, the only methoxychlor product registration was discontinued in mid-1987 (information available from APVMA[6]). Annex E (2019) information from New Zealand indicated that methoxychlor is not approved in New Zealand under the Hazardous Substances and New Organisms Act 1996 (HSNO Act). In Belarus, the use of methoxychlor as an insecticide was banned in 1999 (Annex E, 2019). Egypt indicated that the use of methoxychlor as an insecticide has been banned in Egypt since 1996 by ministerial decree no. 55/1996 (Annex E, 2019). Monaco, Qatar, Republic of Korea, State of Palestine and Thailand do not currently use methoxychlor (Annex E, 2019). Methoxychlor is no longer used in Costa Rica since the permits for the use of this substance were cancelled in 2013 (Annex E, 2020). According to the PAN International Consolidated list of Banned Pesticides[7], methoxychlor is banned in the following countries: Guinea, Indonesia, Mauritania, Oman and Saudi Arabia (Annex E, 2019). According to Cindoruk *et al.* (2020), methoxychlor has been banned in Turkey since 2012. According to Kao *et al.* (2019), OCPs have been banned in Taiwan Province of China, since 1975.

22. Based on a literature search made for the purpose of drafting this risk profile, the following countries (non-exhaustive list) may still use or illegally use methoxychlor: Africa (Gambia, Ghana, Kenya, Libya, Nigeria, Senegal and South Africa), Asia (China, Egypt, India, Lebanon, Nepal, Turkey and Singapore), Europe (use in Italy according to Thiombane *et al*., 2018) and South America (Argentina, Brazil, Mexico, and Nicaragua). According to Adekunle *et al.* (2018), in Nigeria methoxychlor is present in disinfectants and in washing products such as liquid soap, scouring powder, shampoo, conditioner, handwash, at levels from non-detectable to 2.36 ppm.

2.1.3 Releases to the environment

23. Methoxychlor does not occur naturally in the environment (ATSDR, 2002). It is released to the environment mainly as a result of its application to crops and livestock as a pesticide. Since the use of methoxychlor is highly seasonal, the amount that is released to the environment can be expected to be greater during periods of insect control (spring and summer). Smaller amounts of methoxychlor may be released to the environment during its production, formulation, storage, shipment and disposal (ATSDR, 2002). According to the Toxics Release Inventory (TRI), methoxychlor processing facilities listed for 1998 (TRI99 2001) report that the major portion of methoxychlor released to the environment is released to the land (ATSDR, 2002).

24. Methoxychlor is released to soils primarily through its use as an insecticide for agricultural crops, home orchards, and ornamentals. Some methoxychlor may be released to soils through leaks at storage and waste sites. According to TRI (TRI99 2001), three processing facilities in the U.S. reported that no methoxychlor was released to soil in 1999. The TRI data should be used with caution since only certain types of facilities are required to report; therefore, the information may not be exhaustive. Methoxychlor has been identified in 46 soil and 11 sediment samples collected from 58 of 1613 National Priorities List (NPL) hazardous waste sites (HazDat, 2002 as cited in ATSDR, 2002).

25. Release of methoxychlor to the atmosphere occurs mainly as a result of its use as a pesticide. Releases to the atmosphere during production, formulation, and disposal of methoxychlor have been estimated to be 0.1 kg/metric ton produced (HSDB, 2000 as cited in ATSDR, 2002). Based on the 193 tonnes of methoxychlor produced in the U.S. in 1991 (Kincaid Enterprises, 1992 as cited in ATSDR, 2002), atmospheric release during production may be estimated to be 19 kg/y. According to TRI (TRI99 2001), three processing facilities in the U.S. reported the release of 13 kg of methoxychlor to the air in 1999 (ATSDR, 2002). Götz *et al.* (2008) estimated the worldwide use of methoxychlor to be three times higher than the use in the U.S. (i.e. worldwide maximum of 8,000 t/y). The maximum production of 8,000 t/y is extrapolated from information on production in the U.S. during the late 1970s- early 1980s and recent global production figures are not available. Based on the maximum 8,000 t/y of methoxychlor produced worldwide, atmospheric release during production may be estimated to be 800 kg/y at the maximum.

26. Methoxychlor can be released directly to surface water on farms when used to control larvae of insects (Stoltz and Pollock, 1982 as cited in ATSDR, 2002). Methoxychlor was approved for use on cranberries (EPA, 1988b as

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[5] This information is available at: https://www.canada.ca/en/health-canada/services/chemical-substances/fact-sheets/chemicals-glance/pesticidal-uses-substances-domestic-substances-list.html.

[6] This information is taken from the Australian National Environment Protection (Assessment of Site Contamination) Measure 1999, available at the following link.

[7] http://pan-international.org/pan-international-consolidated-list-of-banned-pesticides/

cited in ATSDR, 2002), which are grown in bogs, and therefore methoxychlor could be released directly to surface water where cranberries are grown. Methoxychlor may be released to water from runoff from soil, industrial effluents or from leaks at storage and waste sites (ATSDR, 2002). According to Howard (1991), field studies have shown that methoxychlor does not leach significantly in soil. However, groundwater monitoring data suggest that some leaching of methoxychlor may take place (see section 2.3.1 environmental monitoring data). According to TRI (TRI99 2001), three processing facilities in the U.S. reported that no methoxychlor was released to water in 1999 (ATSDR, 2002). Methoxychlor has been detected at 58 of 1613 National Priorities List (NPL) hazardous waste sites. At those 58 sites methoxychlor was identified in 19 groundwater and seven surface water samples (HazDat, 2002 as cited in ATSDR, 2002). Methoxychlor loading into Lake Ontario from Niagara River was estimated to be 3 kg/year on suspended solids and < 20 kg/year in raw water and loading to Lake Superior from precipitation was estimated to be 120 kg/year (Howard, 1991).

27. Annex E (2019) information from Canada indicated that there are currently no releases of methoxychlor in Canada and information on historical releases is not available. No other information was provided by other Parties on the releases of methoxychlor to the environment while there is some evidence from the literature that the substance may be released to the environment in certain regions (see section “2.1.2 Uses” for further details).

2.2 Environmental fate

2.2.1 Environmental distribution

Adsorption/desorption

28. Methoxychlor is sparingly soluble in water with a water solubility which is in the range of 0.04-0.302 mg/L (see references in Table 3). Based on its log K_{ow} value of 5.08 (experimental Karickhoff *et al.,*1979) and 5.67 (predicted with KOWWIN v1.68 estimate; US EPA, 2012), the substance is expected to be hydrophobic with low water solubility and a high adsorption coefficient. Measured average K_{oc} values in pond and river sediments are as follows: 23,000 in sand, 82,000 in coarse silt, 88,000 in medium silt, 93,000 in fine silt and 83,000 in clay (Karickhoff *et al.,*1979). These K_{oc} values indicate that methoxychlor is expected to adsorb strongly to suspended solids and sediment. Muir and Yarechewski (1984) observed that methoxychlor partitioned rapidly (< 3 days) into sediment following addition to sediment-water systems. In aquatic environments, it is suggested, based on the physicochemical properties discussed here, that methoxychlor will most likely concentrate in the sediment and biota.

29. Weber *et al.* (2004) estimated a mean sorption coefficient (K_d) of 2009 in soil for methoxychlor (number of values used for the calculation: 11) which indicates that methoxychlor is immobile. Modelling data are in agreement with experimental data. EPI Suite KOCWIN v2.00 model (KOCWIN, MCI method; US EPA, 2012) predicts a K_{oc} value of 26,890 L/kg for methoxychlor (equivalent to a log K_{oc} value of 4.43). An experimental log K_{oc} value of 4.9 (Schüürmann *et al.*, 2006) is also reported in EPI Suite (US EPA, 2012). In conclusion, methoxychlor is expected to be immobile in soil. However, soil particles that contain methoxychlor can be blown by the wind or be carried by rainwater or melted snow into rivers or lakes (ATSDR, 2002).

Volatilisation

30. Methoxychlor has an experimental Henry's Law constant of 2.03×10^{-7} atm.m^3/mol (or 2.06×10^{-2} Pa.m^3/mol; wetted wall column-GC) at 25°C (Altschuh *et al.*, 1999). The estimated Henry's Law constant for methoxychlor is 9.75×10^{-8} atm.m^3/mol (or 9.88×10^{-3} Pa.m^3/mol) at 25°C using EPI Suite HENRYWIN v. 3.20 model (bond method; US EPA, 2012). Both experimental and predicted Henry’s Law constant values indicate that methoxychlor can be expected to be non-volatile from water. Furthermore, Bomberger *et al.* (1983) modelled the transport and fate pathways for methoxychlor at the air-terrestrial interface, and the model simulations suggest that the compound is strongly adsorbed to soil and does not leach, and that volatilisation is slow. Based upon its relatively low vapour pressure value (5.56×10^{-3} Pa at 25°C (EPI Suite, MPBPVP v1.43 estimate, modified grain method; US EPA, 2012), methoxychlor is not expected to be volatile.

Distribution modelling

31. The Mackay Level III Fugacity Model in EPI Suite (US EPA, 2012) was used by the drafter of this dossier to model the distribution of methoxychlor. The physico-chemical properties used in the model were the experimental values (if not stated otherwise) reported in Table 3: melting point 87°C; boiling point 346 °C, vapour pressure 5.56×10-3 Pa (modelled value); Henry Law Constant 2.06×10-2 Pa; water solubility 0.1 mg/l; log K_{ow} 5.08; K_{oc} value 79433 (log 4.9). The degradation half-lives used in the model environment are: air 4.8 hours (or 0.2 days derived by AopWin); water 4992 hours (or 208 days (Walker *et al.*, 1988)); soil 2880 hours (or 120 days (Chen, 2014)); sediment 4944 hours (or 206 days (Muir and Yarechewski, 1984)). If methoxychlor is assumed to be released at equal rates to air, water and soil, the model predicts the following distribution: air 0.086 %, water 9.06 %, soil 64.2% and sediment 26.6%, indicating that the substance will be mainly distributed to the soil and the sediment. If it is released only to soil, the calculated distribution is very different: air 1.29×10^{-5} %, water 0.0143 %, soil 99.9% and sediment 0.0422%, predicting that the substance will stay in the soil compartment. It should be noted that there is uncertainty in the half-lives in water, in soil and in air (because the half-life in air was modelled using AopWin).

2.2.2 Persistence

2.2.2.1 Screening information based on modelling data

32. The aerobic biodegradation potential of the substance can be assessed using BIOWIN v4.10 (U.S. EPA, 2012). The predictions for the non-linear model (BIOWIN 2), ultimate biodegradation (BIOWIN 3) and the MITI non-linear model (BIOWIN 6) can be used as a screening assessment of persistence in accordance with the REACH Guidance Chapter R.11 (ECHA, 2017). The following results indicate that a substance may be persistent:

(a) BIOWIN 2: Does not biodegrade fast (<0.5) and BIOWIN 3: ≥ months (< 2.25 (to 2.75)) or

(b) BIOWIN 3: ≥ months (< 2.25 (to 2.75)) and BIOWIN 6: Not readily biodegradable (<0.5).

The predictions for the structure of methoxychor are BIOWIN 2: 0.0162, BIOWIN 3: 1.5126 (recalcitrant) and BIOWIN 6: 0.0063. These values are all significantly below the cut-off values, indicating that methoxychlor is not expected to be aerobically biodegradable and is hence potentially persistent.

(1) Abiotic degradation

Hydrolysis

33. The effect of hydrolysis on the persistence of methoxychlor under environmentally relevant conditions is expected to be negligible. Wolfe *et al.* (1977) investigated the hydrolytic degradation pathways in water at pHs common to the aquatic environment using a standard solution of 1.0×10^{-8} M methoxychlor in distilled water, titrated to pH 5.0 with hydrochloric acid. Five (5) mL aliquots were placed in ampules, sealed and allowed to equilibrate at 85°C. Rate constants were obtained employing the integrated first-order rate expression using a least-squares analysis of the data. Extrapolation of the methoxychlor data obtained at elevated temperatures to 27°C at pH 3–7 gives a first order rate constant of 2.2×10^{-8} s^{-1}, which corresponds to a half-life of 367 days. It was indicated that the half-life of methoxychlor at higher pH (pH 9) was much longer (2100 days; calculated from first-order rate constants assuming buffered conditions). In addition, the extrapolated first-order rate constants at three other temperatures were reported in Wolfe *et al.* (1977), as follows: $3.2 \pm 0.4 \times 10^{-7}$ s^{-1}at 45°C (pH 7); $5.3 \pm 0.8 \times 10^{-6}$ s^{-1}at 65°C (pH 6.9) and $1.5 \pm 0.2 \times 10^{-6}$ s^{-1}at 75°C (pH 7).

34. According to Wolfe *et al.* (1977), the major products of methoxychlor hydrolysis at pH 7 are anisoin, anisil and DMDE [2,2-bis(*p*-methoxyphenyl)-1,1-dichloroethylene]. Anisoin and anisil are anticipated to undergo degradation much faster than methoxychor and not build up in the environment. The minor product, DMDE, is more stable to hydrolysis than methoxychlor and might be anticipated to build up to a small extent. Studies with natural waters were carried out with methoxychlor. At 85°C the reaction obeyed first-order kinetics, and there was no detectable change in the rate of hydrolysis in Oconee River (Athens, Ga.) water (pH 6.6) or Alabama River (Birmingham, Ala.) water (pH 7.2) (Wolfe *et al.,*1977). It is unclear if a solvent control has been used and if the test substance has been incubated under dark conditions. As well, the method of extrapolation to 27°C is unclear. The study is reliable with restrictions as it does not follow good laboratory practice. According to Katagi (2002) as cited in HSDB (2009), the hydrolysis half-lives of methoxychlor in distilled water varies considerably with pH values, with half-life values at 27°C of 1 year (pH 7) and 5.5 years (pH 9). Results of the Katagi (2002) study (as cited in HSDB (2009)) are in agreement with the Wolfe *et al*. (1977) study.

Photolysis

35. Remucal (2014) suggested that methoxychlor undergoes negligible direct photolysis because it does not absorb light in the solar spectrum. Experimental evidence suggests that methoxychlor is susceptible to dissolved organic matter-sensitised indirect photolysis. The addition of dissolved organic matter from natural waters has been reported to accelerate the photodegradation of methoxychlor in water when irradiated at wavelengths >290 nm (Remucal, 2014).

36. Zepp *et al.* (1976) developed a procedure for computing the direct photolysis of pesticides in the aquatic environment, in order to investigate the light-induced degradation of methoxychlor in distilled and natural water samples. Assuming first-order kinetics, the direct photolysis half-life of methoxychlor in natural waters was much more rapid (2 to 5 hours; solution in sealed quartz cells exposed to midday May sunlight, latitude 34°N) than that in distilled water (4.5 months; assuming 12-h days exposure and latitude 40°N), suggesting that photochemical processes other than direct photolysis can cause more rapid degradation of methoxychlor in some natural aquatic environments. The major product of methoxychlor photolysis in pure water was DMDE (Zepp *et al.,* 1976). This study indicates degradation in specific conditions under influence of sunlight. However, since fast attenuation of light intensity in the water column takes place in the environment, photodegradation in real water bodies cannot generally be considered as relevant degradation pathway.

37. It can be concluded that the effect of hydrolysis and photolysis on the persistence of methoxychlor in the environment is expected to be negligible.

(2) Biotic degradation

38. Degradation rates of methoxychlor in water, sediment and soil are shown to be impacted by the relative presence or absence of oxygen. The aerobic degradation rate is slow, possibly negligible, but the anaerobic degradation rate is faster (OSPAR, 2004). As is discussed in subsequent paragraphs, this is likely to be explained by the biotic and abiotic processes, and microbial species prevailing under anaerobic conditions.

39. Walker *et al.* (1988) investigated the first-order biotic and abiotic degradation rate constants of methoxychlor in estuarine water and sediment/water slurry systems. Test systems used environmentally realistic concentrations of methoxychlor (nominal concentration was around 200 µg/L) in sterile and non-sterile samples of water and water-sediment systems taken directly from the field. Salinity ranged from 15 to 30 g/L. Sediment samples were collected from the top 2 cm of the sediment bed (reflecting aerobic conditions). Flasks containing water-only and water-sediment slurries were placed in a shaker incubator and incubated in the dark at 25°C. Duplicate samples were removed periodically from each flasks and analysed for residual test chemical. Control sediment and water systems (no test chemical or formaldehyde added) were used. Recoveries were > 85%. The first-order rate constant (k_1) for methoxychlor was determined. Identification of degradation products was not studied, only the parent substance was followed in the test. The methoxychlor half-lives derived from first-order rate constants in water-only systems were 208 and 8,830 days for non-sterile and sterile conditions, respectively. The derived methoxychlor half-lives in water-sediment systems were 12.2 and 45.2 days for non-sterile and sterile conditions, respectively (under aerobic conditions). The results of this study indicate significantly ($p \leq 0.01$) more degradation in the presence of non-sterile sediment than in the presence of sterile sediment (indicating biotic degradation), and that methoxychlor biodegraded significantly faster in flasks containing non-sterile water-sediment systems than in non-sterile water alone.

40. Disappearance of methoxychlor in the presence of sediment, could be attributed to uncertainty in the extraction methods used to remove methoxychlor (and other non-extracted residues) from sediment, as the presence of non-extracted methoxychlor is not taken into account in the calculation of the half-lives. Half-lives obtained in the study do not represent the most conservative case for methoxychlor. The nominal water-only concentration exceeds the recommended test concentration in the Organisation for Economic Co-operation and Development (OECD) TG 309 (100 µg/L), and only one concentration was tested. A reference substance and a solvent control were not used. As a consequence, it is not possible to assess the microbial activity and potential adverse effects of the solvent to the microorganisms in the test, although it is noted that solvent was removed by flushing the glass bottles used to prepare the test systems with air or nitrogen prior to adding site water. With respect to the water-sediment systems, there were several study deviations under OECD TG 308. Only one sediment was tested, the water-sediment system was mixed, a period of acclimation did not occur, and the experimental set up used the same vessel for each sampling, rather than the sacrifice of a whole test vessel at each sampling time. Due to these deviations from the test guidelines (OECD TG 309 and OECD TG 308 unavailable at the time of the test), the study is considered to be not reliable.

41. Muir and Yarechewski (1984) studied C^{14}-methoxychlor (^{14}C-ring-labelled) degradation in water-sediment systems (water-sediment ratio: 20:1; weight of pond or lake sediments: 10 g dw) under aerobic and anaerobic laboratory conditions using respirometer flasks. Lake (79% clay, 21% silt and 6.0% organic matter) and pond (75% clay, 24% silt, 6.3% organic matter; pH=7.6) sediments were incubated in a controlled environment (22.5°C) using a photoperiod of 16-hour light and 8-hour darkness. Nitrogen aerated flasks were darkened by covering them with aluminium foil. Respirometer flasks were connected to a manifold which delivered air (CO_2 free grade) or nitrogen presaturated with water and included traps for collecting volatiles that were routinely changed up until and including Day 224. Flasks were removed for analysis at intervals over a 448-day period. It was observed that methoxychlor added to sediment-water mixtures (methoxychlor concentration of 0.1 µg/mL (or 100 µg/L) in each flask, from diluting 0.1 mL prepared in acetone) was slowly biodegraded under aerobic conditions (115.9±74.1 days and 206±186.8 days half-lives (assuming first-order kinetics) for pond and lake sediment, respectively; Eh 220 to 464 mv) and degraded more rapidly anaerobically with half-lives of <28 days for both lake and pond sediment (Eh less than -50 mv). Large confidence limits on the half-lives likely reflect the small number of data points (generally 6 points).

42. These results suggest that the degradation of methoxychlor under aerobic conditions, e.g. on suspended sediment or at the sediment-water interface, is relatively slow. Under anaerobic conditions, rapid breakdown of methoxychlor can be expected with dechlorinated methoxychlor (DMDD) and mono- and di-hydroxy degradation products being the major residues present in sediments. However, several deviations from the OECD TG 308 have been noted.

43. The main deviations from OECD TG 308 are as follows: the water-sediment ratio exceeded the recommended range of between 3:1 and 4:1, the water was not collected from the same site as the sediment (dechlorinated water was used), the test duration exceeded 100 days and it is unclear if microbial activity was in decline, the aerobic test was not performed under total dark conditions and it is unclear if a solvent control was included in the test. It is also unclear if the pH of the water increased due to delivery of CO_2 free air to the respirometer flasks. Due to these deviations from the test guideline OECD TG 308 (which was unavailable at the time of the test), the study is considered reliable with restrictions. The presence of non-extracted methoxychlor from sediment is not taken into account in the calculation of the half-lives. The calculated half-lives do not represent the most conservative case for methoxychlor.

44. In addition, ^{14}C ring labelled p,p'-DDT was included in the study for comparison. The half-life for parent DDT was 130.8±18.7 days (lake sediment) and 123.3±71.9 days (pond sediment) (22.5°C, Eh 424-464mV), but half-lives for DDT are significantly longer when the dechlorinated degradation products are included in the calculation. The major difference between behaviour of DDT and methoxychlor in this study was the rate of degradation of the respective dechlorinated degradation products.

45. It is important to note that the test temperatures of the two studies (Walker *et al.* (1988) and Muir and Yarechewski (1984)) were 25°C and 22.5°C, respectively. Test temperature has a significant influence on the degradation half-lives (generally the lower the temperature, the slower the degradation).

46. It is indicated that methoxychlor is persistent in soil, with a half-life reported by Chen (2014) of 120 days (the temperature is unknown and further detailed information is not available in Chen (2014)). According to WHO (2004), methoxychlor residues may persist in top soil for up to 14 months.

2.2.2.2 Monitoring data

47. After its ban in 2003 in the EU and based on the Water Framework Directive (WFD) factsheet[8], methoxychlor was quantified in 1.3% of the 4200 samples of inland water between 2006-2014 at 172 sites in five countries. Thirty (30) of the 4200 samples of inland water representing four countries showed concentrations of methoxychlor above the Predicted No Effect Concentration (PNEC) value of 0.0005 µg/L (derived by INERIS). The European Working Group on Standards (WG-S) concluded that data quality of these monitoring data for methoxychlor was not sufficient to propose it as candidate for quality standard derivation (due to the large number of unquantified results and limited Member States for which data was available). In addition, Annex E (2019) information from Canada indicated that methoxychlor was detected in 16 of the 1582 samples taken from surface waterbodies between 2000-2015. Methoxychlor was measured in one or more surface water samples from Canada in 2001, 2002, 2007, 2008, 2009, and 2011, with concentrations in the range 0.088-7.9 ng/L. The highest measured concentration following phase out of methoxychlor in Canada (in 2005) was 5.25 ng/L (in 2009). These data indicate that methoxychlor continued to be detected in European and Canadian surface waterbodies for years after it was phased out (2003 in the EU and December 2005 in Canada), thus providing evidence that the substance is persistent in the water compartment.

48. Three chemicals, methoxychlor, endosulfan and pentachloroanisole were found in an Arctic lake at water concentrations in the range of 0.017-0.023 ng/L (Muir*et al.*, 1995b as cited in AMAP, 1998). Cai *et al.*, (2010) found methoxychlor in surface seawater samples collected from the Chukchi Sea and western Arctic Ocean from 11 July to 24 September 2008. Concentrations of methoxychlor (0.0033-0.0353 ng/L; mean value: 0.0344 ng/L) in the Chukchi sea were comparable to those found in water samples from the Arctic Ocean collected during the same trip: methoxychlor (0.0033-0.0523 ng/L; mean value: 0.0375 ng/L). Similar concentrations were found in seawater for α-endosulfan, β-endosulfan and Endrin (before endosulfan was added to Annex A of the Stockholm Convention in 2011). However, it is worth noting that the recovery rate of spiking experiments for methoxychlor in the study is low (44.39%), suggesting that the monitoring data reported are uncertain. A more recent study was performed by Gao *et al.* (2019). The authors monitored methoxychlor in surface seawater (from 33°N to 83 °N) in a region covering the North Pacific to the Arctic Oceans. Samples were collected from 12 July to 23 September 2016 and from 27 July to 7 October 2017. Methoxychlor concentration in the North Pacific Ocean was <MDL-0.54 ng/L (mean 0.13±0.13 ng/L) and <MDL-0.38 ng/L (mean 0.15±0.11 ng/L) in the Chukchi Sea. These concentrations are higher than the concentrations reported in the study of Cai *et al.* (2010). The results of this study should be considered with caution since methoxychlor was found in half of the field blank controls (concentration in blanks: 0.01 ng/L). It is not reported if the data have been corrected for this background contamination. The recoveries of the internal standard tetrachloro-*m*-xylene were 79.8-108.9%. Presence of methoxychlor in Arctic lake waters and in Arctic Oceans indicates that methoxychlor is persistent in marine and fresh water compartments.

49. Pinto *et al.* (2016) found methoxychlor in sediment core from the upper part of Óbidos lagoon (Portugal). Sediment samples were collected in November 2013. Methoxychlor was found at concentrations ranging from 21.8 - 89 ng/g dw in the core sediment between 16 and 40 cm depth. As the sedimentation rate is not available, it was not possible to date the concentrations found after 14 cm depth. However, the presence of methoxychlor in sediment core below 14 cm provides evidence of high inputs in the past (before its phased out in the EU in 2003) and that the substance is persistent in sediment. Sediment is expected to be anaerobic at this depth (16-40 cm). The fast biodegradation under anaerobic conditions reported in the laboratory study of Muir and Yarechewski (1984) (see section "Biotic degradation") is not supported by the observations of Pinto *et al.* (2016). Considering the results of Pinto *et al.* (2016), the substance is persistent in some anaerobic sediments.

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[8] The WFD factsheet for methoxychlor is avavailable at the following link: https://circabc.europa.eu/webdav/CircaBC/env/wfd/Library/working_groups/priority_substances/2a%20-%20Sub-Group%20on%20Review%20of%20Priority%20Substances%202014%20start/Monitoring%20based%20exercise/Factsheets/Methoxychlor_draft%20Factsheet_annex%20monitoring%20report.pdf.

50. Duodu *et al.* (2017) found methoxychlor in sediment samples collected between 2014-2015 from the Brisbane River estuary of Southeast Queensland in Australia. The sediment samples were collected in the months of June (winter), September (spring), December (summer) 2014, and May (autumn) 2015; thus, spanning both dry and wet seasons. A total of 22 sampling points were selected along a 75 km stretch of the river from the mouth. Grab sediment (0-3 cm depth) samples were collected with laboratory recoveries > 85% for methoxychlor. The average concentrations of methoxychlor were consistent among the four physio-geographical areas (namely rural, residential, commercial and industrial; average: 4.3±0.2 ng/g; range: 4.1-4.8 ng/g; detection frequency: 100%). These data suggest that the input of methoxychlor was historical in nature. Indeed, the Brisbane River estuary is micro-tidal, with limited inflow of freshwater. Due to the relatively low freshwater inflow, strong tidal mixing acts as a dominant mixing mechanism in the estuary, thereby causing resuspension of fine sediment. This study provides evidence that methoxychlor is persistent in sediment, which in this study is expected to have been aerobic (0-3 cm depth from a river). In Australia, the use of OCPs were banned or restricted from the early 1980s with a complete phase out in October 2010.

51. Annex E (2019) information from Canada indicated that methoxychlor was detected in 48 of the 301 samples of Great Lakes sediments (0-15 cm depth but most of the samples were taken from surface sediments) between May 2013 and September 2017. The mean concentration of these 48 detections was 3.7 ng/g (with concentrations ranging from 0.075 ng/g to 36 ng/g). These data indicate that methoxychlor continued to be detected in Canadian sediments years after its ban in December 2005, thus supporting evidence of its persistence in the sediment compartment.

2.2.2.3 Summary on persistence

52. Modelling data (BIOWIN 2, 3 and 6) indicate that methoxychlor is not expected to be aerobically biodegradable, hence potentially persistent. It is noted that the available hydrolysis studies show zero or negligible hydrolysis rate. Although photolysis rates of methoxychlor seem moderate, photolysis is not expected to contribute to the degradation significantly as photolysis only takes place in the top few tens of centimeters of the water column.

53. The degradation half-life of methoxychlor in water (208 days (half-life > 2 months; Walker *et al.* (1988)) suggests that the substance is very persistent in water. This information is used as supporting information in the persistence assessment. Monitoring data in surface waterbodies from Europe and Canada indicate that methoxychlor continued to be detected in European and Canadian surface waters years after it has been phased out, thus supporting the evidence that the substance is very persistent in water. Monitoring data from Arctic lake waters and surface seawater in the Arctic Ocean and Chukchi Sea in 2016-2017 (concentrations <MDL-0.38 ng/L (mean 0.15±0.11 ng/L); Gao *et al.,* 2019) support the evidence that the substance is persistent in the surface water and marine water compartments. The degradation half-life of methoxychlor in the sediment compartment (206±186.8 days for lake under aerobic conditions (half-life > 6 months); Muir and Yarechewski (1984)) provides evidence that the substance is very persistent in sediment. The persistence of methoxychlor in the sediment compartment is confirmed by the concentrations found in sediment samples from Portugal, Australia and Canada several years after methoxychlor was banned in these countries (Pinto *et al.,* 2016; Duodu *et al.*, 2017 and Annex E, 2019 information from Canada).

2.2.3 Bioaccumulation

2.2.3.1 Screening information based on physicochemical properties

54. Methoxychlor is a strongly hydrophobic substance with an experimental log K_{ow} value of 5.08 (Karickhoff *et al.*, 1979). The substance has an estimated log K_{ow} value of 5.67 (KOWWIN v1.68 (US EPA, 2012) which is consistent with the experimental value. Both experimental and estimated log K_{ow} values indicate a bioconcentration potential of methoxychlor in aquatic organisms (log K_{ow} >5).

55. The bioaccumulation model (BCFBAF v3.01; US EPA, 2012) estimated: a bioconcentration factor (BCF) value of 1044 L/kg wet-wt (based on the regression-based method and using as input data an experimental log K_{ow} value of 5.08), a BCF value of 4134 L/kg and a bioaccumulation factor (BAF) of 9001 L/kg (based on the Arnot-Gobas method (upper trophic) and using as input data an experimental log K_{ow} value of 5.08). The prediction can be considered reliable as the substance is within the applicability domain of the model (both structural and parametric). It is further noted that the somewhat structurally similar compound DDT (CAS 50-29-3) is in the training set of the model and methoxychlor is in the validation set of the model. The BAF value predicted suggest a high bioaccumulation potential of methoxychlor in aquatic organisms (BAF > 5000).

2.2.3.2 Bioconcentration and bioaccumulation studies in aquatic organisms

56. It was observed that for methoxychlor the BCF values vary largely between different aquatic species as a result of species differences in the capacity to metabolise and excrete methoxychlor. Methoxychlor's BCF values for fish are up to 8,300 (Veith *et al.,* 1979).

57. Veith *et al.* (1979) developed a method for estimating BCFs using a laboratory experiment exposing adult fathead minnows (*Pimephales promelas*) (~6 months old) to a non-lethal dose of methoxychlor (included in an acetone solution) in a continuous-flow system at 25±0.5°C. The test water came from Lake Superior. The arithmetic mean of the pH was 7.49±0.15. Dissolved oxygen varied with the number of fish in the tanks and was maintained > 5

mg/L. The fish were fed daily with frozen brine shrimp. The concentration of the substance in the water was measured daily (methoxychlor mean exposure/concentration in water: 3.5 µg/L). Thirty minnows were placed in the tank with the test substance (five fish in the control tank). Five fish were analysed after 2, 4, 8, 16, 24 and 32 days of exposure to methoxychlor. The substance recovery was at least 90%. The steady-state bioconcentration factor was calculated from the 32-d exposure. A BCF value for methoxychlor up to 8,300 was reported for fathead minnow. Veith *et al.* (1979) does not confirm whether steady-state was reached at day 32. The BCF may have been higher than 8,300, however, this is unknown as it is unclear if steady-state was reached.

58. It was noted by the authors that at early stages of this study, occasional spawning was observed, and spawning tiles were used in the exposures to reduce the excitability of the fish. Experimental details are missing so it is difficult to assess the validity of this study. Indeed, it is unclear if the following validity criteria of the OECD TG 305 have been met: the concentration of the test substance was maintained within ± 20% of the mean of the measured values during the uptake phase and the mortality of fish in both control and treated fish is less than 10% at the end of the test. In addition, no depuration phase was performed in the test and it is most likely that the BCF for methoxychlor was not lipid and growth corrected. The study by Veith *et al.* (1979) is considered reliable with restrictions.

59. The OECD Guidelines for Testing of Chemicals (TG 305) outlines a method for determining a chemical's bioaccumulation in fish by exposing test animals to either food or water spiked with the test substance. In a validation study of a ring test for the OECD TG 305 dietary exposure test, the results from eight different laboratories were assessed (OECD, 2012 and OECD, 2013)[9]. The studies were conducted using rainbow trout (*Oncorhynchus mykiss*) with one laboratory conducting a further study using carp (*Cyprinus carpio*) (OECD, 2012). BCF values for methoxychlor were derived from the dietary test data as follows: the equivalent uptake rate constant of methoxychlor from water (k_1) was estimated using the "best" methods identified from a review of 13 different existing methods from the literature. Inter-laboratory kinetic BCF values were then estimated as the ratio of the estimated k_1 value from seven different methods of calculation to the overall mean measured depuration rate constant (k_2), or to the mean measured growth corrected depuration rate constant (k_{2g}). Using the k_{2g} value, modelled BCF values for methoxychlor from six laboratories ranged between 3,335 L/kg and 5,926 L/kg for rainbow trout (mean = 4,421 L/kg), and 1,006 L/kg to 2,015 L/kg for carp (mean = 1,537 L/kg; one lab), using a 3% feeding rate of wet body weight per day (OECD, 2012). Estimated BCF values using a 1.5% feeding rate were lower compared with values estimated using the 3% feeding rate (not growth corrected; OECD, 2013). The mean lipid-normalised biomagnification factor (BMFL) for methoxychlor estimated in the ring test is 0.16 with a relative standard deviation of 63 %. It is noted that several highly bioaccumulative substances exhibit in fish dietary tests BMFs < < 1 and such results are not directly indicative of lack of field biomagnification potential[10].

60. Renberg *et al.* (1985) studied the bioconcentration potential of methoxychlor in a bivalve *Mytilus edulis*. A continuous-flow system was used for the duration of the 21-day study. Bivalves are known to close their valves under unfavourable conditions, which occasionally may bias the results. In order to overcome this disadvantage, an internal standard (pentachlorobenzene) was added to the water simultaneously with methoxychlor. Although there is a risk for interactive effects, the authors stated that unexpected variations in the uptake can be compensated by relating the concentration of the test substance to the concentration of the internal standard in the organisms. The bivalves were collected at a depth of 1-3 m in the Baltic bay Tvären and were kept up to 8 months at 10°C. Mussels with an approximate size of 3.5 cm were selected and 20 individuals were spread over each of the two glass plates which were transferred to the aquarium used for the experiment. The stock solution consisting of an acetone solution of the test substance (level of purity: 100%) was mixed with brackish water using a magnetic stirrer. Recovery experiments for both water and organisms showed recoveries over 85% for the test substances. Mussels were fed with unicellular green algae. A BCF value of 12,000 was observed for methoxychlor at day 21. However, the steady-state was not reached at the end of the 21 days suggesting that the BCF value should be even higher than 12,000 for *Mytilus edulis*. Experimental details are missing so it is difficult to assess the validity of this study. According to ASTM E1022-94, this bioconcentration test should be considered unacceptable as the uptake phase was terminated before either apparent steady-state or 28 days was reached (ASTM, 2003). However, it is used as supporting information in the bioaccumulation assessment.

61. Anderson and DeFoe (1980) conducted an experiment exposing stoneflies, caddis-flies, isopods, snails and bullheads to methoxychlor in a flowing-water test system for 28 days and unfiltered lake water was used under realistic natural conditions (temperature, pH, dissolved oxygen etc.). Methoxychlor BCFs were determined in the snails *Physa integra* with an average BCF of 6,945 (range of 5,000 to 8,570 depending on the concentration tested). It is unclear if steady-state was achieved at the end of the experiment (at day 28), nonetheless, there is sufficient information to conclude that methoxychlor is bioaccumulative in snails. Experimental details are missing in this study, so it is difficult to assess the validity of these BCF values for snails. However, they are used as supporting information in the bioaccumulation assessment.

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[9] OECD (2012) considers the results from eight laboratories (including those in UK, Germany, France, USA, Canada, Norway, Switzerland, Japan).

[10] Please, see further discussion on the difficulty to interpret BMF results from a dietary bioaccumulation test in ECHA Guidance (ECHA, 2017), section R.11.4.1.2.3.

2.2.3.3 Toxicokinetic and metabolism studies

62. Studies in mammals (mice, rats and goats) indicate that methoxychlor is well absorbed by the gastrointestinal tract and to a lesser extent by the skin. However, some of the data from animal studies come from ruminant animals, which may have limited relevance to humans and other non-ruminant species. Once in the bloodstream, methoxychlor appears to distribute to most tissues of the body, with highest levels usually found in fat. Methoxychlor is metabolised rapidly by the liver and neither the parent compound nor the metabolites tend to accumulate in fat or other tissue. The metabolism of methoxychlor has been fairly well studied *in vitro* and *in vivo* in animals and with human liver microsomes. Both sets of data indicate that methoxychlor undergoes demethylation to form phenolic derivatives, with dechlorination and dehydrochlorination reactions occurring to a lesser extent. Most of the ingested dose of methoxychlor is eliminated in the feces via biliary excretion of metabolites. Urinary excretion contributes to a lesser extent (approximately 10% of the total administered dose as indicated in mouse studies). The toxicokinetics of methoxychlor in humans is expected to be similar to the toxicokinetics of methoxychlor observed in animals (ATSDR, 2002).

63. Methoxychlor and its metabolites are cleared fairly rapidly from the body (approximately 92% in 24 hours in mice) (ATSDR, 2002).

2.2.3.4 Conclusion on bioaccumulation

64. The BCF values described in the bioaccumulation section suggest a very high potential of bioaccumulation for methoxychlor in aquatic organisms (log K_{ow} values >5 and BCF values >5,000).

2.2.4 Potential for long-range environmental transport

2.2.4.1 Screening of physicochemical properties

65. The estimated vapour pressure for methoxychlor is 5.56×10^{-3} Pa at 25°C (EPI Suite, MPBPVP v1.43 estimate, modified grain method; US EPA, 2012) indicating that methoxychlor is volatile and can enter the vapour phase in the atmosphere. The reliability of this prediction can be considered good because it is within the parametric domain of the model and there are structurally similar compounds in the training set. Vapour-phase methoxychlor will be degraded in the atmosphere primarily by reaction with photochemically-produced hydroxyl radicals. The rate constant for the vapour-phase reaction of methoxychlor with hydroxyl radicals has been estimated as 5.4×10^{-11} cm^3/mol-sec at 25°C (AOPWin v1.92; US EPA, 2012). The estimated half-life of methoxychlor in air is 2.397 hours of continuous light, or 0.2 day based on a 12-h photoperiod with 1.5×10^6 OH/cm^3 (AOPWin v1.92; US EPA, 2012). There is some uncertainty with the reliability of the AOPWin prediction since although the substance is within the parametric domain of the model, the fragments of the molecule is not fully covered by the training set of the model. However, modelling estimates predict that a portion of methoxychlor in air may be sorbed to particulates, which may increase its residence time and potential for long-range transport. Model estimations of methoxychlor sorbed to airborne particles range from 0.5 to 22% (AEROWIN v1.00). The reliability of the modelled value for vapour pressure and log K_{oa} (applied in AEROWIN) can be considered good because they are within the applicability domains of the respective models. As cited in ATSDR (2002), Kelly *et al.* (2004) describe that methoxychlor is expected to exist in both the vapour and particulate phases (bound to particulate matter) and, to a small degree, in the vapour phase in the atmosphere. The residence time and dispersion of methoxychlor in air is, therefore, a function of particle size, windspeed, and precipitation (ATSDR, 2002).

66. Because the sorbed fraction may be resistant to atmospheric oxidation, the AOPWin half-life value based on reaction with hydroxyl radicals may not adequately predict the atmospheric half-life of this substance. Moreover, based on monitoring data, the majority of methoxychlor in the atmosphere may be removed by wet or dry deposition processes with a residence time of <1 month (Hoff *et al.,* 1992 as cited in ATSDR, 2002). However, evidence of wide dispersion of methoxychlor in the atmosphere by its detection in Canadian Arctic snow suggests that some methoxychlor may remain in air for extended periods of time (Welch *et al.*, 1991). Methoxychlor has been frequently detected in rain (Strachan 1985, 1988 as cited in ATSDR, 2002). In a 6-year study (1986–1991) conducted in the Great Lakes Region, the mean annual concentration of methoxychlor in rain was 2.4 ng/L (Chan *et al.,* 1994 as cited in ATSDR, 2002). These data suggest that wet deposition processes significantly contribute to the removal of methoxychlor from the atmosphere. However, wet deposition of methoxychlor will depend upon the amount of precipitation and will vary from year to year. Dry deposition due to gravity will also act to remove methoxychlor from air (ATSDR, 2002). In the Great Lakes region, dry deposition of chlorinated pesticides was estimated to be 1.5–5.0 times as great as wet deposition (Eisenreich *et al.*, 1981 as cited in ATSDR, 2002).

67. If released to soil, it is expected that wind erosion of the upper layers of the soil can transport methoxychlor that has not degraded and has been incorporated to soil particles.

2.2.4.2 Long-range transport model predictions

68. Overall persistence (Pov) and the potential for long-range transport (LRTP) can be estimated for organic chemicals using the OECD Pov and LRTP Screening Tool (Wegmann *et al.*, 2009). Table 4 shows a summary of input data for methoxychlor to the OECD Pov and LRTP Screening Tool.

Table 4: Input properties used in estimating overall persistence and long-range transport potential of methoxychlor with the OECD Pov and LRTP Screening Tool

Input Property	Value	References	Comments
Log K_{aw}	-5.081 *(experimental)*	US EPA, 2012	
Log K_{ow}	5.08 *(experimental)*	Karickhoff *et al.*, 1979	
Half-life in air	4.8 hours (or 0.2 days) *(estimated based on a 12-h photoperiod, AOPWin v1.92)*	US EPA, 2012	Uncertainty on the estimated value from AOPWin since the substance may be sorbed to particulates and therefore may not undergo atmospheric oxidation.
Half-life in water	4992 hours (or 208 days) *(experimental)*	Walker *et al.*, (1988)	Uncertainty on this value as this study is considered to be not reliable.
Half-life in soil	2880 hours (or 120 days)	Chen, 2014	Uncertainty on this value as no information is provided in Chen (2014).

69. Whilst no absolute criteria for classifying chemicals as compounds with high or low overall persistence (P_{ov}) and LRTP have been established, the threshold values established by Klasmeier *et al.* (2006), based on limit values for reference POPs, can be applied (Pov = 195 days (P_{ov} of α-HCH), Characteristic Travel Distance = 5 097 km (CTD of PCB-28), and Transfer Efficiency = 2.248 % (TE of PCB-28). Using the OECD Pov and LRTP Screening Tool (Wegmann *et al.*, 2009) with input data specified in Table 4, the results obtained for methoxychlor suggest that it has a low potential for long-range transport: CTD of 498 km, Pov of 295 days and Transfer efficiency from air to surface media of 1.94×10^{-2} %. However, the Pov of methoxychlor is higher (295 days) than the Pov of α-HCH (195 days). The results from this modelling are uncertain, because the input parameter "half-life in air" might be underestimated and input "half-lives in water and soil" are uncertain (see section 2.2.2 Persistence for further details). Indeed, a significant portion of methoxychlor in air is expected to be bound to particulates so that it may not undergo reaction with OH radicals in the gas-phase as rapidly as the AOPWin model predicts. Modelling may be of limited value for substances that have low vapour pressure and adsorb to particulates in the air. Atmospheric transport for such substances is likely to be governed by the fate of these particulates. Muir *et al.* (2004) and Hoferkamp *et al.* (2010) suggest that atmospheric transport of methoxychlor is possible via the gas phase or on particles during periods without rainout events OECD Pov and LRTP Screening Tool and other similar models assume continuous low rates of precipitationand lower rates of photodegradation than predicted from standard assumptions due to transport in the periods of lower photolytic activity. This is confirmed for methoxychlor by monitoring evidence.

70. The experimental log K_{ow} (5.08), log K_{oa} (10.48) and log K_{aw} (-5.081) values for methoxychlor suggest high potential to reach the Arctic and to accumulate in the Arctic human food chain. The area of elevated Arctic Contamination and Bioaccumulation Potential (AC-BAP) selected by Brown and Wania (2008) comprises the following thresholds: log $K_{ow} \geq 3.5$; log $K_{oa} \geq 6$; $0.5 \geq$ log $K_{aw} \geq -7$; log $K_{aw} \leq -1.78 \times$ log $K_{oa}+14.56$.

2.2.4.3 Confirmation based on measurements in remote areas

71. The potential for long-range transport of methoxychlor is strongly indicated by monitoring studies and measurements in environmental and biota samples from remote regions.

72. Methoxychlor has been detected in various media in the Arctic, including in air from a region covering the North Pacific to the Arctic Oceans between 2016-2017 (concentrations in the range of 0.02-0.42 ng/m^3 (mean 0.08±0.10 ng/ m^3; Gao *et al.,* 2019), in brown snow sampled in May 1988 (0.234 ng/L; Welch *et al.,* 1991), in an ice core drilled in 1998 from an ice cap in the Svalbard archipelago of arctic Norway (a peak concentration of 4.7 ng/L associated with the early 1980s; Hermanson *et al.*, 2005), in an Arctic lake water (methoxychlor, endosulfan and pentachloroanisole collectively, in concentrations in the range of 0.017-0.023 ng/L; Muir *et al.*, 1995b as cited in AMAP, 1998), in terrestrial, avian and marine biota samples (concentrations in the range of n.d.[11] to 86 ng/g lipid weight (lw) between 1999-2005 (Vorkamp *et al.*, 2004 and Savinov *et al.*, 2011; see details in section 2.3 Exposure) and in plants (concentrations in saxifrage were in the range 0.1-1.0 ng/g (dw); France *et al.*, 1998 as cited in AMAP, 1998). Methoxychlor was also detected in seals sampled from the Antarctic Peninsula and South Shetland Islands during the 2013-2014 austral summer (concentrations in the range 7.97- 40.13 ng/g lw; Vergara *et al.,* 2019). The presence of methoxychlor at sites remote from known point sources like the Arctic and Antarctica indicates a potential for long-range transport.

73. Monitoring data available from sites remote from known point sources, such as the Arctic and Antarctica demonstrate long-range environmental transport with transfer to the receiving environment, including to biota (Vorkamp *et al.*, 2004; Savinov *et al.*, 2011; Filho *et al.*, 2009; Vergara *et al.*, 2019). In particular, methoxychlor has been found in ice cores in Svalbard (Norway) with peak concentrations between 1979-1992 (Hermanson *et al.*, 2005

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[11] Not detected (n.d.)

and Ruggirello *et al.,* 2010). The measured levels in ice cores reflect trends in volumes used at lower latitudes, providing further evidence for long-range transport as a source of methoxychlor to these remote regions (see details of the monitoring data in section 2.3.1).

2.2.4.4 Summary of long-range environmental transport

74. Despite modelling predictions indicating a low potential for long-range transport, transport of methoxychlor to remote areas (Arctic and Antarctic) is taking place based on monitoring data. Presence of methoxychlor in remote areas can be explained by atmospheric transport in the gas phase or on particles during dry periods and during periods of lower photolytic activity (Muir *et al.*, 2004; Hoferkamp *et al.*, 2010). Furthermore, considering the high persistence of the substance in water (half-life of 208 days (Walker *et al.*, 1988), collective concentrations of methoxychlor, endosulfan and pentachloroanisole in the range of 0.017-0.023 ng/L in an Arctic lake (Barrie *et al.*, 1997 as cited in AMAP, 1998)), and measured level in Arctic Ocean and sea (concentrations in the range <MDL-0.38 ng/L (mean 0.15±0.11 ng/L); Gao *et al.,* 2019), long-range transport potential through water and ocean currents is also possible. In the absence of significant local or regional sources, detection in environmental and biota samples from the Arctic and Antarctic are due to the long-range transport of methoxychlor.

2.3 Exposure

2.3.1 Environmental monitoring data

2.3.1.1 Exposure as a result of long-range environmental transport in remote areas (far from point sources)

75. Methoxychlor has been detected in various media in the Arctic (in air, snow, ice core, lake waters, Arctic Ocean and sea, in plants and in biota samples (terrestrial, avian and marine)) and in Antarctica (in marine biota samples).

76. Hung *et al.* (2005) monitored methoxychlor in air at two Canadian and one Russian Arctic sites (between 1993 and 1995), namely Tagish, Yukon; Kinngait, Nunavut and Dunai Island, Russia. Methoxychlor was analysed in both the gas and particulate phases. Samples of air were taken weekly, and concentration data have not been blank- or recovery-corrected. Annual average (arithmetic mean) of methoxychlor concentrations were between 0.12 and 0.41 pg/m^3 at the three arctic sites. As Halsall *et al.* (1998) (as cited in Hung *et al.* (2005)) have found, concentrations of organochlorines (OCs) were similar at all sites indicating a uniformity in contamination in Arctic air. Concentrations of methoxychlor in Arctic air were higher than the concentrations found for the POP endrin at the same sites and time (between 0.15 and 0.29 pg/m^3; before endrin inclusion to the Stockholm Convention in 2001). Gao *et al.* (2019) monitored methoxychlor in the atmosphere (from 61°N to 31°N) in a region covering the North Pacific to the Arctic Oceans. Samples were collected from 12 July to 23 September 2016 and from 27 July to 7 October 2017. Methoxychlor was the most abundant insecticide in the atmosphere with concentrations of 0.02-0.42 ng/m^3 (mean 0.08±0.10 ng/ m^3). Based on methoxychlor seawater-atmosphere fugacity ratio (between 4.52×10^{-3} and 3.57×10^{-2}), Gao *et al.* (2019) concluded that methoxychlor had higher concentrations in the atmosphere than in seawater. However, the results of this study should be considered with caution (see further information in the persistence section).

77. Methoxychlor has also been detected in snow in the Canadian Arctic at levels of 0.234 ng/L in May 1988 (Welch *et al.,* 1991).

78. Methoxychlor has been detected in the Russian Arctic ice caps at a concentration range of 72-2100 ng/l (Boyd-Boland *et al.*, 1996). However, the date when the samples were collected is not clear and it is possible that the levels reported are from composite samples spanning several years or decades (Hoferkamp *et al.,* 2010). A 1998 ice core drilled from the Austfonna ice cap on Svalbard, Norway was analysed for contaminants, with the top 70 m corresponding to the years 1906 (±5) to 1998 (Hermanson *et al.*, 2005). Methoxychlor was found in sections of the core dating to the early 1950s and concentrations were found to increase over subsequent years with a peak concentration of 4.7 ng/L associated with the early 1980s, which is expected to be the period of peak use of methoxychlor globally. The measured levels in the core seem to follow roughly the use volumes at lower latitudes hence providing measured evidence of long-range transport. The route of long-range transport cannot be identified from these results. Ruggirello *et al.* (2010) drilled in April 2005 an ice core on Holtedahlfonna (125 m deep) on Svalbard, Norway to measure the input of pesticides. Methoxychlor was detected in all analysed segments of the ice core dated 1953-1962. The inputs grew to a peak value of 19.6 pg/cm^2/year in the core segment dated 1971-1980 and generally declined from there to the surface layer (10.7 pg/cm^2/year). The authors compared the ice core burdens and peak flux years in the Holtedahlfonna (peak year 1971-1980 and burden 46.4 ng) with the ones in Austfonna (peak year 1986-1992 and burden >400 ng). The authors reported that the general sources of the pesticides between the two ice cores is different and that Austfonna generally receives the greater input. Austfonna has received more atmospheric flow from Eurasia than Holtedahlfonna.

79. The OCPs, endosulfan, methoxychlor, and pentachloroanisole, were detected in lake waters in the Arctic. Muir *et al.* (1995b; as cited in AMAP, 1998) found all three compounds present at similar concentrations (0.017-0.023 ng/L) in water from Peter Lake, a large oligotrophic lake near Rankin Inlet (Northwest Territories (NWT)). The

presence of these compounds is consistent with their presence in Arctic air (Barrie *et al.*, 1997 as cited in AMAP, 1998). Methoxychlor was found in surface seawater in the Arctic Ocean and Chukchi Sea in 2016-2017 (concentrations <MDL-0.38 ng/L (mean 0.15±0.11 ng/L); Gao *et al.,* 2019; see further details in section 2.2.2.2 Monitoring data).

80. Measured data in biota are available for methoxychlor at various trophic levels. The substance was found in muscle, liver, blubber and kidney of terrestrial species (hare, lamb, caribou, muskox), marine invertebrates (snow crab, shrimp, Iceland scallop) and fish (Arctic char, Atlantic cod, Atlantic salmon, wolffish, capelin, shorthorn sculpin), seabirds (thick-billed murre) and marine mammals (ringed seals, harp seals, elephant seals, beluga, minke whale, narwhal) in Greenland (Vorkamp *et al.*, 2004), the Russian Arctic (Savinov *et al.*, 2011) and Antarctica (Filho *et al.*, 2009). Methoxychlor concentrations in biota from Greenland between 1999-2001 were in the range of n.d. to 86 ng/g lw (Vorkamp *et al.*, 2004). The highest concentrations for methoxychlor were observed in the following species: snow crab (1.7 to 86 ng/g lw), capelin (n.d. to 55 ng/g lw), thick-billed murre (n.d. to 37 ng/g lw), Atlantic cod (n.d. to 33 ng/g lw), shrimp and narwhal (n.d. to 32 ng/g lw), muskox (n.d. to 25 ng/g lw), shorthorn sculpin (n.d. to 22 ng/g lw), Arctic char (n.d. to 16 ng/g lw), wolfish (n.d. to 15 ng/g lw) and minke whale (n.d. to 12 ng/g lw)) (Vorkamp *et al.*, 2004). In Russian Arctic, methoxychlor was detected in the blubber of adult ringed seals at levels between <0.5-8.36 ng/g lw between 2001-2005 (Savinov *et al.*, 2011). Similar levels were found in the blubber of ringed seals by Vorkamp *et al.* (2004).

81. Methoxychlor has also been measured in elephant seal (*Mirounga leonina*) pups on Elephant Island in Antarctica during the 1999-2000 austral summer (Filho *et al.*, 2009). The concentration of methoxychlor in samples collected from 7 dam/pup pairs of southern elephant seals were: 2.91 ± 1.17 ng/g lipids in Dam blubber, 1.79 ± 0.32 ng/g lipids in milk and 1.86 ± 0.40 ng/g lipids in Pup blubber. Concentrations of methoxychlor in dam/pup blubber and milk were higher than the concentrations found for the POPs hexachlorobutadiene (0.38-0.43 ng/g lipids) and α-HCH (0.21-0.39 ng/g lipids) before their inclusion to the Stockholm Convention. The authors concluded that methoxychlor as a contaminant in Antarctica may reflect contamination from its potential current or historical use for agriculture purposes in the southern hemisphere. As this species is resident to this location (i.e. not a migratory species) this observation indicates long-range transport from sources in the southern hemisphere, where use of these insecticides may still occur.

82. Vergara *et al.* (2019) found methoxychlor in blubber of adult Antarctic seals (Southern elephant seals, Antarctic fur seals, Weddell seals, Leopard seals and crabeater seals) from two locations in the Antarctic Peninsula. Samples were collected during the 2013-2014 austral summer. Mean concentrations of methoxychlor in Antarctic seals were in the range of 7.97- 40.13 ng/g lw. The concentration of methoxychlor found in Southern elephant seals in this recent study (27.94 ng/g lw) is higher compared to the concentration found in the study of Filho *et al.* (2009) (2.91 ± 1.17 ng/g lipids in Dam blubber).

83. France *et al.* (1998) (as cited in AMAP, 1998) detected the widely used OCPs, tetra- and pentachlorophenol (as anisoles), endosulfan, methoxychlor, trifluralin, and triallate in lichen and saxifrage from Ellesmere Island (Canada). Concentrations of these pesticides in saxifrage were in the 0.1-1.0 ng/g (dw) range, similar to levels of other individual OCs such as dieldrin and chlordane isomers (before their inclusion to the Stockholm Convention in 2001) (France *et al.*, 1998 as cited in AMAP, 1998).

2.3.1.2 Exposure at regional and local scale near point sources

84. In 1974, methoxychlor was detected at a concentration of 254 ng/m^3 in air samples collected from a pesticide formulation plant in Southern Florida (USA; Annex E, 2019 information from IPEN and ACAT). In a survey (conducted during the years 1987, 1988, and 1989) of pesticide levels in air in the U.S., the mean levels of methoxychlor in indoor, outdoor, and personal air samples from Jacksonville, Florida were 200–300, 0–100, and 100–600 pg/m^3, respectively (EPA 1990e as cited in ATSDR, 2002). In a survey of ambient air measurements, atmospheric levels of methoxychlor (from data taken at two locations in the United States from 301 samples) ranged from n.d.-7,000 pg/m^3 (Kelly *et al.,* 1994 as cited in ATSDR, 2002). In Canada, the yearly mean level of methoxychlor in air was 1.7 pg/m^3 from 1988 to 1989 (Hoff *et al.*, 1992 as cited in ATSDR, 2002). Air levels tended to be higher during insect control periods (up to 27 pg/m^3), whereas levels were generally below the detection limit (0.04–0.1 pg/m^3) during non-use periods (ATSDR, 2002). Sofuoglu *et al.* (2004) collected air samples of OCPs in May 2003 in Izmir (Turkey). Concentrations of methoxychlor in air ranged from 43-990 pg/m^3 (mean value: 220±255 pg/m^3; n=20).

85. Adu-Kumi *et al.* (2012) found concentrations range of methoxychlor of 0.8-13.25 pg/m^3 (n=7) in urban and suburban residential air samples from Ghana. Air samples were taken from January to December 2008. Recoveries were higher than 76% for all samples. Data were not corrected for recovery rate. Guida *et al.* (2018) measured methoxychlor in Brazilian mountains 2000 meters above sea level. Air samples were collected between September 2013 to October 2015 at two National Parks in Southeast Brazil where hundreds of endangered species and many endemic species live. Mean recovery for methoxychlor was 91.08%. Concentrations of methoxychlor were in the range of n.d. to 115 pg/m^3 (Limit of detection (LOD) for methoxychlor: 58 pg/m^3). The authors reported that one of the National Park was surrounded by intensive agricultural activities which may explain concentration levels found at the sampling site. The results of this study should be considered with caution since methoxychlor was found in the

blank controls. However, the concentrations reported in the samples have been corrected from the blanks of each analytical batch.

86. No data were found for methoxychlor degradation products and their levels in air (ATSDR, 2002).

87. Strachan and Huneault (1979) reported levels of methoxychlor in snow samples collected in February 1976 and in rain samples collected from seven locations in May–November 1976, from the Canadian side of the Great Lakes. Mean concentrations of methoxychlor measured in rain and snow ranged between 1.6-13.1 ng/L and 0.1–5.8 ng/L respectively. These values were generally much higher than other measured OCPs such as DDT, lindane and dieldrin. The authors attributed this to methoxychlor being 'currently used' at the time the measurements were taken. In a 6-year study (1986–1991) conducted in the Great Lakes Region, the mean annual concentration of methoxychlor in rain was 2.4 ng/L (Chan *et al.*, 1994 as cited in ATSDR, 2002).

88. Methoxychlor has been detected at relatively high concentrations in waters near points of methoxychlor use or application (ATSDR, 2002). Concentrations of methoxychlor up to 50 µg/L were detected in both surface water and groundwater close to agricultural areas where it was applied (Annex E, 2019 information from IPEN and ACAT). Methoxychlor was found in water samples in Costa Rica at a concentration range of 5.6-19 ng/L and at 0.38 ng/L in Nicaragua (0.15 ng/g in suspended solids) (UNEP GEF-REPCar, 2011). Samples were collected in 2008-2010 (before methoxychlor was banned in Costa Rica in 2013). According to Helou *et al.* (2019), measurable levels of methoxychlor (concentration range: n.d.-4.7 ng/L; average: 1.8 ng/L; n=4; sampling in 2011-2012) in the Litani riverbed (Lebanon) indicate that it had recently been used in the area.

89. Zeng *et al.* (2018) found methoxychlor in the surface water (reservoirs, ponds and stream) of Qingshitan Reservoir in Southwest China from 2014 to 2016. Methoxychlor concentrations in water samples (n=283) ranged from n.d.-13.90 ng/L with a detection rate >88.57% (the MDLs of OCPs were in the range: 0.02-2.03 ng/L). The authors derived a PNEC value of 0.0078 µg/L (based on an EC50 48h for Daphnia of 0.78 µg/L and an Assessment Factor (AF) of 100) which they compared to the mean concentrations found in freshwater (mean values of: 2.33 ng/L (reservoir), 2.37 ng/L (pond) and 2.25 ng/L (stream)). They found MEC[12]/PNEC ratios for methoxychlor below 1. However, these ratios do not represent the most conservative scenarios. MEC/PNEC ratios derived from the maximum measured concentrations for methoxychlor (max. values of: 13.90 ng/L (reservoir), 13.64 (pond) and 13.41 (stream)) are > 1, suggesting an unacceptable risk to aquatic organisms.

90. Affum *et al.* (2018) studied the concentration of pesticides in the Ankobra River Basin in the Western Region of Ghana. Samples were collected between August and October 2016. Methoxychlor was detected in 54% of surface water samples at a concentration in the range of n.d.-0.020 µg/L (mean value: 0.012±0.004 µg/L; recovery rate: 70%; the LODs for OCPs ranged from 0.01 to 0.011 µg/L). According to Affum *et al.* (2018), methoxychlor belongs to the pesticides that contributed to the risk quotient RQ > 1 in >50% of the samples in Ghana. The authors defined the RQ as the ratio of MEC/PNEC. The authors derived a PNEC value of 0.00078 µg/L (based on an EC50 for aquatic invertebrates of 0.78 µg/L and using an Assessment Factor (AF) of 1000) which they compared to the min and max concentrations found in freshwater. This result suggests an unacceptable risk to aquatic organisms. The mean concentration of methoxychlor in the study of Affum *et al.* (2018) was relatively higher than that detected in potable water and surface water samples from the Litani River and Lake Qaraoun in Lebanon (0.002 µg/L methoxychlor; Kouzayha *et al.*, 2013 as cited in Affum *et al.*, 2018) and in the Xiaodian River Basin in China (0.0048 µg/L methoxychlor; Qi *et al.*, 2016 as cited in Affum *et al.*, 2018). The ubiquity of methoxychlor in the water resources was mainly due to its current use to control pests, despite being banned for pest control on cocoa crops in Ghana (Affum *et al.,* 2018). Basheer *et al.* (2002) measured methoxychlor in coastal seawater samples collected in 2002 from the sea surface in the Straits of Johor, located between Singapore and the Malaysian peninsula. Methoxychlor concentrations in seawater were in the range of 0.053-0.616 µg/L. The authors mentioned that some minimal agricultural activities remained in Singapore at the time of the measurement.

91. Austria indicated that methoxychlor was not detected in 13 out of 13 groundwater samples (lower Austria) and in 9 out of 9 groundwater samples collected in 2014 and in 2018 respectively after the ban of its use in Austria in 1993 (Annex E, 2019). However, methoxychlor has been detected in groundwater at waste disposal sites. A review of groundwater monitoring data from 479 site investigations indicates that methoxychlor was detected in groundwater at 14 (3%) of the sites (Plumb, 1991 as cited in ATSDR, 2002). According to Helou *et al.* (2019), methoxychlor concentrations in the groundwater of Akkar (Lebanon) were in the range of n.d. to 250 ng/L (average: 57 ng/L; n=30; samples collected in 2015). According to Affum *et al.* (2018), methoxychlor was detected in 64% of the groundwater samples in the Ankobra Basin (Ghana) at a concentration in the range of n.d.- 0.010 µg/L (mean value: 0.010 µg/L; samples collected between August-October 2016; the LODs for OCPs ranged from 0.01 to 0.011 µg/L). The latter mean concentration was higher than that reported in the Xiaodian River Basin in China (0.001 µg/L for methoxychlor) (Wang *et al.*, 2013 as cited in Affum *et al.*, 2018) but lower than that reported by Helou *et al.* (2019) in the groundwater of Akkar (Lebanon).

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[12] Measured Environmental Concentration (MEC).

92. Abong'o *et al.* (2015) found methoxychlor in soil samples (0-30 cm plough layers) from the Nyando basin in Kenya. Soil samples were collected over a period of two years in 2005-2006. Methoxychlor was the OCPs found in the highest concentration (138.97±1.517 µg/kg) and it was in use at the time of sampling. Bolor *et al.* (2018) found methoxychlor in groundwater and topsoil (0-30 cm depth) samples near farms in Kumasi, Ghana. Samples were collected in September 2014. Methoxychlor was found in the groundwater and soil samples at mean concentrations ranging from 1.53-8.87 µg/L and 2.61 to 58.3 µg/kg respectively.

93. Monitoring data from agricultural soils in Belarus after its ban in 1999, indicate that methoxychlor concentrations in soil were below the detection limit in 2007, 2008 and 2011 (Annex E, 2019). Thiombane *et al.* (2018) studied contamination levels of OCPs in urban and rural soils from central and southern Italy. 148 topsoil samples (0-20 cm top layer) were collected from early April to the end of September 2016. Methoxychlor was found in the range of n.d.-53.23 ng/g (mean value: 3.64 ng/g) in urban areas and n.d.-521.79 ng/g (mean value: 10.96 ng/g) in rural areas (detection limit for methoxychlor: 0.025 ng/g). According to the authors, when compared to other studies, the mean concentration of methoxychlor (10.96 ng/g) found in soils from rural areas is comparable to that from agricultural soils of central China (Zhou *et al.*, 2013 as cited by Thiombane *et al*., 2018*)* but greater than concentrations found in southern Mexico (Cantu-Soto *et al.,* 2011 as cited by Thiombane *et al*., 2018) and in hilly areas of Nepal (Yadav *et al.*, 2017 as cited by Thiombane *et al*., 2018). According to Thiombane *et al.* (2018), methoxychlor was found to represent 12.17% of the total OCPs detected in soils from urban areas, which is likely to be related to recent applications (particularly in Apulia) while the use of the substance as a pesticide has been banned in Europe since 2003. Austria indicated that methoxychlor was not detected in 15 out of 15 solid waste samples collected in 2016 and in 2018, after the ban of its use in Austria in 1993 (Annex E, 2019).

94. Panday *et al.* (2011) found methoxychlor in the surface sediments of river Yamuna in Dehli (India). Sediments samples were collected in June, August and October 2006. Concentrations of methoxychlor in sediments were in the range 7.72-62.78 ng/g. The authors concluded that methoxychlor was found in significant concentrations at all sites and all seasons indicating their wide use. Similar levels were found in the Coastal lagoon watershed (Argentina) in 2001 (<0.2-127 ng/g; Menone *et al.*, 2001 as cited in Panday *et al.,* 2011). However, concentrations of methoxychlor found in Panday *et al.* (2011) seem to be higher than concentrations found in sediments of the river Yamuna in Dehli (India) in 2010 (mean concentration of 0.09 ng/g; Parween *et al.,* 2014), in the Coastal marine sediment (Singapore) in 2005 (<0.4-1.2 ng/g; Wurl and Obbard, 2005 as cited in Panday *et al.,* 2011), in Tampa Bay Florida (U.S.) in 2004 (0.1 ng/g; Grabe and Barro, 2004 as cited in Panday *et al.,* 2011) and in Pearl river estuary (China) in 2001 (n.d.-1.49 ng/g; Li *et al.*, 2001 as cited in Panday *et al.,* 2011).

95. Methoxychlor was found in sediment samples in Costa Rica at a concentration of 0.29 ng/g and at 0.08 ng/g in Nicaragua (UNEP GEF-REPCar, 2011). Samples were collected between 2008 and 2010 (before methoxychlor was banned in Costa Rica in 2013). Tao *et al.* (2019) analysed OCPs from one sediment core (depth: 20 cm) collected in the Southern lake Taihu (China) in 2012. OCPs recoveries varied from 71.3 to 94.2%. Methoxychlor was one of the dominant congeners of the 13 OCPs analysed. The average concentration of methoxychlor was 7.01±2.82 ng/g dry weight. Annex E (2019) information from Canada indicated that methoxychlor was detected in 48 of the 301 samples of the Great Lakes sediments between May 2013 and September 2017 with a maximum concentration of 36 ng/g. These data indicate that methoxychlor continued to be detected in Canadian sediments years after its ban in December 2005, thus supporting the evidence of its persistence in the sediment compartment.

96. Castañeda-Chávez *et al.* (2018) measured the concentrations of methoxychlor in the sediments (0-20 cm) from the Alvarado lagoon system in Veracruz (Mexico). The sediment collection was performed in triplicate during the dry season corresponding to April-June 2011. Concentrations of methoxychlor were in the range of 1.13-29.4 ng/g dw (mean: 5.650 ng/g dw and standard deviation: 6.561 ng/g dw). The authors reported that the concentrations measured in Alvarado were lower than those reported in Lagos (Nigeria) with maximum concentrations of 146.7±8.2 ng/g dw for methoxychlor (Williams, 2013 as cited in Castañeda-Chávez *et al.,* 2018). The authors reported that the organochlorine compounds in the sediments are in direct contact with benthic organisms that inhabit this zone that are of commercial interest for human consumption, thus representing a potential concern. The authors state that the methoxychlor levels detected in the Alvarado Lagoon system suggest its use in Mexico.

97. Annex E (2019) information from Canada indicated that methoxychlor was detected in 3 out of the 141 samples of fish between 1977 and 1993 with a maximum concentration of 18 µg/kg. Fish data show measurable levels of methoxychlor in fish tissues during the period methoxychlor was used in Canada and no recent information is available (Annex E, 2019). Unyimadu *et al.* (2018) found methoxychlor in high concentrations in brackish water fish from the Niger river (Nigeria) (concentration range of 29.3-740.8 µg/kg fresh weight; n=60; recovery rate: 77%; fish purchased from the landing sites in July 2009). Enbaia *et al.* (2014) found methoxychlor in Libyan fish collected in September-November 2013. Mean concentrations of methoxychlor in fish were in the range 0.8-4 µg/kg.

98. Facemire *et al.* (1995) studied the Florida panther (*Felis concolor coryi*), an endangered species. The authors suspected that the exposure of the Florida panther to a wide variety of environmental contaminants (including methoxychlor) via their diet may play a role in decreased male fertility. The Florida panther feeds extensively on the aquatic food chain, and on raccoons which may account for a significant proportion (approximately 12%) of the Florida panther's diet. Raccoons have been shown to bioaccumulate mercury, as well as a variety of organochlorine

compounds (including methoxychlor). Nalley *et al.* (1975) measured the concentration of methoxychlor in omental fat samples of raccoons (*Procyon lotor*) live-trapped in southern Florida. Methoxychlor was detected in 10 of the 20 samples in the concentration range 0.16-36.82 ppm. Salvarani *et al.* (2019) studied concentrations of OCPs in the eggs of two sea turtle species (*Eretmochelys imbricata* and *Chelonia mydas*) collected from the Punta Xen and Isla Aguada (Mexican coast) in 2014 and 2015. Methoxychlor was identified in all 114 of the eggs analysed (mean concentration range of 0.059-1.060 ng/g dw). According to the International Union for Conservation of Nature (IUCN) Red list, the hawksbill sea turtle (*Eretmochelys imbricata*) is a critically endangered species, while the green turtle (*Chelonia mydas*) is in the category 'least concern'. Buah-Kwofie *et al.* (2018) studied the accumulation of OCPs in fat tissues of live wild Nile crocodiles from iSimangaliso Wetland Park (South Africa). The park forms part of a biodiversity hotspot. A total of 15 crocodiles were sampled in 2016-2017. The sampled population consisted of nine adults and six sub-adults. Methoxychlor concentrations in fat samples of Nile crocodiles were in the range of 79-300 ng/g wet wt (mean value: 170±62 ng/g wet wt). The authors suggested that crocodiles have been recently exposed to methoxychlor. They also mentioned that the OCPs detected in the fat samples likely originate from agricultural and pest control activities outside the boundaries of the Wetland Park and are introduced via groundwater and fluvial processes.

99. Cindoruk *et al.* (2020) monitored OCPs in pine (*Pinus Pinea*) (needles and branches) from Gemlik (Turkey) in 2016. The maximum concentration determined for methoxychlor was 4.4 ng/g dry weight for pine branches. According to the authors, methoxychlor concentration in pine can be attributed to illegal usage of this pesticide for agricultural purposes as it has been banned in Turkey since 2012. Austria indicated that methoxychlor was detected but not quantified (<10 µg/kg) in 1 out of 13 herb samples collected in 2012, after the ban of its use in Austria in 1993 (Annex E, 2019).

2.3.2 Human exposure

100. According to US EPA (2000), the most probable route of exposure to methoxychlor would be from inhalation or dermal contact by workers involved in the manufacture, handling or application of this compound. Farmers and pesticide applicators who use methoxychlor are the populations most likely to receive above average exposures (ATSDR, 2002).

101. The general population can be exposed to low levels of methoxychlor by inhaling dusts and aerosols in air surrounding areas where methoxychlor is used. Based on the results of the Non-Occupational Pesticide Exposure Study (conducted between 1986 and 1988), inhalation exposure to methoxychlor ranged from 0.002 to 0.012 µg/day in one U.S. city. In a survey of methoxychlor residues in house dust in 28 homes in an agricultural area of Colorado where pesticide use was common, levels ranged from 1.6 to 103 mg/kg (mean: 14.9 mg/kg) in 8% of the homes of farmers, from 1.9 to 144 mg/kg (mean:18.2 mg/kg) in 9% of the homes of pesticide formulators, and from 1.5 to 29 mg/kg in 2% of the homes of the control group (Starr *et al.*, 1974 as cited in ATSDR, 2002). It is not clear if the presence of methoxychlor in the homes of the control group was due to migration of methoxychlor from nearby buildings or fields where it was applied by farmers, or to in-house use of methoxychlor-containing products by the residents. Populations that live or work on or near a farm where methoxychlor has been used recently on crops or livestock or that live near a hazardous waste site that contains methoxychlor could be exposed to above-average levels of methoxychlor in soil and possibly in water (ATSDR, 2002).

102. Although methoxychlor is poorly soluble in water, it has been found in surface water, groundwater and drinking-water (WHO, 2004). Surface water that has been treated with methoxychlor for control of insect larvae should be avoided until methoxychlor residue has decreased below the level of concern (ATSDR, 2002). In Slovakia, chlorinated pesticides (such as methoxychlor) have been found in the drinking water at the level of 0.01 mg/L which is higher than the EU limit in drinking water for individual pesticide of 0.1 µg/L. This level reflects a past contamination to these pesticides which were used in Slovakia for agricultural purpose in the 80-90s (Slovak Republic, 2016).

103. For the general population, the most likely source of methoxychlor exposure is from low-level contamination of food (concentrations ranging from 0.001 to 0.004 mg/kg in dairy products, grains, fruits, and vegetables (survey performed in 1980-1982)). The FDA's Total Diet Study program monitors chemical contaminants in the U.S. food supply and has calculated average daily intakes of methoxychlor in adults (age 25–65) ranging from 0.1 to 0.3 ng/kg/day for the period 1986–1991. In Canada from 1980 to 1985, methoxychlor was detected at level of 4 µg/kg in strawberries (Frank *et al.,* 1987a as cited in ATSDR, 2002). Exposure to methoxychlor from food may be elevated in persons who consume large amounts of fish and seafood from methoxychlor-contaminated waters. While fish from the Great Lakes generally did not contain detectable levels of methoxychlor, high levels ranging from 10 to 120 µg/kg were in the past infrequently reported (Camanzo *et al.*, 1987; Devault, 1985 as cited in ATSDR, 2002).

104. The 2013 pesticide monitoring results in the EU (including Iceland and Norway) (EFSA, 2015) summarises the results provided by the reporting countries and identifies areas of concern regarding sample compliance with the legal limits of pesticide residue in foods. EFSA also assessed the consumer dietary exposure to pesticide residues in the sampled food commodities and performed an analysis of the chronic and acute dietary risks for European consumers. The outcome of this monitoring (EFSA, 2015) showed that methoxychlor was detected in milk and honey

while it was banned in the EU in 2003. In addition, Maximum Residue Level (MRL) (0.01 mg/kg set at the limit of quantification) exceedances were noted for methoxychlor in animal products (fat of swine, bovine and poultry from ES and BE, the range of measured residue levels: 0.018–0.021 (mg/kg)). Methoxychlor was found in concentrations above the limit of quantification (LOQ), but the calculated dietary exposure was below the toxicological reference values (acceptable daily intake (ADI) of 0.1 mg/kg bw per day). Based on the analysis of the 2016 pesticide monitoring results in the EU (including Iceland and Norway) (EFSA, 2018), methoxychlor was again quantified in honey. It was reported that methoxychlor is an environmental contaminant resulting from its past use as a pesticide. Based on concentrations found for methoxychlor in the consumer products from the 2016 monitoring, it was concluded that the short- and long-term dietary exposures were unlikely to pose a health risk to EU consumers.

105. Shaker and Elsharkawy (2015) analysed raw buffalo milk samples from Upper Egypt for OCPs. Samples were collected in the city of Assiut between February and August 2013. According to the authors, pesticides in milk originate from contaminated feed, grass or corn silage, and from direct application of pesticides on dairy cattle. Methoxychlor was detected in 66% of the samples (n=30). Concentrations of methoxychlor in raw buffalo milk were in the range of 0.130-0.200 mg/kg. Methoxychlor was banned in Egypt in 1996, but the levels detected in buffalo milk were suggestive of its continued use.

106. Bolor *et al.* (2018) studied the levels of OCP residues in 3 different vegetables: lettuce, onion and cabbage from farms in Kumasi, Ghana in September 2014. Mean concentrations of methoxychlor in the vegetables were in the range of 9.02-184.1 µg/kg. The authors reported that the measured concentrations were higher than the EU MRL of 0.01 mg/kg for these vegetables. However, rather than being based on specific risks, the EU MRL appears to be based on the limit of quantification for methoxychlor. Furthermore, Bolor et al. (2018) reported that methoxychlor levels in vegetables did not exceed acceptable daily intake (ADI) values, nor did they result in increased carcinogenic risk. Therefore it is not clear whether the levels reported would result in identifiable risks to the population. In addition, levels detected in some of the vegetables significantly exceeded levels in corresponding soil samples. Therefore, it is likely that ongoing use of methoxychlor was occurring in Ghana at the time of the study.

107. Adeleye *et al.* (2019) studied concentration of methoxychlor in leafy vegetables (amaranth and fluted pumpkin) collected in November 2017 to January 2018 in southwestern Nigeria. The mean concentration of methoxychlor in amaranth was 4.590±2.774 mg/kg dw and 6.223±2.489 mg/kg dw in fluted pumpkin. The authors estimated the non-carcinogenic health risk (based on the reference dose for reproductive and developmental effects (RfD) of 0.005 mg/kg/d) for amaranth and fluted pumpkin and found that the hazard quotient for methoxychlor was above 1 for both children and adults thus representing a potential risk for consumers for these vegetables. In addition, the residue levels of methoxychlor in these vegetables exceeded the acceptable standard for leaf vegetables (EU MRL of 0.01 mg/kg (EU Pesticides Database (2019)), suggesting a potential risk for the population. However, rather than being based on specific risks, the EU MRL appears to be based on the limit of quantification for methoxychlor. The authors reported that the use of water from the river by farmers might contribute to the OCP residues detected in the vegetables. According to Adeleye *et al.* (2019), contamination can come from the soil on which the vegetables were planted or from long-range transportation of the OCPs applied to crops elsewhere.

108. Oh (2009) detected methoxychlor at concentrations of 0.312 and 0.382 mg/kg (recovery rate: 82.4%) in herbal drug materials from China (in two different Chinese Jinpi which is the pericarp of the ripe fruit of *Citrus reticalata* used in traditional stomach medicines). The herbal medicines were commercially available in 2002. These values are above the EU MRL of 0.05 mg/kg for methoxychlor which appears to be based on the limit of quantification for methoxychlor.

109. In a human population exposed to heavy agricultural spraying of pesticides (area sprayed 16–30 times per year), serum levels of methoxychlor were generally below the level of detection in southern Honduras (detection limit of 0.24–4.07 mg/L; detected in 1 out of 39 males) (Steinberg *et al.*, 1989 as cited in ATSDR, 2002). However, Carreño *et al.* (2007) [NOTE: Email sent to the authors asking for sampling date and recovery rate for methoxychlor] found levels of OCPs in the serum of 220 healthy young men (mean age: 20.75 years old; range: 18-23 years old) living in Southern Spain. Mean concentration of methoxychlor in the serum samples of young men was 2.84 ng/mL (standard deviation: 5.09 ng/mL; maximum: 53.8 ng/mL; n=220; frequency: 60.7%).

110. There are little data about children's exposure to methoxychlor or its degradation products. The available data suggest that exposure of children to methoxychlor differs from that of adults. Small children may play close to the ground and are therefore more likely than adults to come in contact with dirt (dermal exposure) and dust found in home carpets, dirt found outside the home, and lawns (inhalation of airborne soil particles). Children also may intentionally or unintentionally ingest soil that contains low levels of methoxychlor (ATSDR, 2002).

111. In a study conducted in residential areas of North Carolina (the Research Triangle area), house dust was collected in November 1996, separated into seven size fractions (<4–500 µm in diameter), and monitored for pesticide residues (Lewis *et al.,* 1999 as cited in ATSDR, 2002). The concentration of methoxychlor reported by the authors for various dust particle sizes is as follows: 250–500 µm, 120 ng/g; 150–250 µm, 210 ng/g; 106–150 µm, 310 ng/g; 53–106 µm, 570 ng/g; 25–53 µm, 740 ng/g; 4–25 µm, 680 ng/g; and <4 µm, 1,000 ng/g. Lewis *et al.* (1999; as cited in ATSDR, 2002) state that ingestion, dermal exposure, and inhalation of house dust may represent a substantial portion

of a child's exposure to pesticides. In another study, foods that are representative of the diets of eight population groups (ranging from infants to elderly adults) were prepared for consumption and analyzed for pesticide residues using the methods in the FDA's revised (April 1982) Total Diet Study (Gunderson, 1995a as cited in ATSDR, 2002). The mean daily intakes for children and young adults for the test period 1986–1991 were calculated to be 0.4 ng/kg/day for 6–11-month old infants, 0.9 ng/kg/day for 2-year-old children; 0.3 ng/kg/day for 14–16-year-old females and 0.4 ng/kg/day for 14–16-year-old males (Gunderson 1995b as cited in ATSDR, 2002).

112. Other possible sources of concern for exposure of methoxychlor to children are parents' work clothes and equipment used to apply products that contain methoxychlor. This mode of exposure would be of special concern in agricultural areas and around homes where pesticides are applied for lawn and garden or indoor use (ATSDR, 2002). Lopez-Espinosa *et al.* (2008) investigated the presence of OCP residues in 52 fat samples of boys (mean age 7 years old (0-15 years old) living in Southern Spain. According to the authors, children can be exposed to OCPs *in utero* via the placenta (Lopez-Espinosa *et al.*, 2007) and after birth via lactation (Noren and Meironyte, 2000; Solomon and Weiss, 2002) and infant formula (Cressey and Vannoort, 2003). Children are especially vulnerable to pesticides exposure because they consume a larger amount of food and water relative to their body weight as compared to adults. Fat samples were collected between 1994-1996 while methoxychlor was still in use in the EU. Methoxychlor was found in adipose tissues of 3 out of 52 children with a mean concentration of 16±20 ng/g lipid (Percentiles among ≥ limit of detection (LOD): P25=52 ng/g lipid; P50=121 ng/g lipid and P75=680 ng/g lipid). Comparable concentrations in adipose tissues were found for Lindane (mean value of 11±12 ng/g lipid; Percentiles among ≥ LOD: P25 = 29 ng/g lipid; P50=71 ng/g lipid and P75=106 ng/g lipid) which was found in 6 out of 52 children, before its inclusion to the Stockholm Convention on POPs in 2009.

113. Methoxychlor or its metabolites can be transferred from a pregnant mother to a developing fetus in animals, since abnormal reproductive development has been seen in the newborn animals born to mothers exposed during pregnancy. In animals, methoxychlor and metabolites of methoxychlor that are estrogenic can be transferred from a nursing mother to her newborn babies through breast milk. Methoxychlor and its metabolites can cross the placenta and have been detected in human breast milk (ATSDR, 2002).

114. Damgaard *et al.* (2006) studied 62 milk samples from mothers of cryptorchid boys (29 Danish and 33 Finnish) and 68 from mothers of healthy boys (36 Danish and 32 Finnish). This study was performed in Finland and Denmark from 1997 to 2001. Concentrations of methoxychlor in human breast milk samples were in the range of 0.06-1.12 ng/g lipid (milk of mothers of boys with cryptorchidism) and 0.05-0.41 ng/g lipid (milk of mothers with healthy boys) with a total detection rate of 26.9%. Methoxychlor was measured at slightly higher concentrations in milk from mothers giving birth to cryptorchid boys than in mothers giving birth to healthy boys. However, there were no significant differences between cryptorchid and healthy boys for individual chemicals (Damgaard *et al.*, 2006). Kao *et al.* (2019) found methoxychlor in breast milk of 26 out of 55 healthy mothers (mean age 29.5 years old) in southern Taiwan, Province of China. Milk samples were collected between 2007 and 2010. Mean concentration of methoxychlor in breast milk was 0.106±0.149 ng/g lipid (range values: n.d.-0.620 ng/g lipid; n=55; n>LOD = 26; LODs for the OCPs were in the range: 0.0151 to 0.0540 ng/g lipid). According to the authors, OCPs have been banned in Taiwan, Province of China, since 1975.

115. Luo *et al.* (2016) measured the level of methoxychlor in the umbilical cord blood from 972 healthy pregnant women (mean age: 26.6 years old) residing in the Huaihe River Basin (China). None of the women had been occupationally exposed to OCPs. The recoveries of all compounds ranged from 72-119% in plasma samples and LODs and LOQs were 0.08 to 2.31 ng/mL and 0.26 to 7.69 ng/mL, respectively. Samples were collected between November 2013 and June 2014. Methoxychlor was one of the OCP the most frequently found in samples (range: n.d. to 33.75 ng/mL; mean: 0.98±1.42 ng/mL, median 1.00 ng/mL, frequency: 74.49%; recovery rate: 98.5%). According to the authors, presence of methoxychlor in cord blood was mainly due to its recent use in China. However, the authors also suggest that the long-range transport of methoxychlor is also another inevitable route for OCP contamination in China. Concentrations of methoxychlor in cord blood were significantly and positively correlated with consumption of red meat (including pork, beef and lamb) of mothers from the study. The authors compared the level they found in umbilical cord bloods with levels found in other countries or regions. They reported that the level of methoxychlor in umbilical cord bloods was higher in their study than that of Shanghai (mean level: 0.0259 µg/L, median 0.02 µg/L, maximum 1.23 µg/L; Cao *et al.*, 2011 as cited in Luo *et al.* (2016)) and lower than that of Granada (mean level 3.32±4.01 ng/mL, median 1.44 ng/mL; maximum: 21.51 ng/mL; frequency: 34.4%; samples were collected in 2000-2002 in a cohort of 318 mother-son pairs (mothers mean age: 31.91 years old); Mariscal-Arcas *et al.* (2010)).

116. Cabrera-Rodriguez *et al.* (2020) found methoxychlor in 4 out of 447 umbilical cord blood samples from La Palma (Canary Islands, Spain) collected between March 2015 to April 2016. Concentrations of methoxychlor in umbilical cord blood samples were in the range 0.004-0.132 ng/mL, while methoxychlor was banned in the EU in 2003. Similar levels have been found for aldrin (0.002-0.161 ng/mL; it was banned in Europe in the early 1980s) and mirex (0.019-0.09 ng/mL; it has never been authorised in Europe). Jimenez Torres *et al.* (2006) [NOTE: Email sent to the authors asking for sampling date] determined the level of OC in the adipose tissue and serum of 72 women giving birth (aged from 18-35 years) in Southern Spain. Methoxychlor was found in 3 out of 72 (4.1%) adipose tissue

samples from pregnant women at a concentration range of 106-817.85 ng/g of fat (mean value: 347.73 ng/g of fat; SD: 407.19 ng/g of fat). However, methoxychlor was not detected in the serum. Mean concentration of methoxychlor in the fat of the women was higher than the mean concentration of the POP Lindane (mean:113.82 ng/g of fat; concentration range: 4.22-407.37 ng/g of fat detected in 36 out of 72 (50%) adipose tissue samples).

117. Insufficient data is available to adequately define the bioavailability of methoxychlor (Office of Parliamentary Counsel of Canberra, 2013). However, it is expected that the high potential of adsorption (high log K_{oc} values) of methoxychlor to solids (sediments, soils and particulate matters) may reduce its bioavailability in sediment, soil and water compartments.

2.4 Hazard assessment for endpoints of concern

118. No harmonised classification is reported for methoxychlor at the EU level (cf. Annex VI of Regulation (EC) No. 1272/2008 (CLP Regulation)).

119. The European Chemicals Agency (ECHA) online Classification & Labelling (C&L) Inventory database[13], which was checked on 07 February 2020, reports 99 notifications for methoxychlor. 94 notifiers have classified methoxychlor as harmful if swallowed (Acute Toxicity Category 4, H302), may cause damage to organs (STOT SE 2, H371 (not specified)) and very toxic to aquatic life (Aquatic Acute Category 1, H400). Three notifiers indicated no classification according to the CLP criteria. One notifier has classified methoxychlor as harmful if swallowed, in contact with skin or if inhaled (Acute Toxicity Category 4, H302, H312, H332); suspected of causing cancer (Carcinogen Category 2, H351), very toxic to aquatic life (Aquatic Acute Category 1, H400) and very toxic to aquatic life with long lasting effects (Aquatic Chronic Category 1, H410). One notifier has classified methoxychlor as suspected of damaging fertility or the unborn child (Reprotoxic Category 2, H361); may cause damage to organs (STOT SE 2, H371 (nervous system)), may cause damage to organs through prolonged or repeated exposure (STOT RE 2, H373 (Liver, nervous…)), very toxic to aquatic life (Aquatic Acute Category 1, H400) and very toxic to aquatic life with long lasting effects (Aquatic Chronic Category 1, H410).

2.4.1 Ecotoxicological effects

2.4.1.1 Adverse effects on aquatic organisms

120. Methoxychlor is highly toxic to aquatic invertebrates and fish. Acute lethal concentrations (LC50s[14]) for invertebrates were below 1 µg/L and around 10 µg/L for fish. Chronic No Observed Effect Concentrations (NOECs) are scarce for methoxychlor but those reported for fish and aquatic invertebrates are below 1.3 µg/L. Based on a literature/databases search, invertebrates are the most sensitive species in acute and chronic tests for methoxychlor (Anderson and DeFoe (1980), HSDB (2009) and US EPA (2019)).

121. The latter information is confirmed by the study made by Maltby *et al.* (2005). The authors calculated the species sensitivity distribution (SSD) for methoxychlor by using acute toxicity data (due to the lack of NOEC values for this substance) and log-normal model. SSDs are used to calculate the concentration at which a specified proportion of species will be affected, referred to as the hazardous concentration (HC) for *p* (%) of species (HC*p*). The most frequently estimated HCs are the HC5. Data were collated from existing toxicity databases (e.g., RIVM database), published literature, and unpublished industry data. Criteria used to select single-species toxicity data were related to test endpoint and duration, and outliers were checked using original publications. Selected endpoints were median lethal concentration or median effect concentration (EC50) regarding immobility for animals. Test duration was 2 to 21 days for fish and 1 to 7 days for invertebrates.

122. The geometric mean was calculated when more than one toxicity value was reported for a species. The method of Aldenberg and Jaworska, as incorporated in the ETX software, was used to generate SSD and associated lower (95% confidence) and median (50% confidence) HC5 estimates. A log-normal distribution model was fitted to a minimum of six data points, with model fit being evaluated using the Anderson-Darling goodness-of-fit test. For methoxychlor, the HC5 is 0.21 µg/L (95% confidence) and 0.47 µg/L (50% confidence) for aquatic arthropods (including freshwater and saltwater arthropods) and 2.48 µg/L (95% confidence) and 4.56 µg/L (50% confidence) for vertebrates. It was concluded that methoxychlor is more toxic to arthropods than vertebrates (fish and amphibians). The authors stated that the increased sensitivity of arthropods to insecticides is not surprising given the toxic mode of action[15] of these compounds. In addition, methoxychlor appears to have similar toxicity to aquatic arthropods and

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[13] https://echa.europa.eu/information-on-chemicals/cl-inventory-database/-/discli/details/112624

[14] **Acute toxicity** related to waterborne exposure is generally expressed in terms of a concentration which is lethal to 50% of the test organisms (lethal concentration, LC50), causes a measurable adverse effect to 50% of the test organisms (e.g. immobilization of daphnids), or leads to a 50% reduction in test (treated) organism responses from control (untreated) organism responses (e.g. growth rate in algae) following an exposure in the range of hours to days, expressed as effective concentration, EC50.

[15] *Mode of Action of DDT and methoxychlor:* Sodium channel modulators are neurotoxins that act on the action potential sodium channel. They slow the closing and inactivation of the channel, causing it to remain open longer than normal,

vertebrates as the POP lindane (HC5 of 0.34 µg/L (95% confidence) for aquatic arthropods and HC5 of 2.39 µg/L (95% confidence) for vertebrates).

123. HCs derived from single-species SSDs were then compared to threshold levels for the direct toxic effects ($NOEC_{eco}$ (i.e., highest test concentration at which class 1[16] effects were observed) and Lowest Observed Effect Concentration ($LOEC_{eco}$; i.e., lowest test concentration at which slight and transient effects (class 2[17]) were observed)) of insecticides in freshwater (micro)mesocosms. Data from (micro)mesocosms have been collected from a review of studies published between 1980 and 2001. For methoxychlor, the HC5 is 0.14 µg/L (95% confidence) and 0.37 µg/L (50% confidence) for freshwater arthropods and the $NOEC_{eco}$ is 3 µg/L and the $LOEC_{eco}$ is 5 µg/L for micro(mesocosms) (for a single application). The authors considered that the HC5 is considered to be protective when it is smaller than the $NOEC_{eco}$ or $LOEC_{eco}$, because in the present study, the latter represents the concentration at which only transient, slight effects are observed. For methoxychlor, the HC5 (95% confidence and 50% confidence) estimates from laboratory SSDs were less than the $NOEC_{eco}$ and the $LOEC_{eco}$ from (micro)mesocosm studies, suggesting the HC5 values were conservative estimates of the ecosystem threshold concentration. It is worth noting that SSD are normally performed with NOEC values and not acute ecotoxicity data. To be conservative enough for the ecosystem an assessment factor should be applied to these HC5 values. Finally, methoxychlor appears to have similar toxicity to freshwater arthropods and similar $NOEC_{eco}/LOEC_{eco}$ values in (micro)mesocosms than lindane (HC5 of 0.74 µg/L (95% confidence) for freshwater arthropods, $NOEC_{eco}$ of 0.25 µg/L and $LOEC_{eco}$ of 1 µg/L).

124. Whether methoxychlor causes estrogenic effects in aquatic wildlife has been investigated in a number of experiments (ATSDR, 2002). Data indicate that methoxychlor has endocrine disruptive effects in fish (Nimrod and Benson 1997 and Smeets *et al.,* 1999 as cited in ATSDR, 2002), amphibian (Ingermann *et al.,* 1997 and Ingermann *et al.,* 1999 as cited in ATSDR, 2002), and sea urchin (Mwatibo and Green, 1997 as cited in ATSDR, 2002) fertility, growth, and development. Sometimes the effects of methoxychlor parallel those of estradiol and sometimes there are either subtle or drastic differences from the effects of estradiol. Thus, it is likely that not all of the effects of methoxychlor in aquatic wildlife are mediated through estrogen receptors. There may be many different mechanisms involved in the varied effects and the different species (ATSDR, 2002).

125. No ecotoxicity data have been find on sediment organisms.

2.4.1.2 Adverse effects on terrestrial organisms

126. According to US EPA (2004), methoxychlor is practically nontoxic to birds on both an acute oral (LD50 >2000 mg/kg) and a subacute dietary (LC50>5000 mg/kg/day) exposure basis.

127. According to US EPA OPP Pesticide Ecotoxicity Database, methoxychlor has a LD50-48h of 23.57 µg/bee (contact LD50 studies) for *Apis mellifera* (Honey bee). Technical grade methoxychlor and adult bees were used for testing. This study has been considered as core (acceptable) data by US EPA. The test was performed following guideline: [141-1] Honey Bee Acute Contact LD50 (FIFRA 158.590). This test was an acute contact study: methoxychlor was topically applied or dermally adsorbed (US EPA, 2019).

128. According to ATSDR (2002), oral exposure of laboratory animals to methoxychlor has shown that high doses of methoxychlor are capable of causing neurological injury (tremors, convulsions; in rats and dogs), but most studies indicate that the reproductive system is the most sensitive target for methoxychlor. The resultant types of reproductive effects are indicative of interference with the normal actions of estrogen or androgen. According to ATSDR (2002), mechanistic studies have confirmed that metabolites of methoxychlor can compete with estrogen for binding to estrogen receptors and can mimic some and antagonize other effects of estrogen. Additional studies have shown that methoxychlor or its metabolites can interact with the androgen receptor and antagonize androgenic effects (ATSDR, 2002). In females, these interactions can result in disruption of estrus cyclicity, reduced fertility, and increased pre- and post-implantation losses (ATSDR, 2002). Effects in males can include delayed sexual maturation, atrophy of reproductive organs and accessory glands, and altered sexual or socio-sexual behaviour (ATSDR, 2002). Many of these effects may be mediated through altered hormone levels (ATSDR, 2002). Because methoxychlor and its metabolites are cleared fairly rapidly from the body (approximately 92% in 24 hours in mice; ATSDR, 2002), there does not appear to be much potential for bioaccumulation in mice.

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which has the effect of prolonging the action potential. When the action potential is not promptly terminated, it can re-excite the same area of membrane, leading to repetitive firing.

Because nerve axons occur throughout the insect's body, even near the surface of the cuticle in sensory organs and motor nerve terminals, pyrethroids and DDT cause symptoms as soon as they enter the body and are considered extremely fast-acting, causing immediate "knockdown".

This information is available at: https://products.basf.com/documents/pim;save/en/8797465586133.Insecticide%20Mode%20of%20Action%20Technical%20Training%20Manual.pdf

[16] Class 1: 'Effect could not be demonstrated'.

[17] Class 2: 'Slight effect'.

129. Observable changes in the liver (altered liver weight, altered enzyme and protein levels, pale and mottled appearance) and kidneys (cystic tubular nephropathy, elevated blood urea nitrogen [BUN]) of animals, as well as weight loss, are caused only by relatively large doses of methoxychlor; these effects are probably not mediated by an estrogenic mechanism (ATSDR, 2002).

130. In animals, signs of fetotoxicity (decreased fetal body weight, increased incidence of wavy ribs, resorptions, and death) were noted following exposure to methoxychlor *in utero*. These effects may be due to the maternal toxicity of methoxychlor and may not be true signs of teratogenicity (ATSDR, 2002).

131. Vom Saal *et al.* (1995) (as cited in OEHHA (2005)) discussed evidence that during fetal life, hormones have marked effects on subsequent behaviors. Male mice are particularly active in urine-marking behavior to indicate their social status. Urine marking was used as the end point to measure the effect of methoxychlor. Females received 0, 1, 10, 100, 1000, or 5000 µg/d from day 11 to day 17 of pregnancy. Two males from each litter were randomly selected when they were 60 days old and housed individually for four weeks to eliminate any effects of having been housed with other males. Urine-marking tests were conducted for one hour in clean cages with the floor lined by a sheet of Whatman No. 2 filter paper. The filter paper was then removed and discrete urine marks (which fluoresce under UV light) deposited on it were counted. The lowest dose (1 µg/day or 20 µg/kg-day based on 0.05 kg maternal weight) of methoxychlor significantly increased urine-marking behavior in male offspring.

132. Methoxychlor exposure during development can adversely affect the reproductive system of both developing and adult animals. These effects are the result of the disruption by estrogenic methoxychlor metabolites of the normal delicate balance of time-sensitive hormone levels during fetal and post-natal development (ATSDR, 2002).

133. The primary metabolite of methoxychlor is 1,1,1-trichloro-2,2-bis(4-hydroxyphenyl) ethane (HPTE). Studies have shown that endocrine disruptors like methoxychlor, have adverse effects on immune cells, but no studies have addressed the impact of HPTE, the primary metabolite of methoxychlor (Leung-Gurung *et al.*, 2018). To elucidate the presence and significance of HPTE adverse effects, Leung-Gurung *et al.* (2018) explored the impact of HPTE on a critical window and component of immune system development, embryonic T-cell development. Lesions at this phase of development can lead to lifelong immune dysfunction and increased incidence of immune disease, such as autoimmunity. Embryonic thymocytes (GD 16-18) from C57BL/6 mice were subjected to an *in vitro* differentiation culture that mimicked early steps in thymocyte development in the presence of 0.005, 0.05, 0.5, 5, or 50M HPTE, or a model endocrine disruptor, DES. The results indicated that compared to the vehicle control, HPTE- and DES-induced death of thymocytes (Leung-Gurung *et al.,* 2018). Annexin-V staining and Caspase 8, markers of programmed cell death, revealed that the loss of cells was due at least in part to induction of apoptosis. Moreover, HPTE-induced cell death not only resulted in selective loss of double positive thymocytes, but also loss of developing CD4 intermediate cells (post-double positive partially differentiated thymocyte population). Phenotypic analysis of thymocyte maturation (T-cell receptor, TCR) and TCR ligation (CD5) surface markers revealed that surviving embryonic thymocytes expressed low levels of both. Taken together these data demonstrate that immature embryonic thymocytes are sensitive to HPTE exposure and that HPTE exposure targets thymocyte populations undergoing critical differentiation steps. The authors (Leung-Gurung *et al.*, 2018) suggested that HPTE may play a pivotal role in methoxychlor exposure-induced immune dysfunction.

134. Manikkam *et al.* (2014) examined the actions of methoxychlor to promote the epigenetic transgenerational inheritance of adult-onset disease and associated differential DNA methylation regions (i.e. epimutations) in sperm. Gestating F0 generation female rats were transiently exposed (a dose of 200 mg/kg bw/day (4% of oral LD50) via intraperitoneal injection) to methoxychlor during fetal gonadal development (gestation days 8 to 14) and then adult-onset disease was evaluated in adult F1 and F3 (great-grand offspring) generation progeny for control (vehicle exposed) and methoxychlor lineage offspring. There were increases in the incidence of kidney disease, ovary disease, and obesity in the methoxychlor lineage animals. In females and males, the incidence of disease increased in both the F1 and the F3 generations and the incidence of multiple disease increased in the F3 generation.

135. Furthermore, Manikkham *et al.* (2014) observed increased disease incidence in F4 generation reverse outcross (female) offspring indicating disease transmission was primarily transmitted through the female germline. Analysis of the F3 generation sperm epigenome of the methoxychlor lineage males identified differentially DNA methylated regions (DMR) termed epimutations in a genome-wide gene promoters analysis. These epimutations were found to be methoxychlor exposure specific in comparison with other exposure specific sperm epimutation signatures. Observations indicate that the pesticide methoxychlor has the potential to promote the epigenetic transgenerational inheritance of disease and the sperm epimutations appear to provide exposure specific epigenetic biomarkers for transgenerational disease and ancestral environmental exposures. Similar epigenetic transgenerational effects on male fertility were found by Anway *et al.* (2005).

136. No ecotoxicity data have been found on soil organisms while this compartment is considered as the most relevant compartment due to the use of the substance.

2.4.1.3 Summary of ecotoxicological effects

137. Methoxychlor is highly toxic to aquatic invertebrates and fish. The freshwater arthropods are the most acutely sensitive species with a HC5 of 0.14 µg/L (95% confidence). Methoxychlor is suspected to have endocrine disruptive effects in fish, amphibian, and sea urchin fertility, growth, and development. Methoxychlor is practically nontoxic to birds (US EPA, 2004). Animal studies indicate that high doses of methoxychlor are capable of causing neurological injury (tremors, convulsions), but most studies indicate that the reproductive system is the most sensitive target for methoxychlor. The resultant types of reproductive effects are indicative of interference with the normal actions of estrogen or androgen. In addition, studies in mice indicate methoxychlor exposure-induced immune dysfunction. Furthermore, observations in rats indicate that methoxychlor has the potential to promote the epigenetic transgenerational inheritance of disease and associated sperm epimutations.

2.4.2 Adverse effects on human health

138. Available data on the toxicity of methoxychlor in humans are very limited. A study found no clinical or histopathological changes in four men and four women who ingested 2 mg/kg/day of methoxychlor for 6 weeks (Wills, 1969 as cited in ATSDR, 2002). These data are too limited to allow assessment of the health risks of methoxychlor to humans (ATSDR, 2002).

139. Based on a review of all the available data, IARC has classified methoxychlor as a Group 3 carcinogen (not classifiable as to its carcinogenicity to humans). Similarly, EPA has classified methoxychlor as a Group D carcinogen (not classifiable as to human carcinogenicity) (ATSDR, 2002). However, a study by Kim *et al.* (2014) demonstrated that methoxychlor may induce ovarian cancer cell growth by distinctly disrupting cyclin D1, p21 and Bax expressions in ER-positive BG-1 ovarian cancer cells. The genotoxic potential of methoxychlor appears to be negligible (WHO, 2004). Methoxychlor is likely to be a tumour promoter because it disturbs the metabolic cooperation between 6-thioguanidine-sensitive and -resistant V79-cells (WHO, 2004).

140. In mutagenicity assays, negative results were obtained (with or without metabolic activation) in bacteria, yeast, in assays of methoxychlor-induced DNA damage, or in assays of unscheduled DNA synthesis in mammalian cell cultures (Probst *et al.*, 1981 as cited in IRIS, 2003). A weakly positive increase was observed in a transformation study using BALB/3T3 cell line (Dunkel *et al.*, 1981 as cited in IRIS, 2003). When testing mutagenicity in humans, methoxychlor did not produce mutations at the thymidine kinase (TK) locus in human lymphoma cells (Caspary *et al.*, 1988 as cited in ATSDR, 2002).

141. Although human data on the reproductive effects of methoxychlor are limited, the animal and *in vitro* data strongly suggest that sufficient exposure to methoxychlor may adversely affect the development, histopathology, and function of the human reproductive system (ATSDR, 2002). There are no human data that report adverse effects on the reproductive system following exposure to methoxychlor, but *in vitro* studies reveal that human liver microsomes are capable of metabolising methoxychlor to estrogenic compounds. Therefore, it is likely that methoxychlor could produce reproductive estrogen-like effects in humans (ATSDR, 2002).

142. Taken together, the animal data suggest that human exposure to methoxychlor during critical stages of development may adversely affect reproductive development, causing effects that may not be detected until after puberty (ATSDR, 2002). Progesterone and estradiol produced by the human placenta are critical for maintenance of pregnancy and fetal development. In the human placenta, 3 beta-hydroxysteroid dehydrogenase 1 (HSD3B1) is responsible for the formation of progesterone from pregnenolone and aromatase (CYP19A1) for the production of estradiol from androgen. According to Liu *et al.* (2016), methoxychlor and its metabolite hydroxychlor (HPTE) may disrupt the activities of these 2 enzymes. Liu *et al.* (2016) investigated the effects of methoxychlor and HPTE on steroid production in human placental JEG-3 cells and on HSD3B1 and CYP19A1 activities. Methoxychlor and HPTE inhibited progesterone and estradiol production in JEG-3 cells. Methoxychlor and HPTE were potent HSD3B1 inhibitors with the half maximal inhibitory concentration (IC50) values of 2.339 +/- 0.096 µmol/L (808.476 +/- 33.182 µg/L) and 1.918 +/- 0.078 µmol/L (609.138 +/- 31.759 µg/L), respectively. Methoxychlor had no inhibition on CYP19A1 at 100 µmol/L (34.565 mg/L), while HPTE was a weak inhibitor with IC50 of 97.16 +/- 0.10 µmol/L (30857 +/- 31.759 µg/L). When pregnenolone was used to determine the inhibitory mode, methoxychlor and HPTE were found to be competitive inhibitors of HSD3B1. When cofactor NAD(+) was used, methoxychlor and HPTE were the noncompetitive inhibitors of HSD3B1. When testosterone was used, HPTE was a mixed inhibitor of CYP19A1. The authors concluded that methoxychlor and its metabolite HPTE are potent inhibitors of human HSD3B1, and HPTE is a weak CYP19A1 inhibitor.

143. According to US EPA (2000), an OSHA PEL of 15 mg/m^3 has been derived for methoxychlor (Occupational Safety and Health Administration's permissible exposure limit expressed as a time weighted average; the concentration of a substance to which most workers can be exposed without adverse effect averaged over a normal 8-h workday or a 40-h workweek).

144. A minimal risk level is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. A minimal risk level of 0.005 mg/kg/day has been derived for intermediate-duration oral exposure (15–364 days) to methoxychlor.

This minimal risk level is based on a Lowest Observed Adverse Effect Level (LOAEL) of 5 mg/kg/day from gestation day 14 to postpartum day 42 for accelerated onset of puberty (i.e., precocious vaginal opening) in immature female rats exposed to methoxychlor in utero, during lactation, and after weaning. Precocious vaginal opening was evident (statistically significant) in all methoxychlor-treated groups (vaginal opening occurred on postnatal days 37.4, 35.2, 30.8, and 33.4, respectively, for groups 0, 5, 50, and 150 mg/kg/day). The LOAEL was divided by an uncertainty factor of 1,000 (10 for variation in sensitivity among humans, 10 for extrapolation of animal data to humans, and 10 for extrapolation from a LOAEL to a No Observed Adverse Effect Level (NOAEL)) (ATSDR, 2002).

145. In general, the reference dose (RfD) is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime (ATSDR, 2002). An RfD of 0.005 mg/kg/day (for chronic oral exposure) was derived (in 1990) by the US EPA based on the NOEL of 5.01 mg/kg/day for maternal toxicity (observed as excessive loss of litters) in rabbits dosed during gestational days 7-19 (IRIS 2003; Kincaid Enterprises 1986 as cited in ATSDR, 2002). However, these values were based on an incomplete database, as several international regulators (PMRA, 2001; US EPA, 1989; and Cal-DPR, 1986) noted that deficiencies in the available data precluded a comprehensive risk assessment. Accordingly, the NOAEL was divided by an uncertainty factor of 1,000 (100 for the inter-and intraspecies differences and 10 for the poor quality of the critical study and for the incompleteness of the database on chronic toxicity).

146. OEHHA (2005) calculated a child-specific reference dose (chRD) of 2.0 x 10^{-5} mg/kg/day using an uncertainty factor of 1000 (10 each for interspecies variability, human variability, and extrapolation from LOAEL to NOAEL). The chRD for the non-carcinogenic effects of methoxychlor is based on two studies. One is a 1995 study by vom Saal *et al.*, which demonstrates increased urine marking in male mice, an index of territorial behavior, subsequent to prenatal exposure. The other is a 1999 study by Welshons *et al.*, which shows an increase in adult prostate size in mice following prenatal exposure. However, the study of Welshons *et al.* (1999) presents a certain number of limitations such as: a small sample size (5-6 pregnant dams), only one male per litter examined, no histopathology performed, lack of a dose-response. The LOAEL identified from these studies is 0.02 mg/kg/day. A tolerable daily intake (TDI) is an estimate of the amount of a substance in air, food or drinking water that can be taken daily over a lifetime without appreciable health risk. A TDI value of 0.005 mg/kg/day for methoxychlor was derived by WHO (2004) based on the NOEL of 5.01 mg/kg/day for maternal toxicity in rabbits. Allocation of 10% of the TDI to drinking-water results in a guideline value of 20 µg/L (WHO, 2004).

2.4.2.1 Epidemiological studies

147. An epidemiological study of men in Minnesota and Iowa suggested an association between leukemia and farming (Brown et al., 1990). In this study, there were positive correlations with odds ratios (ORs) of 2.2 for methoxychlor. This represented 11 cases of leukemia among 578 farmers with occupational exposure to methoxychlor versus 16 cases out of 1,245 controls with no known exposure. The statistically significant OR of 2.2 for methoxychlor incorporated adjustments for vital status, age, state, tobacco use, family history of lymphopoietic cancer, high-risk occupations and high risk exposures. However, firm conclusions as to a relationship between methoxychlor and leukemia are not possible on the basis of this single study with multiple exposures and risk factors.

148. Mills and Yang (2006) evaluated breast cancer incidence rates from the California (USA) Cancer Registry (CCR) that includes state-wide and county-and race/ethnic-specific data from 1988–1999. The authors used regression analysis to evaluate breast cancer incidence as a function of organochloride use after controlling for known risk factors for breast cancer including age, fertility, and socioeconomic status. The pesticide use data were evaluated for the years 1970–1988 at the county level. The study reported a statistically significant 16–18% elevation in risk of breast cancer among Latinas in the highest exposure quartiles for methoxychlor. This report also stated that carcinogenicity testing has been largely negative although one strain of mice was found to have increased incidence of testicular tumors (National Library of Medicine, 1995 as cited by Mills and Yang, 2006). However, since these studies only imply an association and do not prove causation, based on the weight of evidence there is insufficient evidence to support the carcinogenicity of methoxychlor in experimental animals or humans.

149. An epidemiology study of adults from a rural village (Cidade dos Meninos) in Rio de Janeiro (Southeast Brazil) near a closed pesticide factory with abandoned stocks found differential effects on males and females associated with OCPs exposure (Freire *et al*., 2013). A cross-sectional study was carried out in 303 men and 305 women (mean age of 39 years old) from November 2003 to March 2004. Intravenous blood samples were collected for analysis of serum concentrations of each OCPs and levels of thyroid hormones (total triiodothyronine (T3) and free thyroxine (T4), thyroid-stimulating hormone (TSH), anti-thyroperoxidase (TPOAb) and anti-thyroglobulin (TgAb)). The LOD was 0.02 ng/mL for methoxychlor. Higher concentrations of methoxychlor exposure were significantly associated with increased total T3 levels in women. Men with detected methoxychlor had a statistically significant 2-fold increased of risk estimate (OR 2.19) for presence of TPOAb antibodies an indicator of thyroid injury or inflammation in men.

2.4.2.2 Neurotoxicity

150. Animal studies suggest that exposure to large amounts of methoxychlor can produce neurological effects, such as apprehension, nervousness, increased salivation, decreased locomotor activity, tremors, convulsions, and death. Methoxychlor undergoes demethylation to form phenolic derivatives, with dechlorination and dehydrochlorination reactions occurring to a lesser extent. (ATSDR 2002). In people with compromised liver function, neurological signs may occur at lower methoxychlor exposure levels. Methoxychlor has been demonstrated to be a neurotoxicant even in the absence of metabolism. This suggests that it is the parent compound that is neurotoxic, and that neurotoxicity is of concern only when the metabolic capacity for O-demethylation is exceeded. This is supported by the observation that the neurological effects of methoxychlor are similar to those associated with exposure of humans and animals to DDT, a structurally similar chemical that is very slowly metabolized. The mechanism by which DDT, and therefore possibly methoxychlor, produces neurological effects has been proposed to involve the membrane-association of a lipophilic species, which alters ion transport across neural membranes (ATSDR, 2002).

151. The rapid demethylation of methoxychlor decreases its neurotoxicity and leads to a rapid elimination from the body (Lehman, 1952 as cited in ATSDR, 2002), making it significantly less toxic than its structural analogue, DDT. However, this detoxification pathway also is thought to act as an activation pathway for reproductive and developmental effects.

2.4.2.3 Endocrine disruption

152. According to US EPA (2004), methoxychlor has been discussed extensively in the public literature in connection with its effects on endocrine-mediated processes and disruption of the hypothalamic-pituitary-gonadal axis. Methoxychlor can be metabolized *in vivo* into two demethylated compounds (2,2-bis-(p-hydroxyphenyl)- 1,1,1-trichloroethane (HPTE) and 2,2-bis-(p-hydroxyphenyl)- 1,1,1-dichloroethane (HPDE)) and two O-ring methylated compounds. These metabolites interact with the estrogen and androgen receptors. Exposure to methoxychlor, therefore, may impair reproductive function through actions on estrogen and androgen receptors (Chen, 2014). For example, decreased serum progesterone levels may result from the estrogenic effects of methoxychlor on the ovaries that cause decreased follicular and corpus luteum development. The effects on the ovaries may be caused directly by methoxychlor metabolites or may result from effects on the pituitary and hypothalamus, which alter the release of regulatory hormones that affect the reproductive and accessory sex glands (ATSDR, 2002).

153. One common mechanism by which endocrine disrupting chemicals, produce lasting reproductive tract defects is through permanent alteration of developmental gene expression. Fei *et al.* (2005) found that methoxychlor treatment (1mg/day) of mice inhibited the expression of Hoxa10, a gene necessary for uterine development and function. This suppression in Hoxa10 expression was immediate when mice were exposed neonatally (for 14 days to 2 mg/kg/day) and a permanent generalized decrease in expression persisted in these mice when adult.

154. Zama and Uzumcu (2009) reported on studies looking at effects on rats during gestation and early stages post-birth. Based on doses of methoxychlor at 20 µg/kg/day, and 100 mg/kg/day between embryonic day 19 and postnatal day 7, the authors concluded that, even at the lower dose, methoxychlor exposure during fetal development caused changes to the genetic code resulting in impaired function of ovaries in newborns. In particularly, this affected the function of receptors (ERβ promoter regions) responsible for production and processing of oestrogen.

155. Aoyama *et al.* (2012) conducted a two-generation reproduction toxicity study in rats according to OECD TG 416. Both sexes of SPF Sprague Dawley rats were exposed to methoxychlor in their diet (0, 10, 500 and 1500 ppm) for two successive generations. In females, the following reproductive effects were observed at 500 and 1500 pm: prolonged estrous cycle, reduced fertility, decreased numbers of implantation sites and newborns, decreased ovary weights and/or increased incidences of cystic ovary. Estrogenic effects were demonstrated by an increase in uterine weights of weanlings at 500 and 1500 pm. Adverse effects on male reproduction were limited. The authors concluded that the NOAEL was a dose level of 10 ppm (at least 0.600 mg/kg per day for males and 0.866 mg/kg per day for females).

2.4.2.4 Interaction with other chemicals

156. Nishino *et al.* (2014) demonstrated the combined effects of three well-known environmental immunotoxic chemicals - methoxychlor (MXC), an organochlorine compound; parathion (PARA), an organophosphate compound; and piperonyl butoxide (PBO), an agricultural insecticide synergist - by using a short-term oral exposure method. Seven-week-old Balb/cAnN mice received daily oral exposure to either one or two of the environmental immunotoxic chemicals for 5 consecutive days. On Day 2, all mice in each group were immunized with sheep red blood cells (SRBC), and their SRBC-specific IgM responses were analyzed by using an enzyme-linked immunosorbent assay and plaque-forming cell assay. T- and B-cell counts in the mouse spleens were also assessed via surface antigen expression. Mice that received MXC + PARA and PBO + MXC treatment showed marked decreases in SRBC-specific IgM production and T- and B-cell counts compared with those in mice that received vehicle control or the corresponding individual test substance. This suggests that simultaneous exposure to multiple environmental chemicals increases the immunotoxic effects of the chemicals compared to individual exposure.

157. Embryonic exposure to estrogens and estrogenic pollutants is known to demasculinize sexual behaviour in adult male Japanese quail. Halldin *et al.* (2005) administered methoxychlor to quail eggs before sexual differentiation of the brain at a dose of 150 µg/g egg and then studied sexual behavior and other reproductive variables in adult males. In a second experiment the authors administered the same dose of methoxychlor together with 10 µg/g egg of the commercial polychlorinated biphenyl (PCB) mixture Clophen A50 (CA50) and also CA50 alone. Neither methoxychlor nor CA50 had any significant effects by themselves, but when they were administered together a significant reduction in male sexual behaviour was observed, specifically in a significant reduction ($p=0.0010$) in the number of positive tests for mount attempt and cloacal contact movement. According to the authors, it seems likely that induction of biotransformation enzymes in the embryos by CA50 resulted in increased conversion of methoxychlor to the more estrogenic metabolite 2,2-*bis*(*p*-hydroxyphenyl)-1,1,1-trichloroethane (HPTE).

158. In mice receiving 25 mg/kg/day methoxychlor by gavage in an olive oil suspension along with 12 mg/kg/day bromfenvinphos for 6 weeks, inflammatory infiltrations of the liver were larger and denser than observed in animals receiving bromfenvinphos alone (Zaleska-Freljan *et al.*, 1983 as cited in ATSDR, 2002). Small changes were observed in the kidneys at similar frequencies and severities in both treatment groups. Although it was not investigated in this study, methoxychlor usually does not produce effects of the liver by itself at such low doses. Thus, the results of this study suggest that there may be an interaction between methoxychlor and bromfenvinphos in producing hepatic effects (ATSDR, 2002).

159. Ziem (1982) reported the development of fatigue and bruising of a 49-year-old male several weeks after accidental inhalation of dust of a pesticide mixture containing methoxychlor and captan, followed by aplastic anemia after 2 months which proved fatal at 6 months. The exposure level was not reported.

160. The joint toxic actions of binary mixtures of methoxychlor and other pesticides (including organophosphates and other chlorinated hydrocarbons) on acute lethality were examined in mice (Keplinger and Deichmann, 1967 as cited in ATSDR (2002)). After determining oral LD50 values for the individual compounds, binary mixtures (with components at equitoxic doses based on LD50 values) were administered to fasted mice in corn oil via gavage at the same dose ranges as the individual compounds. Based on the assumption of joint additive action, an expected LD50 value was calculated for each mixture and compared with the observed LD50. The authors took under consideration biological variation and other factors that influence results with experimental animals, and choose ratios of ≤0.57 to be indicative of a significantly reduced degree of toxicity, or antagonism, and ratios of ≥1.75 as indicative of definitely more than additive effect, possibly a synergy. The ratio of expected:observed LD50 values for the methoxychlor/DDT mixture (0.66) indicated a less than additive action (i.e., mutual protection). Ratios for the methoxychlor/aldrin (0.81), methoxychlor/diazinon (0.82), methoxychlor/malathion (0.84), methoxychlor/toxaphene (0.92), and methoxychlor/aramite (1.25) mixtures were close to one, indicating joint additive action. Ratios for the methoxychlor/parathion (1.51), methoxychlor/delnav (1.96), methoxychlor/dieldrin (2.06), and methoxychlor/chlordane (2.26) mixtures were suggestive of greater than additive joint action (i.e., potentiation or synergism).

161. When methoxychlor was administered orally to rats previously treated with carbon tetrachloride, DDT-like neurological symptoms were observed (Lehman, 1952 as cited in ATSDR, 2002). In addition, methoxychlor was found to accumulate in the fat and liver in amounts approximately 15–19 times the levels observed in control animals. Carbon tetrachloride is known to inactivate certain hepatic enzymes (CYPs or cytochrome P450s) which metabolize xenobiotics, thereby increasing their retention. These data suggest that carbon tetrachloride and other chemicals which inhibit the metabolism of methoxychlor may increase the risk of neurotoxicity (ATSDR, 2002).

2.4.2.5 Summary of adverse effects on human health

162. At this time, there is insufficient evidence to support the carcinogenicity of methoxychlor in experimental animals or humans. Epidemiological studies, cited above, have implied an association but have not proven causation with respect to the carcinogenicity potential of methoxychlor. Thus, methoxychlor is not recognised as a carcinogen even if epidemiological retrospective studies suggest that it increases the risk of leukemia in farmers, the risk of breast cancer and it might induce ovarian cancer cell growth. The genotoxic and mutagenic potential of methoxychlor appears to be negligible. Animal and *in vitro* data strongly suggest that methoxychlor may adversely affect the development, histopathology, and function of the human reproductive system. Reprotoxic effects may be based on estrogenic mimicking effects of methoxychlor and its metabolites. Indeed, methoxychlor and its metabolites have estrogen-like activity with several metabolites having proestrogen activity. Methoxychlor has been demonstrated to be a neurotoxicant at high doses only. The simultaneous exposure to multiple environmental chemicals increases the immunotoxic effects, the endocrine disrupting effects, the hepatic effects, the risk of neurotoxicity and the additive action of methoxychlor compared to individual exposure when mixed with certain other pesticides.

3. Synthesis of information

163. Methoxychlor is an organochlorine pesticide which has been used as a replacement for DDT. It has been restricted/banned in several countries for over 15 years. In response to the call for information (Annex E information submission (2019)), no Parties have indicated current use of methoxychlor. However, a literature search made for the

purpose of drafting the risk profile suggests that ongoing, or recent use of methoxychlor may still be occurring in certain regions. In 1975, three U.S. companies produced 2500 tonnes of methoxychlor. The production decreased to 1361 tonnes in 1982. After 1992, production of methoxychlor in the U.S. was significantly reduced until its ban in 2000. No information on the current level of production or use of methoxychlor is publicly available. Methoxychlor does not occur naturally in the environment. It is released to the environment mainly as a result of its application to crops and livestock as a pesticide. Smaller amounts of methoxychlor may be released to the environment during its production, formulation, storage, shipment and disposal. Based on the maximum 8,000 t/y of methoxychlor produced worldwide, atmospheric release during production may be estimated to be 800 kg/y at the maximum.

164. Methoxychlor is highly hydrophobic. Based on its physicochemical properties, methoxychlor will most likely concentrate in the sediment and biota. Methoxychlor is expected to be immobile in soil. However, soil particles that contain methoxychlor can be blown by the wind or be carried by rainwater or melted snow into rivers or lakes. Based upon its relatively low vapour pressure value, methoxychlor is not expected to be volatile.

165. Modelling data (BIOWIN 2, 3 and 6) indicate that methoxychlor is not expected to be aerobically biodegradable and hence potentially persistent. Methoxychlor hydrolysis is considered to be negligible. Although photolysis rates of methoxychlor seem moderate, photolysis is not expected to contribute to the degradation significantly as photolysis only takes place in the top layers of the water column. The degradation half-life of methoxychlor in water (208 days (half-life > 2 months) suggests that the substance is very persistent in water. This information is used as supporting information in the persistence assessment. Measured data in surface waterbodies from Europe and Canada indicate that methoxychlor continued to be detected in European and Canadian surface waters years after it has been phased out, thus supporting that the substance is very persistent in water. Monitoring data from Arctic Lakes and surface seawater in the Arctic Ocean and Chukchi Sea in 2016-2017 (concentrations <MDL-0.38 ng/L (mean 0.15±0.11 ng/L)) support that the substance is persistent in the surface water and marine water compartments. The degradation half-life of methoxychlor in the sediment compartment (206±186.8 days for lake under aerobic conditions (half-life > 6 months)) provides evidence that the substance is very persistent in sediment. The persistence of methoxychlor in sediments is confirmed by the measured concentrations found in sediment samples from Portugal, Australia and Canada several years after methoxychlor was banned in these countries.

166. Methoxychlor is a lipophilic substance with an experimental log K_{ow} value of 5.08. The BAF value (9001 L/kg) predicted by the Arnot-Gobas method (upper trophic) suggest a high bioaccumulation potential of methoxychlor in aquatic organisms (BAF > 5,000). In two laboratory BCF studies (including an OECD TG 305 ring test) with fathead minnow and rainbow trout, BCF values are 8,300 (steady-state BCF) and between 2,358 and 5,207 (kinetic BCFs). Based on experimental studies in fish species methoxychlor has a high bioaccumulation potential (BCF >5,000). In addition, supporting information such as a BCF value of 12,000 in a bivalve *Mytilus edulis* and an average BCF of 6,945 (range of 5,000 to 8,570) in the snails *Physa integra* indicate that methoxychlor has a high bioaccumulation potential in aquatic organisms.

167. Methoxychlor is expected to exist in both the vapour and particulate phases (bound to particulate matter) and, to a small degree, the vapour phase in the atmosphere. Despite modelling predictions indicating a low LRTP, transport of methoxychlor to remote areas (Arctic and Antarctica) is taking place based on monitoring data. Presence of methoxychlor in remote areas can be explained by atmospheric transport in the gas phase or on particles during dry periods and during periods of lower photolytic activity. Furthermore, considering the high persistence of the substance in water (half-life of 208 days) and methoxychlor, endosulfan and pentachloroanisole collective concentrations in the range of 0.017-0.023 ng/L in an Arctic lake and measured level in Arctic Ocean and sea (concentrations in the range <MDL-0.38 ng/L (mean 0.15±0.11 ng/L), long-range transport potential through water and ocean currents is also possible. In the absence of significant local or regional pesticide sources, findings in environmental and biota samples from the Arctic and Antarctica are due to the long-range transport of methoxychlor.

168. Methoxychlor is found ubiquitously spread throughout the environment and in biota globally. It has been detected in numerous environmental matrices worldwide including in the Arctic (in air, snow, ice core, lake waters, Arctic Ocean and sea, in plants and in biota samples (terrestrial, avian and marine)) and in the Antarctica (in marine biota samples and in milk of elephant seals). Methoxychlor was one of the most abundant insecticide in the atmosphere, it was found in the Arctic air at higher concentration than the POP substance endrin. Environmental trend data are not available and monitoring data are insufficient to conclude on a trend. However, over the last 15 years, it was observed that the concentrations of methoxychlor in Southern elephant seals in Antarctica have increased. No data are available on trends of methoxychlor in humans.

169. Humans are exposed to methoxychlor mainly through intake of contaminated food and drinking water but also through the indoor environment via exposure to dust and aerosols in air. Small children may play close to the ground and are therefore more likely than adults to come in contact with dirt and dust. Children also may intentionally or unintentionally ingest soil that contains low levels of methoxychlor. Methoxychlor has been detected in human serum, adipose tissues, umbilical cord blood and human breast milk. Children can be exposed to methoxychlor *in utero* via the placenta and after birth via lactation and infant formula.

170. Methoxychlor is highly toxic to aquatic invertebrates and fish. The freshwater arthropods are the most sensitive species with a HC5 is 0.14 µg/L (95% confidence). Methoxychlor is suspected to have endocrine disruptive effects in fish, amphibian, and sea urchin fertility, growth, and development. The acute toxicity to mammals and birds is low. Animal studies indicate that high doses of methoxychlor are capable of causing neurological injury (tremors, convulsions), but most studies indicate that the reproductive system is the most sensitive target for methoxychlor. The resultant types of reproductive effects are indicative of interference with the normal actions of estrogen or androgen. In addition, studies in mice indicate methoxychlor exposure-induced immune dysfunction. Furthermore, observations in rats indicate that methoxychlor has the potential to promote the epigenetic transgenerational inheritance of disease and associated sperm epimutations.

171. In humans, methoxychlor is not recognised as a carcinogen even if studies suggest that it increases the risk of leukemia in farmers, the risk of breast cancer and it might induce ovarian cancer cell growth. The genotoxic and mutagenic potential of methoxychlor appears to be negligible. Animal and *in vitro* data strongly suggest that methoxychlor may adversely affect the development, histopathology, and function of the human reproductive system. Reprotoxic effects may be based on estrogenic mimicking effects of methoxychlor and its metabolites. Indeed, methoxychlor and its metabolites have estrogen-like activity with several metabolites having proestrogen activity. Methoxychlor has been demonstrated to be a neurotoxicant. The combined exposure of methoxychlor with other substances increases the immunotoxic effects, the endocrine disrupting effects, the hepatic effects, the risk of neurotoxicity and the additive action of methoxychlor compared to individual exposure. A TDI value of 0.005 mg/kg/day for methoxychlor was derived by WHO (2004) based on the NOEL of 5.01 mg/kg/day for maternal toxicity in rabbits. Allocation of 10% of the TDI to drinking-water results in a guideline value of 20 µg/L.

172. The level of methoxychlor found in the drinking water from Slovakia exceeded the EU quality standard indicating the drinking water being unfit for human consumption. Comparison of measured levels of methoxychlor in the environment or in human food with (eco)toxicity data indicate that some of the concentrations found in human food and surface water were in excess compared to RfD or PNEC values derived by the authors. This suggests a potential risk for human populations and for aquatic organisms. However, it is worth noting that the POP properties of methoxychlor lead to an increased uncertainty in the estimation of risk to human health and the environment when applying quantitative risk assessment methodologies. For POP substances a “safe” concentration in the environment cannot be established using the methods currently available with sufficient reliability for an acceptable risk to be determined in a quantitative way. Indeed, experience with POP substances has shown that they can give rise to specific concerns that may arise due to their potential to accumulate in parts of the environment and that the effects of such accumulation are unpredictable in the long-term; such accumulation is in practice difficult to reverse as cessation of emission will not necessarily result in a reduction in substance concentration.

173. Furthermore, POP substances may have the potential to contaminate remote areas that should be protected from further contamination by hazardous substances resulting from human activity because the intrinsic value of pristine environments should be protected. These specific concerns occur particularly with substances that can be shown to persist for long periods and to bioaccumulate in biota and which can give rise to toxic effects after a longer time and over a greater spatial scale than substances without these properties. These effects may be difficult to detect at an early stage because of long-term exposures at normally low concentration levels, and long life-cycles of species at the top of the food chain. Thus, concentrations of methoxychlor in biota from Arctic and Antarctica and in humans indicate a potential risk for adverse effects in wildlife and in humans. Methoxychlor was also found: in the eggs of a critically endangered sea turtle, in the fat tissues of crocodiles living in a biodiversity hotspot in South Africa and in the air of two national parks in Southeast Brazilian mountains where hundreds of endangered species and many endemic species live thus suggesting a potential concern for these species. Methoxychlor was also suspected of decreasing male fertility of Florida panther (*Felis concolor coryi*), an endangered species.

174. Based on its inherent properties, methoxychlor as a result of its long-range environmental transport is likely to lead to significant adverse environmental effects and may lead to significant adverse human health effects, such that global action is warranted.

4. Concluding statement

175. Methoxychlor does not occur naturally in the environment. It is released to the environment mainly as a result of its application to crops and livestock as a pesticide. Smaller amounts of methoxychlor may be released to the environment during its production, formulation, storage, shipment and disposal. Methoxychlor is persistent, bioaccumulative, toxic to aquatic organisms and mammals (including humans) and it has the potential to undergo long-range environmental transport, making emissions of this substance a transboundary pollution problem including in remote areas. Globally, the occurrence and distribution of methoxychlor is shown for humans, wildlife and the environment. Detections include measurements in the Arctic and Antarctic.

176. Methoxychlor is found ubiquitously spread throughout the environment and in biota globally. It has been detected in numerous environmental matrixes worldwide including in the Arctic (in air, snow, ice core, lake waters, Arctic Ocean and sea, in plants and in biota samples (terrestrial, avian and marine)) and in the Antarctica (in marine biota samples and in milk of elephant seals). Methoxychlor has been detected in human: serum, adipose tissue,

umbilical cord blood and breast milk. It was also found in human food at significant levels including in drinking water and groundwater.

177. The concern for adverse effects relates to toxic effects to reproduction, including potential endocrine disrupting property, immune dysfunction, potential for promoting epigenetic transgenerational inheritance of diseases and associated sperm epimutations and neurotoxic effects. Methoxychlor is also toxic to aquatic organisms. Due to its POP properties, concentrations of methoxychlor in biota from Arctic and Antarctica and in humans indicate a potential risk for adverse effects in wildlife and in humans. Methoxychlor was also found: in the eggs of a critically endangered sea turtle, in the fat tissues of crocodiles living in a biodiversity hotspot in South Africa and in the air of two national parks in Southeast Brazilian mountains where hundreds of endangered species and many endemic species live thus suggesting a potential concern for these species. Methoxychlor was also suspected of decreasing male fertility of Florida panther (*Felis concolor coryi*), an endangered species.

178. Methoxychlor has been restricted/banned in several countries for over 15 years. However, the outcome of a literature search suggests that ongoing, or recent use of methoxychlor may still be occurring in certain regions. Since methoxychlor demonstrates persistence and long-range transport, measures taken nationally or regionally are not sufficient to safeguard a high level of protection of the environment and human health, and therefore wider international action is necessary.

179. Based on the persistence, bioaccumulation, toxicity to aquatic organisms and in mammals (including humans) and the widespread occurrence in environmental compartments including at remote regions, it is concluded that the use of methoxychlor is likely, as a result of its long-range environmental transport, to lead to significant adverse human health and environmental effects such that global action is warranted.

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