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Persistent Organic Pollutants Review Committee
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Item 5 (b) (ii) of the provisional agenda*

Technical work: consideration of chemicals proposed for listing in Annexes A, B and/or C to the Convention: methoxychlor

Proposal to list methoxychlor in Annex A to the Stockholm Convention on Persistent Organic Pollutants

Note by the Secretariat

I. Introduction

1. The European Union has submitted a proposal to list methoxychlor in Annex A to the Convention pursuant to paragraph 1 of Article 8 of the Convention (see annex to the present note). The proposal is being circulated as submitted and has not been formally edited. The Secretariat's verification of whether the proposal contains the information specified in Annex D to the Convention is set out in document UNEP/POPS/POPRC.15/INF/6.

II. Proposed action

2. The Committee may wish:

(a) To consider the information provided in the present note;

(b) To decide whether it is satisfied that the proposal fulfils the requirements of Article 8 of and Annex D to the Convention;

(c) To develop and agree on, if it decides that the proposal fulfils the requirements referred to in subparagraph 2 (b) above, a workplan for preparing a draft risk profile pursuant to paragraph 6 of Article 8.

* UNEP/POPS/POPRC.15/1.

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Annex

Proposal to list methoxychlor in Annex A to the Stockholm Convention on Persistent Organic Pollutants

1. Introduction

1. Methoxychlor (CAS No: 72-43-5) is an organochlorine pesticide originally developed as a replacement for DDT (US EPA, 2011). It was first synthesized in 1893 with commercial production in the USA starting in 1948. Methoxychlor has been used as an insecticide combating a wide range of pests including biting flies, houseflies, mosquito larvae, cockroaches, and chiggers. It has commonly been used in both agricultural and veterinary practices, for example for treating field crops, vegetables, fruits, stored grains, livestock, pets, homes, gardens, lakes, and marshes (US Department of Health, 2002). Methoxychlor was also used against the elm bark-beetle vectors of Dutch elm disease. In veterinary practices, methoxychlor was used as an ectoparasiticide.[1]

2. Very few data on the levels of production of methoxychlor are readily available. U.S. production in 1982 was reported to be 3 million lbs/yr (1.36 million kg/yr) but pesticide uses of methoxychlor in the U.S. were suspended in 2000, and all products were expected to have been voluntarily cancelled by 2004 (US Department of Health, 2002). It is reported that the use of methoxychlor as a pesticide has ceased in most countries since the 1990s (OSPAR, 2004). The EU banned production of methoxychlor in 2002, with some Member States having put bans in place prior to this. World Wild Fund for Nature (2005) reported that no producers or importers of methoxychlor existed in Europe and 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). The Australian acceptable daily intakes (ADI) for agriculture and veterinary chemicals used in food producing crops for animals (Australian Government, 2017) provides ADI's for methoxychlor, but also notes that it is no longer actively used in Australia, with use ceasing around 2003.

3. In 2004, it was expected that methoxychlor was still widely used in developing countries (OSPAR, 2004). Data from the CP Sigma database suggested that methoxychlor was in use in Mexico with data available from 2013–2016 (FAO, 2018). However, no further data on the current levels of production or use of methoxychlor are publicly available. It has been noted that the chemical industry has not provided any information on the production volumes of methoxychlor in Europe or elsewhere (OSPAR, 2004).

4. Methoxychlor is included in the Convention for the Protection of the Marine Environment of the North-East Atlantic (OSPAR) List of Chemicals Identified for Priority Action (OSPAR, 2004). Methoxychlor is also listed as a persistent, bioaccumulative, and toxic (PBT) chemical under the Environment Protection Agency Toxics Release Inventory (TRI) program (US EPA, 1989). The European Chemicals Agency (ECHA) indicate that methoxychlor is likely to meet the REACH Annex III criteria,[2] due to its hazardous properties (specifically identified as a suspected bioaccumulative, carcinogen, hazardous to the aquatic environment, suspected mutagen, suspected persistent in the environment, and suspected toxic for reproduction).

5. This dossier provides an assessment of methoxychlor based on the information required under paragraphs 1 and 2 of Annex D to the Stockholm Convention covering the criteria which define the characteristics of a Persistent Organic Pollutant (POP) substance under the Stockholm Convention. It is mainly based upon the following data sources:

(a) A screening fact sheet prepared for the European Commission by Bio Intelligence Service and INERIS (2017);

(b) A report by the OSPAR Commission on methoxychlor as part of the Hazardous Substances Series (2004 Update);

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

[2] REACH Annex III criteria are the following: (i) substances predicted (i.e. by the use of QSARs or other evidence) to likely meet criteria for carcinogenic, mutagenic or toxic to reproduction (CMR) category 1A or 1B or Annex XIII criteria (i.e. PBT and vPvB); (ii) substances with dispersive or diffuse use(s) and predicted to likely meet criteria for any health or environmental hazard classes or differentiations under Classification, Labelling and Packaging (CLP) Regulation. See https://echa.europa.eu/information-on-chemicals/annex-iii-inventory/-/dislist/details/AIII-100.000.709.

(c) A fact sheet on methxychlor by the US Environment Protection Agency (US EPA, created in April 1992, updated in January 2011);

(d) A toxicological profile for methoxychlor produced by the U.S. Department of Health and Human Services Public Health Service Agency for Toxic Substances and Disease Registry, US Deparment of Heath (2002);

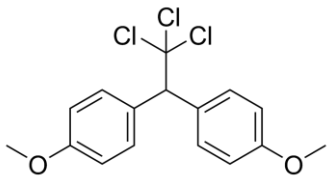
(e) Additional literature review of relevant sources (including TOXNET, Google Scholar, Science Direct and Scopus).

2. Identification of the chemical

2.1 Names and registry numbers

Common name IUPAC	Methoxychlor 1,1'-(2,2,2-Trichloroethylidene)bis(4-methoxybenzene)
CAS registry number EINECs number	72-43-5 200-779-9
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)
Abbreviations	None

2.2 Structure

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

3. Persistence

6. As discussed in the Bio Intelligence Service and INERIS (2017) factsheet, a number of experimental studies have investigated the rates and mechanisms of degradation for methoxychlor in different environmental media.

7. Using the (USEPA) EPI Suite Probability of Rapid Biodegradation (BIOWIN v4) model, a Biowin 3 ‘ultimate survey’ value of 1.51 is derived. According to ECHA (2017) guidance on PBT assessment, a value of <2.5 can be indicative of P or vP potential. The Biowin 6 ‘MITI Non-Linear Model’ gives a probability value of 0.0063 for methoxychlor, indicating a low potential for biodegradation, according to the ECHA (2017) guidance.

8. The physico-chemical properties of methoxychlor suggest that it will display a hydrophobic behavior in the natural environment. Methoxychlor does not dissolve readily in water, with a water solubility of 0.3 mg/L, derived using the EPI Suite WSKOW v 1.4.1 model. Chen (2014) reports, based on field and laboratory studies that methoxychlor is insoluble in water. A modelled Log K_{OW} value of 5.67 for methoxychlor, is obtained using the EPI Suite KOWWIN v. 1.67 model. It is suggested, based on these properties, that methoxychlor will therefore most likely concentrate in the sediment and biota within aquatic environments, but can also be found within the water column adsorbed to organic matter in suspended sediment (Wolfe et al., 1977).

9. The EPI Suite KOCWIN model (MCI method) predicts a soil adsorption coefficient (K_{OC}) value of 26,890 for methoxychlor. Measured K_{OC} values in sediment ranging from 23,000 to 93,000, reported by Karickhoff et al. (1979), further indicate that methoxychlor is expected to adsorb to suspended solids and sediment. Muir and Yarechewski (1984) observed that methoxychlor partitioned rapidly into sediment following addition to sediment-water systems. Furthermore, water and soil sampling studies in Africa (Manirakiza et al., 2003) and India (Singh, 2001) demonstrate that DDT-related pesticides (including methoxychlor) adsorb strongly on soil, resulting in higher concentrations in soil relative to water. No correlations between water and soil concentrations were observed in these studies for DDT-related pesticides (including methoxychlor), unlike other organochlorine pesticides (OCPs) such as hexachlorocyclohexanes and endosulfans. Mass balances in pond, river and wet sand (25% moisture) systems spiked with methoxychlor indicate that 98.6%, 97.0%, and 92.1%, respectively, of all methoxychlor was retained in the sediment (Muir et al., 1993).

10. An estimated Henry's Law constant for methoxychlor of 2.03 x 10^{-7} atm.m^3/mol at 25°C has been derived (Altschuh et al., 1999). A modelled value for the Henry's Law constant for methoxychlor, of 9.75 x 10^{-8} atm.m^3/mol at 25°C, is derived using the EPI Suite HENRYWIN v. 3.20 model. The relatively low value would therefore suggest that methoxychlor can expected to be essentially non-volatile from water (Lyman, Reehl and Rosenblatt, 1990). The EPI Suite model predicts, based on the derived Henry's Law constant, the half-life for volatilisation of methoxychlor from model river and lake waters will be 223.5 days and 2445 days respectively, further suggesting that volatilisation from the water surface is not a significant loss process for methoxychlor in the aquatic environment.

11. In water, methoxychlor can be potentially degraded by abiotic (chemical, photochemical) and biological processes. While degradation of methoxychlor in water is expected to be slow, reported estimates in studies using natural water as test medium are highly variable, dependent on the specific conditions applied in the studies. For example, EXTOXNET (1996) report that the half-life of methoxychlor in distilled water is 37 to 46 days but in some river waters the half-life may be as rapid as 2 to 5 hours.

12. Methoxychlor is reported to undergo a spontaneous elimination reaction in aqueous solution to yield dehydrochlorinated products, including 1,1-bis(4-methoxyphenyl)-2,2-dichloroethylene (methoxy-DDE). The half-life for the degradation of methoxychlor by this process was estimated to be approximately one year.[3]

13. It is suggested that methoxychlor undergoes negligible direct photolysis because it does not absorb light in the solar spectrum, but that experimental evidence suggests it is susceptible to dissolved organic matter sensitized indirect photolysis (Remucal, 2014). The half-lives for photodecomposition of methoxychlor (40 ppb) under sunlight in distilled water (pH 6.3), Suwannee river water (pH 4.7), Tombigbee river water (pH 7.6), Alabama river water (pH 7.7), and 20 ppm “humic acid” in distilled water (pH 5.2) were 300, 2.2, 5.4, 2.9, and 7.3 hours, respectively, and there was no decomposition in 2 hours for Withlacoochee river water (pH 8.2) and South Georgia stream water (pH 7.2) (Sundstrom and Ruzo, 1978).

14. Zepp et al. (1976) developed a procedure for computing the direct photolysis of pesticides in the aquatic environment, using this to investigate the light-induced degradation of methoxychlor in both distilled and natural water samples. The photolysis rate of methoxychlor in natural waters was found to be much more rapid (2 to 5 hours) than that in distilled water (4.5 months), suggesting that photochemical processes other than direct photolysis can cause more rapid degradation of methoxychlor in some natural aquatic environments. In a review by Remucal (2014), the study by Zepp et al. (1976) was the only study identified providing a quantitative assessment of the

[3] 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.

photochemical degradation of methoxychlor in surface waters. 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 (Zepp et al., 1976). It is noted, that this study provides indication of degradation in specific conditions under influence of sunlight. However, in the environment the fast attenuation of light intensity in the water column takes place and therefore photodegradation in real water bodies cannot be considered as relevant degradation pathway in the overall mass balance.

15. The effect of hydrolysis on the persistence of methoxychlor under environmentally relevant conditions is expected to be negligible (Wolfe et al., 1977; Park et al., 1982; OSPAR, 2004). Wolfe et al. (1977) investigated the hydrolytic degradation pathways in water at pH's 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. 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 (9) was much longer (2100 days). It is suggested that, although methoxychlor is shown to undergo hydrolytic degradation by two competing pathways at pH's common to the aquatic environment (pH 6–9), the dehydrochlorination pathway is slow and hydrolysis predominates (Wolfe et al., 1977). In a review by Katagi, (2002) it is indicated the hydrolysis half-lives of methoxychlor in distilled water vary considerably with pH values, reporting half-life values at 27°C of 1 year (pH 7), 5.5 years (pH 9), 0.21 days (pH 13).

16. Menzie (1978) reported a chemical decomposition of methoxychlor in water results in a half-life at pH 5–9 and 27°C of 100 days. Details of the precise water conditions were not provided for these values.

17. Paris and Rogers (1986) investigated the biotransformation of methoxychlor in natural water samples taken from four lake and pond sites near Athens, GA, USA. The authors investigated the effect of preincubation of environmental waters amended with inorganic nutrients (nitrogen, phosphorus, and traces of iron and magnesium) on the kinetics of the microbial transformation. Both portions were incubated 12 h overnight at 22°C to yield an untreated and an enhanced bacterial suspension. The pH values of the solutions tested were not disclosed. The derived half-lives for the microbial transformation of methoxychlor, based on the reported first-order rate constants, were 4.8 to 28.9 days in the 'unamended' samples and 2.6 to 4.8 days in the 'nutrient-amended' samples. The authors reported that, although the preincubation of environmental waters with inorganic nutrients in batch culture led to an increase in the rate of transformation when compared with untreated waters, no differences were observed for second-order rate constants derived from these experiments. The authors attributed the increase in transformation rate because of a corresponding proportionate increase in the number of transformer microorganisms in amended samples. Because of the testing conditions, this study did not intend to measure realistic degradation half-lives in the environment.

18. Degradation rates of methoxychlor in water, sediments and soils 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. A more detailed explanation of the degradation process(es) of methoxychlor in soils and sediments is provided below.

19. Methoxychlor has been shown to undergo biodegradation by microbial action in sediments. A number of studies have investigated the biological degradation of methoxychlor in natural sediments under various different redox conditions. For example, Satsuma et al. (2012) identified a strain of *Bradyrhizobium* sp. that mediates oxidative transformation of methoxychlor, including o-demethylation and dechlorination in river sediment. The authors also report that various microaerobic-facultative anaerobic bacteria rapidly mediate reductive dechlorination of methoxychlor under weak, slightly reductive conditions. The authors suggest that methoxychlor can be transformed to dechlorinated methoxychlor relatively easily in a submerged, surface water environment. Satsuma et al. (2013) also report that single culture bacterial assays with *Bradhyrhizobium elkani* have shown that degradation through microbial mediation is possible.

20. Bourguignon (2014) investigated the ability of the actinobacterium Streptomyces bacteria to biodegrade methoxychlor in a sediment culture medium incubated at 30°C and pH 7. At initial methoxychlor concentrations of 16.60 and 8.33 mg kg-1, the maximum removal percentages were shown to be 40% and 76% respectively after 28 days of incubation. Based on the degradation products identified, the authors suggested that methoxychlor is dominantly degraded by dechlorination, dehydrogenation and CN-replacement.

21. 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 pesticides in sterile and nonsterile samples of water and sediment taken directly from the field. First-order decay rates in sterile and nonsterile flasks were compared in the presence and absence of sediment to determine if sediment and/or biotic factors were significant in controlling the observed decreases in parent compound concentrations. The derived methoxychlor half-lives in water were 208 and 8,830 days for non-sterile and sterile conditions respectively. The derived methoxychlor half-lives in sediment were 12.2 and 45.2 days for non-sterile and sterile conditions respectively. The results of this study indicate significantly ($p \leq 0.01$) more degradation in the presence of nonsterile sediment than in the presence of sterile sediment and that methoxychlor biodegraded significantly faster in flasks containing sediment than in those with water alone.

22. Masuda et al. (2012) studied the metabolic fate of methoxychlor in a water-sediment model system. This study utilised samples of sediment and associated water from a brackish lake (temperature 14–15°C, salinity 0.44%, sediment pH 6.6, water pH 7.1), and a freshwater river (temperature 15°C, salinity 0.00%, sediment pH 6.9, water pH 7.5). Sediment samples were pre-incubated for 23–25 days in the dark at 25°C, with reductive conditions maintained throughout. The average redox potential of the samples were -176.2mV(river) and -162.1 mV (brackish lake). The measured half-lives of methoxychlor in the water-sediment system were 4.4 days and 6.6 days for the river and lake sediment systems respectively. The authors suggested that, based on the reaction products detected, in both sediments, initial degradation is caused by the dechlorination reaction, followed by demethylation. The authors also indicate that, both biotic and abiotic processes are responsible for the observed degradation. Abiotic dechlorination and CN-replacement is suggested to occur in some environments (under low oxygen levels in the presence of humic acid). However, in the lake sediment, the abiotic reaction was shown to proceed much more slowly.

23. Baughman et al. (1980) report second-order rate constants of 5.2×10^{-14} and 6.1×10^{-16} L/organism/h (half-lives of 111 and 9,500 days, respectively, assuming a bacterial concentration of 5×10^9 organisms/L) measured dependent on 15% and 90% sorption, respectively, to sediments in river die-away studies.

24. Muir and Yarechewski (1984) studied methoxychlor degradation in water-sediment systems (water-sediment ratio, 10–20:1) under laboratory conditions in lake sediment (79% clay, 21% silt and 6.0% organic matter) and pond sediments (75% clay, 24% silt , 6.3% organic matter; pH=7.6), incubated under various redox conditions in a controlled environment (22.5°C) with a photoperiod of 16-hour light and 8-hour darkness and removed at intervals over a 448 day period. It was observed that methoxychlor added to sediment-water mixtures was slowly biodegraded under aerobic conditions (115.9±74.1 days and 206±186.8 days half-lives for pond and lake, respectively) (Eh 220 to 464 mv) and more rapidly degraded anaerobically with half-lives of <28 days for both lake and pond sediment (Eh less than -50 mv).

25. The authors note that these results suggest methoxychlor degradation in well aerated conditions e.g. on suspended sediment or at the sediment-water interface will be relatively slow. Under anoxic conditions rapid breakdown of methoxychlor can be expected with dechlorinated methoxychlor and mono- and dihydroxy degradation products being the major residues present in sediments. Under nitrogen aeration in the Muir and Yarechewski (1984) study, Eh values ranged from -56 to -156 mv in sediment and from 164 to 264 mv in water above sediment while under air flow Eh values of 364 to 384 mv were observed in sediment and water, respectively.

26. As indicated from the discussion above, and discussed by Satsuma and Masuda (2012), methoxychlor degrades faster under flooded (anaerobic) conditions than under upland (aerobic) conditions. A variety of strict anaerobes and facultative anaerobes are known to be capable of reductive dechlorination of organochlorine compounds and are apparently most active at Eh values <0 mv (Sethunathan, 1973). For methoxychlor, several degrading microbial species have been identified (Golovleva et al., 1984). As discussed above, methoxychlor has been found to be transformed to yield dechlorinated methoxychlor degradation products relatively readily through both biotic and abiotic activity. Satsuma and Masuda (2012) concluded that reductive dechlorination under microaerobic conditions in submerged (anoxic) environments, serves to increase the susceptibility of methoxychlor to biodegradation.

27. Fogel et al. (1982) reported that primary degradation of methoxychlor occurred under anaerobic conditions, but not under aerobic conditions after 3 months of incubation. When anaerobically incubated methoxychlor was subsequently transferred to an aerobic environment, it underwent biodegradation at a rate 10 to 70 times greater than that of methoxychlor exposed solely to

aerobic incubation. This could be attributed to the reductive removal of one chlorine atom from the trichloro moiety of methoxychlor, increasing it susceptibility to aerobic biodegradation. The sequential exposure of OCPs, first to reductive conditions and then to oxidative conditions, is considered an ideal environment for biodegradation (Satsuma and Masuda, 2012).

28. Based upon its relatively low vapour pressure value (0.0219 Pa, at 25°C, derived using the EPI Suite AEROWIN v1.00 model), methoxychlor is not expected to volatilize from dry soil surfaces to a large extent (Lyman, 1985).

29. Odabasi and Cetin (2012) estimated an octanol-air partition coefficient (K_{OA}) for methoxychlor at 25°C of 10.48. A modelled log K_{OA} value of 10.161, is derived from the EPI Suite KOAWIN v1.10 model (25°C). The log K_{OA} value derived by Odabasi and Cetin (2012) was used to derive net soil-air gas exchange fluxes, which suggest volatilization fluxes are generally much lower than the sum of input fluxes (e.g. the calculated dry deposition rate, and measured wet deposition rate) indicating a net deposition of methoxychlor to soils (Odabasi and Cetin, 2012). As noted above, the relatively high measured and modelled K_{OC} value, the low solubility of methoxychlor, and observations from laboratory and field studies, suggest that in soil is tightly bound to organic matter and leaches slowly, if at all.

30. Furthermore, Bomberger et al. (1983) modelled the transport and fate pathways for methoxychlor at the air-terrestrial interface, suggesting the compound is strongly adsorbed to the soil and does not leach, and that volatilization is slow. Additionally, it was considered there is no evidence for oxidation and, although photolysis is shown to potentially occur in the aquatic environment, it is assumed not to occur in the soil environment.

31. It is indicated that methoxychlor is persistent in soil, with a half-life quoted by Chen (2014) of 120 days. Methoxychlor residues may persist in top soil for up to 14 months (WHO, 2004). As with is environmental degradation in sediments, it is suggested that methoxychlor is much more persistent under anaerobic conditions than under aerobic conditions. Half-lives of <30 days in anaerobic soils and >100 days aerobic soils were observed.

32. The hydrolysis half-life in soil is likely to be longer than in water due to adsorption to organic matter (Park, 1982). From the discussion above, this would suggest hydrolysis is not a significant process for methoxychlor degradation in soil.

33. A study by Golovleva et al., (1984) provided a quantitative assessment of the persistence of methoxychlor in soil and its rates of biodegradation in different conditions using laboratory experiments (using 50–200 mg/L methoxychlor cultures) and a two-year field trial using both chernozem and grey forest loam soils. Methoxychlor applied to soil during a two-year field study was fairly persistent; residues remaining in the chernozem soil after 1, 2, and 3 months made up 92%, 38%, and 27% of the original application respectively). Over one year later, measurable concentrations of methoxychlor were still present in soil, but concentrations were not quantified. The authors concluded that anaerobic conditions favour methoxychlor degradation in nature and microbial cultures. For example, in the laboratory tests, in relatively well-aerated soils (humidity 15–20%), degradation was estimated at 70% in 4.5 months, while under anaerobic conditions (Eh 10–20) with soil covered by 2–3cm of water, 100% degradation was observed in 4 months. It was noted that products of the partial dechlorination and demethylation of methoxychlor were shown to accumulate in the humidified and flooded soils.

34. Fuentes et al. (2017) investigated the removal of methoxychlor from different types of natural surface soils, including clay silty loam (pH 7.3), sandy (pH 6.2), loam (pH 7.6) using a native Streptomyces consortium. The prepared cultures were incubated at 30°C for a 16-day study period. Texture of soils was shown to be an important factor in determining the level of degradation in soils. In the sterile soil experiments, 39% of removal of methoxychlor was noted in the clay silty loam. The authors observed that 18% of that removal was due to abiotic processes (i.e. due to chemical reactivity of pesticides), indicating that the majority of the degradation occurred through microbial activity. For sandy and loam soils, removal rates of 27% and 4% were noted respectively. In contrast to the observation for clay silty loam, these soils did not observe a significant difference between the biotic tests and abiotic controls, suggesting the elimination of methoxychlor may not be provided by the activity of the microbial consortium, but probably due to the chemical reaction between the pesticides and the soil particles. This study would suggest the rate and pathway of degradation in the environment can vary considerably dependent on the soil type. The dissipation of methoxychlor was observed after 4 days of incubation, showing a maximum removal of 21% in non-sterile clay silty loam soil. However, it was indicated that the abiotic removal of the pesticide was only about 1%. Therefore, in soil microcosms without inoculation with the actinobacteria consortium the

concentration of methoxychlor remained almost constant over time. Texture of soils was shown to be an important factor in determining the level of degradation in soils.

35. Baczynski et al. (2010) investigated the anaerobic methoxychlor in field polluted soil, sandy clay loam (57% sand, 17% silt, 26% clay, pH 3.8), tested at different temperatures (12, 22 and 30°C), using methanogenic granular sludge as inoculum. It was noted that, in the first two weeks, methoxychlor concentration decreased by 90% at 30°C and by 78% at 12°C. However, it was reported that this initial rapid loss is followed by a plateau, leaving an almost constant residual until the end of the experiment (16 weeks). Residues remaining in soil after 72 h of desorption made up 5% for methoxychlor. Additional experiment demonstrated that removal was limited to readily desorbing fractions of pesticides, while their desorption-resistant fractions persisted in the soil. It is noted that this study is not reflecting degradation potential in ambient environment, but the microbial population involved in the study has been heavily preadapted due to the contaminated soil. The study results provide that methoxychlor can generally be degraded in anaerobic conditions, however from this study it is not possible to infer about the rate of such degradation in environmentally relevant conditions.

36. Fogel et al. (1982) investigated biodegradation in sandy loam garden soil (pH 6.7) incubated at 27°C, separately under aerobic, anaerobic, and denitrifying conditions. Primary degradation of methoxychlor occurred under anaerobic conditions, but not under aerobic conditions, after 3 months of incubation. The results of this study demonstrate that the incubation of methoxychlor in soil under both anaerobic and denitrifying conditions results in significant alteration of molecular structure via dechlorination. Methanogenic organisms, however, were probably not involved, as strong inhibition of methane production was observed in all soils treated with methoxychlor (Fogel et al., 1982). When anaerobically incubated methoxychlor was subsequently transferred to an aerobic environment, it underwent biodegradation at a rate 10 to 70 times greater than that of methoxychlor exposed solely to aerobic incubation. Cometabolic processes may be responsible for the extensive molecular changes which occurred with methoxychlor because the rate of its disappearance from soil was observed to level off after exhaustion of soil organic matter (Satusuma and Masuda, 2013).

37. To summarise, there are studies available investigating various aspects of degradation potential of methoxychlor. Most of the studies have not been carried out in environmentally relevant conditions comparable with today's standards on testing of realistic degradation half-lives, but provide useful information about the degradation pathways in specific conditions as well as about degrading populations. The studies which closest resemble conditions of current test simulation degradation testing guidelines are Walker *et al.*, (1988), Muir and Yarechewski (1984). It should be noted that none of the two studies applied environmentally relevant temperatures in the tests. Realistic average temperatures in water bodies range from <10°C in the Arctic and 12°C average temperature in Europe to even higher temperatures in specific Asian and South-American regions, whereas laboratory temperatures normally vary between 20 and 25°C. Test temperature has a significant influence on the results.

38. Degradation half-life from Walker et al. (1988) in water was 208 days. 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 layer of the water column. In conclusion, based on the available information, methoxychlor meets the criteria for persistence in water as defined in Annex D 1b of the Convention.

39. For sediment-water system tests, the half-lives in sediment were between 115.9±74.1 days and 206±186.8 days in the study of Muir and Yarechewski (1984) for anaerobic and aerobic conditions, respectively. Walker et al. (1988) observed 12.2 days half-life in sediment. 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 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 (Hermanson et al., 2005), which is expected to be the period of peak use of methoxychlor globally. This observation would suggest a continuous input of methoxychlor at high latitudes. However, the sediment core findings trigger reason for precaution in interpreting the environmental relevance of the experiments cited above on fast degradation in anaerobic conditions. The interpretation of the sediment core results as indication of persistence should be carried out as next step. Overall, the sediment studies suggest that the Annex D 1b criteria are met for sediment

40. To conclude, methoxychlor is shown to display persistence in water, soils and sediments, and indicated to degrade within the scale of weeks to months depending on aeration intensity. The available data indicate that methoxychlor meets the criteria for persistence as defined in subparagraph

1 (b) of Annex D, in terms of degradation in water, in soils and sediments, with indicated half-life of >6 months observed under aerobic conditions.

4. Bioaccumulation

41. As discussed by Bio Intelligence Service and INERIS (2017), values for the octanol-water partition coefficient (K_{OW}) of methoxychlor have been derived from both experimental and modelling methods.

42. A modelled Log K_{OW} value of 5.67 for methoxychlor, is obtained using the (US EPA) EPI Suite (KOWWIN v. 1.67) estimate. The EPI Suite BCFBAF model derives a Log BCF value of 3.019 for methoxychlor, using a regression-based method (corresponding BCF value of 1044 L/kg wet-wt). The stated Log BCF value using the Arnot-Gobas method (upper trophic) is 3.616 (BCF value of 4134). These values are derived using an experimental Log K_{OW} value of 5.08, reported by Hansch, Leo and Hoekman (1995). The Log K_{OW} value quoted in the CIRABC factsheet on methoxychlor is 5.1.[4]

43. Methoxychlor has also been identified as a chemical of potential ecological concern (COPEC) in ecological risk assessments carried out by the US EPA, partly due to its bioaccumulative properties (Corl, 2001).

44. Veith, DeFoe and Bergstedt (1979) developed a method for estimating bioconcentration factors (BCFs) using a laboratory experiment exposing a specific species of fish – fathead minnows (*Pimephales promelas*) – to a non-lethal dose of the organic chemical in a continuous-flow system, analysing concentrations in the fish at different exposure times. BCF values for methoxychlor as high as 8,300 were reported. The study also indicates that the temperature and fish species used in the exposure experiment will impact the BCF values due to differences in metabolism and excretion of different species (WWF, 2005). Indeed, the BCF values of various organochlorine pesticides (e.g., hexachlorobenze and 1,2,4-trichlorobenzene) were shown to be lower for rainbow trout compared with fathead minnow (Veith, DeFoe and Bergstedt, 1979). These results suggest the extent of bioconcentration of methoxychlor can vary widely between different aquatic species.

45. For example, in a study by Parrish et al. (1977), of sheepshead minnows (*Cyprinodon variegatus*), exposed for 140 days in flowing seawater – whole body, wet weight, measured BCF (based on 6 samples) ranged from 113 to 264. In a study by Renberg et al. (1985) of methoxychlor bioaccumulation in mussels, also using a continuous-flow system, a BCF value of 12,000 was observed.

46. The Organisation for Economic Co-operation and Development (OECD) Guidelines for Testing of Chemicals (TG 305) outlines a method for determining a chemical's bioaccumulation in fish. The revised test method outlined in OECD (2012) involves exposing test animals to food spiked with the test substance. In a validation study of the OECD TG 305 ring test method, the results of eight different laboratories carrying out the dietary test method were assessed (OECD, 2012) [5]. The studies were conducted using rainbow trout (*Oncorhynchus mykiss*) with one laboratory conducting a further study using carp (*Cyprinus carpio*).

47. 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[6]. BCF values for methoxychlor were derived from the dietary test data using this approach. In the OECD (2012) study, 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. BCF was then estimated as the ratio of the k_1 value to the overall depuration rate constant or the growth corrected depuration rate constant determined in the OECD 305 ring test studies. The reported BCF values from the OECD (2012) study

[4] 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.

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

[6] 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.

varied according to the different laboratories conducing the assessment, ranging between 2,358 and 5,207 for rainbow trout, and 804 to 2,251 for carp.

48. Metcalf et al. (1971) developed a laboratory "model ecosystem" to simulate the application of pesticides to crop plants and assess the contamination of the aquatic environment. This was used to study the biodegradability and accumulation of methoxychlor in fish and snails. The results indicated that, in fish, methoxychlor was readily metabolized to mono- and di-OH derivatives and was stored at comparatively low levels, suggesting that methoxychlor is environmentally degradable and will not be stored in high concentrations in most organisms.

49. Anderson and DeFoe (1980) conducted an experiment exposing stoneflies, caddis-flies, isopods, snails and bullheads to methoxychlor in a flowing-water (22 litres per hour) test system for 28 days. The animals used in the exposures were collected from natural lakes, ponds and streams and unfiltered lake water was used under realistic natural conditions (temperature, pH, dissolved oxygen etc.). Methoxychlor BCFs were determined in the stoneflies and snails that survived the exposures. The average BCF for methoxychlor in stoneflies was 573 (range of 348 to 1130). The average BCF for methoxychlor in snails was 6,945 (range of 5,000 to 8,570).

50. Zhao et al. (2009) investigated the spatial distribution and bioaccumulation of OCPs including methoxychlor in surface sediments and benthic organisms from Taihu Lake, China. Concentrations of OCPs and lipids in typical large benthic organisms, *Bellamya aeruginosa* (*B. aeruginosa*) (freshwater snail) and *Corbicula fluminea* (*C. fluminea*) (freshwater clam) were measured. Biota-sediment accumulation factors (BSAF) of total OCPs for *B. aeruginosa* was 0.11– 0.36 suggesting minimal bioconcentration, while *C. fluminea* BSAFs of 0.33–3.86 were measures, suggesting concentration was occurring. BSAF values increased with body weight. There was significant bioaccumulation in *C. fluminea* when wet weight exceeded 3.0 g, and it was suggested that biomagnification might occur for individuals larger than 4.0 g to accumulate OCPs. The higher OCP BSAF values in *C. fluminea* compared with B. aeruginosa was attributed to higher lipid contents. Thus, lipid content played a key role in bioaccumulation.

51. Experimental data on the bioaccumulation of methoxychlor from soil to terrestrial organisms is lacking (US EPA, 2011).

52. Measured data in the environment are available on substance at various trophic levels. The substance was found in both muscle and kidney of terrestrial species (e.g. hare, lamb, caribou), marine invertebrates (e.g. snow crab, shrimp) and fish (e.g. Atlantic cod, Atlantic salmon, halibut), seabirds (e.g. eiders, kittiwake) and marine mammals (e.g. seals, beluga, minke whale) in Greenland (Vorkamp et al., 2004), Russian Arctic (Savinov et al., 2011) and Antarctic (Miranda Filho et al., 2009). From the limited data available, it is indicated that methoxychlor is detected at low levels (relative to major persistent organochlorines) in Arctic freshwater fish with concentrations ranging from <0.01 to 0.17 ng/g whole weight (ww) in lake trout muscle from lakes in the Inuvialuit Settlement Region (Northwest Territories) in Canada (AMAP, 1998). Vorkamp and Rigét (2014) measured methoxychlor concentrations in biota from the terrestrial, freshwater and marine environment of Greenland in 1999–2001, reporting a concentration range of <0.05–8.36 ng/g lipid weight (lw). The authors noted that concentrations detected in Arctic biota were generally close to detection limits, with the exception of levels of 12 and 29 ng/g lw respectively in the liver and muscle of snow crab (*Chionoecetes opilio*) (Vorkamp et al., 2004). In general, methoxychlor concentrations were up to 1-2 orders of magnitude lower than other OCPs such as endosulfan and hexachlorobenzene (HCB). For example, in the blubber of harp seals, mean methoxychlor concentration of 1.1 ng/kg lw., compared with 12 ng/kg (lw) for endosulfan and 66 ng/kg (lw) for HCB. However, little is known about circumpolar trends of methoxychlor or its levels in Arctic fish or sediments.

53. The BCF values described in this section suggest bioconcentration of methoxychlor in aquatic organisms can occur to considerable degree, however variation is noted in a number of studies between the ability of different species to metabolize this compound and hence there is a wide range of BCF values reported between different studies (Metcalf, Sangha and Kapoor, 1971). Measured data in biota in the environment suggest that the substance might be ubiquitously present in biota in remote areas. However, field data are scarce and no field estimate is available on the level of bioaccumulation in the food chain.

54. To conclude, the data available suggest that methoxychlor meets the criteria for bioaccumulation as defined in subparagraph 1 (c) (i) of Annex D, with the K_{OW} values >5 and BCF values >5 000. Field data do not contradict the experimental data but confirm the presence of the substance in biota.

5. Potential for long-range environmental transport

55. For methoxychlor, the (USEPA) EPI Suite model derives a vapour pressure of 5.56×10^{-3} Pa (25°C, derived using the AEROWIN v1.00 model) and a Henry's Law Constant of 9.88×10^{-3} Pa m^3 $mole^{-1}$. It is indicated, based on these properties, that methoxychlor will exist in both the vapour and particulate phases in the atmosphere (Bidleman, 1988).

56. As discussed by Bio Intelligence Service and INERIS (2017), vapour-phase methoxychlor will be degraded in the atmosphere primarily by reaction with photochemically-produced hydroxyl (OH) radicals. The rate constant for the vapour-phase reaction of methoxychlor with OH radicals has been estimated as 5.35×10^{-11} cm^3/$molecule^{-1}$ s^{-1} at 25°C. This corresponds to an atmospheric half-life of about 0.2 days, assuming an atmospheric concentration of 1.5×10^6 hydroxyl radicals per cm^3 and 12-hour/day (derived using the EPI Suite AOPWIN model).

57. Its physico-chemical properties and reactivity with OH radicals, might therefore suggest that methoxychlor may not be considered as a candidate for Long Range Transport (LRT), based on the criteria defined in subparagraph 1 (b) (iii) of Annex D, if only the gas-phase component of methoxychlor and the atmospheric compartment is considered. However, as noted in section 3, methoxychlor can be expected to have a strong affinity for particulate matter, so may not undergo reaction with OH radicals in the gas-phase as rapidly as models predict. Furthermore, based on the water solubility and partitioning properties of methoxychlor, long-range transport potential via aqueous environment should be in focus of the assessment.

58. The potential for long range transport for methoxychlor can be assessed using the OECD POV & LRTP Screening Tool ('The OECD Screening Tool' hereafter) as described by Wegmann et al. (2009). The OECD Screening Tool produces an estimate for the overall potential for environmental persistence (P_{OV}) and long-range transport potential (LRTP) of organic chemicals through air and water, based on the physical-chemical properties and estimated half-life in air, water and soil.

59. The OECD Screening tool has been run for methoxychlor, using a 'best case' and 'worst case' scenarios for the half-lives in water and soil, using values quoted in section 3. The results are displayed in Table 1, along with a comparison with values generated for a number of pesticides currently listed at POPs under the Stockholm Convention.

60. The lower range for the "characteristic travel distance" (CTD) constant of methoxychlor, calculated with the OECD Screening Tool is estimated to be 55 km, which is consistent with the value derived by (Hoferkamp, Hermanson and Muir, 2010). These authors noted that the CTD for methoxychlor is very low compared to some other current use pesticides (e.g. lindane with a CTD of 2,500 km and pentachloronitrobenzene (Quintozene) with a CTD of 12,100 km). However, it should be noted the half-life in water (from study on organic matter sensitized photodegradation) applied in the model is not realistic in environmentally relevant conditions, but results a CTD which would apply for specific laboratory conditions only.

61. The upper range of calculated CTD of 848.6 may represent a more realistic value, however, it is noted that the half-life in water applied in the modelling is for hydrolysis half-life (see discussion in section 3 conclusions about the representativeness of hydrolysis half-life of half-life in water). In general, it can be concluded that the CTD distance predicted for methoxychlor is much lower than those derived for lindane and HCB. For further comparison, for hexabromocyclododecane a CTD of ca. 1500 km was estimated in the Annex D proposal (UNEP/POPS/POPRC.5/4).

62. The estimated transport efficiency[7] of 0.005% is very low in all cases. This estimation is based on the very fast atmospheric degradation of the substance. However, it is interesting to note that the CTD and transfer efficiency values for methoxychlor are comparable to those for dieldrin, despite a lower P_{OV} and atmospheric half-life, while comparable P_{OV} to lindane is observed. Reason for this pattern in the presented LRTP metrics is that the fast atmospheric degradation gets a high weight in the model. However, the pattern suggests that LRTP in aqueous environment needs to be more thoroughly assessed and verified, e.g. with monitoring data.

[7] The estimated percentage of emitted chemical that is deposited to surface media after transport away from the region of release.

Table 1. Screening methoxychlor overall persistence (P_{OV}) and long-range transport potential (LRTP) by running the OECD Screening Tool.

	Methoxychlor[1,2]	**Dieldrin[2]**	**Lindane[2]**	**Hexachlorobenzene[2]**	**Hexabromo-cyclododecane[3]**
Half-life in air (hours)	2.4	13.95	223.9	7597.34	
Potential for LRTP with overall persistence (P_{OV}) (days)	43.2–511.7	2931.8	54.2–746.8	1110–1958.6	
Characteristic Transfer Distances (CTD) (km)	55.2–848.6	678.7	2353.9–2414.1	57441.6–74705.1	1500 km
Transfer Efficiency (%)	0.005	0.007	5.16–5.43	153.5– 259.6	

[1] Lower range calculated using $T_{1/2}$ (water) of 2 hours, $T_{1/2}$ (soil) of 30 days; upper range calculated using $T_{1/2}$ (water) of 365 days, $T_{1/2}$ (soil) of 120 days.
[2] K_{OW}, K_{AW} and $T_{1/2}$ (air) derived from USEPA EPI Suite model; $T_{1/2}$ (water) and $T_{1/2}$ (air) derived from US National Library of Medicine Toxnet HSDB.
[3] UNEP/POPS/POPRC.5/4 (ELPOS model used for the estimation).

63. Contrary to the modelling results, the potential for long range transport of methoxychlor is strongly indicated by monitoring studies and measurements in environmental and aquatic biota samples in remote high latitude regions (AMAP, 1998; Vorkamp and Rigét, 2014).

64. 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 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 (Hermanson et al., 2005), 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.

65. Methoxychlor is not included in the Arctic Monitoring and Assessment Programme (AMAP) monitoring program (AMAP, 1998) so only limited monitoring data are available for this compound from a number of individual studies. Methoxychlor has been detected in measurable concentrations in air samples at six Arctic monitoring stations, where sampling of the circumpolar atmosphere was conducted on a weekly basis in 2000-2003, although concentrations were reported to be low, compared with other OPCs such as chlordane, DDT-related compounds and dieldrin, and were mostly below the method detection limit (MDL) (Su et al., 2008).

66. Methoxychlor has also been detected in various media in the Arctic, including in air (e.g. Halsall et al., 1998; Hung et al., 2005), snow (e.g. Franz et al., 1997; Welch et al., 1991; Boyd-Boland, Magdic and Pawliszyn, 1996), ice core (e.g. Boyd-Boland, Magdic and Pawliszyn, 1996; Hermanson et al., 2005) and in terrestrial, avian and marine biota samples (see details in section 4).

67. For example, Halsall et al. (1998), detected methoxychlor in arctic air samples collected from three locations in the Canadian and Russian Arctic between January, 1992 and March, 1993 with concentrations ranging from 0.26 to 0.41 pg/m^3 It is noted from this monitoring study, that methoxychor is detected at much lower (up to 1-2 orders of magnitude) levels than a number of other OCPs including, for example, dieldrin (0.93–1.42 pg/m^3), endosulfan (3.60–8.33 pg/m^3), and HCB (41.8–56.7 pg/m^3).

68. From the limited data available, it is indicated that methoxychlor is detected at low levels (relative to major persistent organochlorines) in Arctic biota (see details in section 4). In general, methoxychlor concentrations were up to 1–2 orders of magnitude lower than other OPCs such as endosulfan and HCB. However, little is known about circumpolar trends of methoxychlor or its levels in Arctic fish or sediments.

69. The above observations suggest, despite modeling predictions, indicating a low potential for LRT, transport of methoxychlor from low latitudes to remote high latitudes is taking place. It is suggested that the presence of methoxychlor in the arctic can be explained by transport in the gas phase or on particles during periods without rainout events (the OECD LRT tool and other similar

models assume continuous low rates of precipitation), and lower rates of photodegradation than predicted from standard assumptions due to transport in the periods of lower photolytic activity (e.g. dark polar winter and spring) (Muir et al., 2004; Hoferkamp et al., 2010). Furthermore, the long-range transport of methoxychlor may be based on the physical-chemical properties and low degradation rate in aqueous environment take place via marine environment. It is also noted that methoxychlor use in northern agricultural areas of Canada, Scandinavia, Russia and China may also explain the appearance of methoxychlor at some high latitude locations, but in the absence of significant local or regional pesticide sources, findings in the Arctic can be assumed to be due to long-range transport from agricultural areas in lower latitudes (Hoferkamp et al., 2010).

70. Strachan and Huneault (1979) reported the levels of methoxychlor in snow samples from the winter of 1975-6 and rain samples (seven locations) from the period May–November 1976, from around the Canadian side of the Great Lakes. Mean concentrations of methoxychlor measured in rain and snow ranged between 2.0–14.9 ng/L and 0.1–5.8 ng/L respectively. These values were generally much higher than other measures OCPs such as DDT, Lindane and Dieldrin. The authors attributed this to methoxychlor being 'current use' at the time the measurements were taken.

71. Strachan (1985) reports the results of further sampling in 1983, in rainfall at two open-lake locations at opposite ends of Lake Superior. Based on the sampling results, an estimated loading from rainfall and snowfall of 120 kg/yr was estimated (based on a measured rainfall concentration of 2.4 ng/L; rainfall of 580 mm; snowmelt of 225 mm, and lake surface area of 82,100 km^2). This value is lower than those measured for PCBs (300 kg/yr) and lindane (290 kg/yr) but higher than those measured for dieldrin (28 kg/yr) and endrin (4.2 kg/yr).

72. Hoferkamp et al. (2010) reported the measured flux in 2007, of contaminants to the Devon ice cap in Canada (i.e. total input to the watershed from seasonal snowpack). The flux of methoxychlor is reported to be <0.1 ng/m^2/yr, compared with a value of 3–5 ng/m^2/yr for lindane. It should be noted that values of concentrations and fluxes for contaminants at high latitudes will be dependent on a number of factors including the current and historical patterns and volumes of use, as well as precipitation/deposition levels in different locations, so differences in values reported between different contaminants are not necessarily indicative of differences in LRTP.

73. To conclude, while models tend to estimate the long-range transport potential for methoxychlor as low due the rapid reaction with OH radicals, monitoring studies and measured levels of methoxychlor in environmental and biota samples in remote high latitude regions provide clear evidence that long range transport has taken place. This suggests that methoxychlor does meet the criteria for long-range environmental transport as defined in Annex D, subparagraphs 1 (d) (i) and 1 (d) (ii).

6. Adverse effects

74. As part of the assessment for adverse effects to both humans and other species the authors have completed a Klimisch evaluation of the references used to assess adverse effects. Klimisch scores for the references used in this section can be found in the appendix to this document. An indication of the adverse effect (human health, ecotoxicity) to which each reference applies is provided in this table. It can be seen from this table, that the quality of references used in the assessment of reprotoxic effects is "reliable with restrictions", with all references cited being assigned a score of '2'.

6.1 Human health effects

75. From a human health perspective, available data on the repeated dose toxicity of methoxychlor are limited. Krieger (2001) found no clinical or histopathological changes in humans who ingested 2 mg/kg/day of methoxychlor for 8 weeks. Groups of volunteers were given methoxychlor at rates of 0, 0.5, 1, and 2 mg/kg/day for 8 weeks. Even the highest dosage was without detectable effect on health, clinical chemistry, or the morphology of blood, bone marrow, liver, small intestine, or testis. However, these data alone are too limited to allow assessment of the hazard represented by methoxychlor for humans.

76. Pure erythroid aplasia (i.e. where the bone marrow stops making red blood cells) was observed in a patient after an approximately 3-week chronic exposure to muchozol (an insecticide containing methoxychlor and pyrethrin). The patient recovered after 1 year (Sokołowski and Zawilska, 1983).

77. Ziem (1982) reports the development of fatigue and bruising several weeks after accidental exposure to a tomato pesticide dust containing methoxychlor and captan, followed by aplastic anemia after 2 months which proved fatal at 6 months.

78. Brown et al. (1990) conducted a case-control study of leukemia in Iowa and Minnesota (USA) for mortality rates for leukemia from various pesticides, including methoxychlor. The study compared the incidence of leukemia between farm workers using individual pesticides and families of pesticides, including methoxychlor against a control set based on non-agricultural workers from the general population. Without latency considerations, significantly elevated risks were seen for methoxychlor (odds ratio =2.2) for all leukemia subjects who ever personally mixed, handled, or applied pesticides.

Reprotoxic effects

79. A number of studies exist demonstrating the reprotoxic properties of methoxychlor with a summary of the key studies and findings provided in the paragraphs below.

80. 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 conclude that even at the lower dose methoxychlor exposure during fetal development caused changes to the genetic code resulting in impaired function of ovaries in new borns, in particularly this affected the function of receptors responsible for production and processing of oestrogen. Masutomi et al., (2003) reports on another study where Sprague-Dawley rats were fed pellets containing methoxychlor at 0, 24, 240, and 1200 ppm (equivalent to 1.2, 12, and 60 mg/kg –day) from day 15 of gestation to postnatal day 10. There were no effects to the litter size in female rats. However, at the 60 mg/kg/day dose, adverse symptoms were observed such as obvious body weight reductions, changes in the ovaries of all 60 mg/kg/day dosed female offspring (enlarged uterus, Increased number of follicles in the ovary but decrease in corpora lutea (which produces oestrogen)) likely to affect fertility and development. Body weights in male rats were also reduced and there were changes in the testes at the 60 mg/kg/day dose also affecting function and fertility. Another study by Alworth et al. (2002) on pregnant CD-1 mice corroborates these findings. Mice fed methoxychlor at 10 µg/kg/day over a period of 18 days showed significantly enlarged uteri in the prenatally exposed females.

81. Armenti et al. (2008) exposed rats to a low dose (20 µg/kg/day) and high dose (100 µg/kg/day) to determine if methoxychlor could cause adult ovarian dysfunction. The study demonstrated that developmental methoxychlor exposure results in reduced ovulation and fertility and premature aging, possibly by altering ovarian gene expression and folliculogenesis.

82. Paulose et al (2012) dosed two groups of cycling female CD-1 mice (ages 32–25 days) with methoxychlor. Group A were dosed for 5 days with 64, 128, or 160 mg/kg/day methoxychlor or the control via intraperitoneally injection (IP) or for 10 days at doses of 8, 16, 32, 64, 128, or 160 mg/kg/day with methoxychlor or the control. Group B mice were dosed with methoxychlor dissolved in sesame oil via IP for 20 days at 64, or 96 mg/kg/day or 30 days at 48, 64, or 96 mg/kg/day methoxychlor. In Group A, methoxychlor significantly decreased the percentage of follicle degeneration at the 64 mg/kg/day and 128 mg/kg/day doses. In the Group B 20-day exposures, there was a significant increase in the percent of follicle degeneration compared to control at the 64 mg/kg/day dose but not in the 96 mg/kg/day dose. Additionally, ovarian weights were significantly lower than control. It was concluded that developing ovaries may be more sensitive to methoxychlor induced toxicity resulting in decreased fertility manifested only at adulthood, at the time of reproduction.

83. Chedrese and Feyles (2001) studied the effects of methoxychlor using cultures of porcine granulosa cells and Chinses hamster ovary to evaluate the ability of follicle stimulating hormones to perform normally in the development and release of eggs from ovaries. Exposure to 10 µM methoxychlor inhibited progesterone synthesis by 0.4-fold and estradiol-17β-stimulated progesterone synthesis but stimulated estradiol-17B synthesis by 2.5-fold. The Author's conclude that methoxychlor has the potential to mimic estrogen-like effects mainly attributed to the biotransformation of methoxychlor to its metabolite HPTE in the liver. HPTE has a greater affinity for estrogen receptors than methoxychlor and has the potential to stimulate protein synthesis and cell growth in target tissues beyond the natural function of the body.

84. Miller et al (2006) further explored the effects of methoxychlor and its metabolites mono-OH methoxychlor and HPTE on *in vitro* follicle culture assays to assess the development of follicles, including growth and atresia (degeneration of follicles). Cultures were exposed to 0.01, 0.1, 1, 10, and 100 µg/mL over a period of 96 hours. At the 71- and 96-hour timeframes mono-OH methoxychlor significantly inhibited follicle growth (compared to the control sample) at 0.01–10 µg/mL. Furthermore at 10 µg/mL mono-OH methoxychlor caused atresia in follicles. HTPE inhibited antral follicle growth at 96 hour and only in small follicles at 10 µg/mL. The study concluded that methoxychlor and its metabolites mono-OH and HPTE are directly toxic to antral follicles and induce atresia indicating that toxicity may be mediated by estrogen-regulated pathways. This would affect the

development and release of eggs from the ovary and have direct impacts upon fertility and hormonal function of female rats.

85. Hamdy and Axhar (2013) investigated the testicular response to methoxychlor in adult male albino (Wistar) rats treated with methoxychlor at doses of 0, 50, 100 or 200 mg/kg/day by gavage for 15 consecutive days. Measured parameters included testicular weight/sperm count/motility, epididymal α-glucosidase activity, plasma testosterone, and testicular androgenic enzymes activities. The administration of methoxychlor induced significant oxidative stress in the testis of rats which is associated with impairment of spermatogenesis, reduced testosterone production, inhibition of steroidogenic enzyme activity, altered marker enzymic patterns, decreased levels of both enzymatic and non-enzymatic antioxidants and apoptosis. These effects would likely have an impact on the fertility of male rats and physiological development during puberty. Another study by Latchoumycandane et al. (2002) assessed the effects of methoxychlor on adult male rats (aged 90 days old). The rats were exposed to methoxychlor orally at doses of 0, 50, 100, and 200 mg/kg/day for 1, 4, or 7 days. Methoxychlor exposure caused the weights of male sex organs and sperm counts to decrease, potentially as a result of estrogenic effects. The authors determined a LOAEL of 50 mg/kg/day.

Carcinogenicity

86. International Agency for Research on Cancer (IARC) evaluates methoxychlor as a Group 3 carcinogen: “the agent is not classifiable as to its carcinogenicity to humans”.

87. Mills and Yang (2006) evaluated breast cancer incidence rates from the California (USA) Cancer Registry (CCR) that includes statewide 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 where pesticide active ingredients at the county level were summed and found to be skewed. Therefore, the results were log-normalized. Breast cancer incidence rates were used as the dependent variable in the negative-binomial (NB) regression models. In the regression models, pounds of active ingredients of the OCPs were entered as categorical values in quartiles that were created after the distributions of the log-normalized values were examined. Adjustments for age, fertility, and a measure of socioeconomic status were made by inclusion of terms for each of these variables simultaneously with the terms for the organochlorine. The results are expressed as incidence rate ratios (IRRs) and 95 percent confidence intervals (Cis). PROC GENMOD in the SAS statistical software (SAS Institute, 1990) was used to fit the models. The methoxychlor results are shown in Table 2. The study reported found a statically significant 16–18% elevation in risk of breast cancer among Latinas in the highest exposure quartiles for methoxychlor. This reported cited previous epidemiological studies of pesticides in Iowa and Minnesota (USA) where elevated risks of leukemia (odds ratio = 2.2) were observed among men exposed to methoxychlor (Brown et al., 1990, as cited by Mills & Yang). 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 & Yang).

Table 2. Adjusted (for age, socioeconomic status, and fertility level) Incidence Rate Ratios for Methoxychlor (1970-1988) and Breast Cancer in Hispanic Women in California (USA)*: 1988-1993 and 1994–1999. Methoxyclor (MXC).

Chemical	1988–1993			1994–1999		
	IRR	95% CI	p-value	IRR	95% CI	p-value
MXC (low)	1.00	--	--	1.00	--	--
MXC	1.13	1.02–1.27	0.023	1.06	0.96–1.17	0.2733
MXC	1.06	0.95–1.20	0.2854	1.04	0.94–1.16	0.4299
MXC (high)	1.18	1.03–1.35	0.0142	1.16	1.02–1.30	0.0190

*excludes counties with fewer than 10 cases.

88. 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 authors examined the cell function within ovarian cells following exposure to

methoxychlor. Human BG-1 ovarian cancer cells were cultured and treated with E2 (positive control, 10^{-8}, 10^{-9} M), Methoxychlor (10^{-6}, 10^{-7}, 10^{-8}, 10^{-9} M) and DMSO (negative control) for four days. E2 and Methoxychlor significantly increased cell proliferation at all concentrations compared to DMSO. Changes in cyclin D1 gene expression were not observed between 0 and 6 h, but significant alterations were observed between 6 and 24 h of treatment with E2 and methoxychlor. In conclusion, the authors demonstrated that methoxychlor may accelerate ovarian cancer cell growth through an ER-mediated signaling pathway. The expression of cell cycle and apoptosis factors appears to be regulated by treatment with methoxychlor in BG-1 ovarian cancer cells. In detail, methoxychlor induces ER-positive BG-1 ovarian cancer cell proliferation by promoting cell cycle progression and by suppressing apoptosis via an ER signaling pathway.

Mutagenicity

89. No evidence of mutagenicity could be drawn from the available experimental data for animals or for humans. Methoxychlor has not been found to be mutagenic in bacteria, yeast or *Drosophila melanogaster*. Cytogenic and dominant lethal tests in mice were also negative (IARC, 1979). When testing mutagenicity in humans, methoxychlor did not produce mutations at the thymidine kinase (TK) locus in human lymphoma cells (ATSDR, 2002).

6.2 Ecological effects

90. The acute LC_{50} values for methoxychlor for fish are quoted as 52 and 67 µg/L for rainbow trout and bluegill sunfish, respectively and the acute toxicity to water fleas was quoted as 0.8 µg/L (Tomlin, 1997).

91. Thorpe et al., (2001) reported a chronic test for a 14-day exposure of *Oncorhynchus mykiss* (rainbow trout) to methoxychlor, which derived a no effect concentration (NOEC) of 2.2×10^{-3} mg/L.

92. The US Environmental Protection Agency reports an acute toxicity test for a 96-h exposure of *Oronectes nais* (Water Nymph Crayfish) to methoxychlor with an LC_{50} of 5×10^{-4} mg/L and another test consisting of 96-hour exposure of *Crassostrea virginica* (Eastern Oyster) resulting in an EC_{50} of 0.09 mg/L (US EPA, 2009).

93. Anderson and DeFoe (1980) reported an acute toxicity test for a 96-hour exposure of *Asellus communis* (brine shrimp) to methoxychlor and a corresponding LC_{50} of 1.8×10^{-3} mg/L. This study also reported a chronic LC_{50} of 4.2×10^{-4} mg/L after a 28-day exposure of *Asellus communis* (brine shrimp) to methoxychlor. The NOEC for this test is not available.

94. In mice and rats, 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).

95. Tomic et al., (2006) found that methoxychlor caused a dose-dependent increase in the percentage of degenerating follicles/oocytes in the ovary of CD-1 mice compared with controls at the 32 and 64 mg/kg/day doses. This can have a significant impact on the number of follicles available for maturation and fertilisation in adult life and can (once devoid of all follicles) ultimately lead to infertility. However, methoxychlor treatment did not affect gonadotropin or estradiol levels, nor did it affect the levels of follicle-stimulating hormone or estrogen receptors. These data suggest that methoxychlor induces degeneration of late stage ovarian follicles through direct effects on the Bax and Bcl-2 signaling pathways in the ovary (Borgeest et al., 2004).

96. Miller et al., (2005) used a culture system to test the hypothesis that methoxychlor is directly toxic to late stage ovarian follicles (prior to ovulation). Methoxychlor (10–100 µg/mL) significantly inhibited follicle growth at 72 and 96 hours, and increased degeneration of ovarian follicles (100 µg/mL) compared to controls at 96h. Furthermore, methoxychlor increased Bax mRNA levels between 48–96 hours and decreased Bcl-2 mRNA levels at 96-hour. These data suggest that methoxychlor directly inhibits follicle growth partly by Bcl-2 and Bax pathways and increases degeneration of follicles partly through Bcl-2 pathways.

97. Fei, Chung and Taylor (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. One common mechanism by which endocrine disrupting chemicals, such as methoxychlor, produce lasting reproductive tract defects is through permanent alteration of developmental gene expression.

98. Ortiz-Zarragoitia and Cajaraville (2005) recommended that the endocrine disrupting properties of methoxychlor should be further studied as a 15-day exposure of fish to 100 µg/L methoxychlor caused significant proliferation of liver peroxisomes as well as significantly increased vitellogenin levels in fish exposed compared to controls. Moreover, a significant correlation between vitellogenin levels and the oxidase activity was found, suggesting early estrogenic effects that are associated with liver peroxisome proliferation.

Conclusion

99. Methoxychlor is not recognised as a carcinogen or mutagen. However, based on the evidence presented methoxychlor demonstrates clear reprotoxic effects, which may be based on estrogenic mimicking effects of methoxychlor and its metabolites. This has caused reduced fertility in both male and female rats and mice. Further within female rats there is evidence for damage to follicle development, and hormone function in both parent and female offspring including enlarged uteri, enlarged liver, reduced body weight and disrupted hormonal function. Additionally, studies by Kim et al. (2014) suggests that methoxychlor may accelerate ovarian cancer, and Brown et al (1990) suggests increased incidence of leukemia in agricultural workers exposed to methoxychlor as part of their occupational duties.

7. Statement of the reasons for concern

100. A comparison between the criteria laid out in Annex D to the Stockholm Convention criteria with the reported data in the literature can be found in Table 3.

101. The evaluation of existing information indicates that there is reason for concern due to clear evidence that methoxychlor meets the criteria for bioaccumulation due to its BCF>5000 and K_{OW}>5, its potential for long-range environmental transport, and persistence in water, soil and sediment.

102. Furthermore, concerns exist regarding the toxicity to aquatic organisms in addition to other health hazards including a potential endocrine disrupting property with toxic effects to reproduction.

103. Toxicity testing indicates that methoxychlor has clear toxic effects on reproduction, which may be due to estrogen mimicking effects of methoxychlor and its metabolites. These have been shown to damage fertility in both male and female rats and mice, including damage to follicle development, enlarged uteri and hormonal function in females, and reduced weight of testes and sperm count in males.

104. Methoxychlor has been restricted/banned in several countries for over 10 years. However, OSPAR (2004) suggested that it continues to be made and used in many countries. Methoxychlor demonstrates persistence and long-range transport and therefore single countries or groups of countries alone cannot abate the pollution caused by them. Therefore, international action may be warranted to control this pollution.

105. Overall, it is considered that methoxychlor meets all four criteria set out within Annex D of the Stockholm Convention to be considered a POP, and therefore may warrant further investigation under the Convention.

Table 3. Comparison of Stockholm Convention Annex D criteria vs. reported data in the literature

Screening criteria	Stockholm Convention Annex D definition	Observed methoxychlor results in the literature
Persistence	Evidence that the half-life of the chemical in water is greater than two months (60 days), or that its half-life in soil is greater than six months (180 days), or that its half-life in sediment is greater than six months (180 days).	Degradation half-life in water 200 days – 367 days. In sediments and soil, half-lives >6 months have been reported in aerobic conditions with shorter (~1 month) values reported in anaerobic conditions.
Bio-accumulation	Evidence that the bio-concentration factor (BCF) or bio-accumulation factor in aquatic species for the chemical is greater than 5,000 or, in the absence of such data, that the log K_{OW} is greater than 5.	Measured BCF values of >5000 found in fish and snail species. Experimental and modelled K_{OW} values of >5

Potential for long-range environmental transport	Measured levels of the chemical in locations distant from the sources of its release that are of potential concern; monitoring data showing that long-range environmental transport of the chemical, with the potential for transfer to a receiving environment, may have occurred via air, water or migratory species.	Models based on physico-chemical properties tend to estimate the atmospheric long-range transport potential for methoxychlor is low. However, monitoring studies and measured levels of methoxychlor in environmental and biota samples in remote high latitude regions, indicate that long range transport takes place. The route of long-range transport may be via water or via air or both.
Adverse effects	Evidence of adverse effects to human health or to the environment that justifies consideration of the chemical within the scope of this Convention; or toxicity or ecotoxicity data that indicate the potential for damage to human health or to the environment.	The evidence reviewed suggests that methoxychlor is not acutely toxic to humans and has not been identified as a carcinogen or mutagen. However, the evidence reviewed does suggest potential effects to reproductive systems, particularly folical development within ovaries with potential ferility and development issues. Furthermore, the evidence has indicated that methoxychlor is very toxic to aquatic species.

Appendix

Klimisch scores for references relating to adverse effects

Klimisch et al. (1997) developed a system for the critical evaluation of the reliability of studies developed to assess the environment. In particular this includes adverse health effects of substances to humans and other species. The ECHA (2008) guidance for chemical safety assessments under REACH further explains how this scoring system works:

1 = reliable without restrictions: "studies or data [...] generated according to generally valid and/or internationally accepted testing guidelines (preferably performed according to Good Laboratory Practices (GLP)) or in which the test parameters documented are based on a specific (national) testing guideline [...] or in which all parameters described are closely related/comparable to a guideline method."

2 = reliable with restrictions: "studies or data [...] (mostly not performed according to GLP), in which the test parameters documented do not totally comply with the specific testing guideline but are sufficient to accept the data or in which investigations are described which cannot be subsumed under a testing guideline, but which are nevertheless well documented and scientifically acceptable."

3 = not reliable: "studies or data [...] in which there were interferences between the measuring system and the test substance or in which organisms/test systems were used which are not relevant in relation to the exposure (e.g. unphysiological pathways of application) or which were carried out or generated according to a method which is not acceptable, the documentation of which is not sufficient for assessment and which is not convincing for an expert judgment."

4 = not assignable: "studies or data [...] which do not give sufficient experimental details, and which are only listed in short abstracts or secondary literature (books, reviews, etc.)."

The references used within the review the adverse effects chapter of this dossier have been evaluated using the Klimisch evaluation criteria with scores presented in the table below.

Author	Year	Adverse Effects	Klimisch Score	Further notes on scoring
Alworth et al.	2002	Human health (Reprotoxic effects)	2	Methods referenced, not GLP; controls conducted
Anderson & DeFoe	1980	Ecotoxicity	1	USEPA methodology
Armenti et al.	2008	Human health (Reprotoxic effects)	2	Method in accordance with Rutgers University protocols; controls conducted
ATSDR	2002	Ecotoxicity; Human health (Mutagenicity)	-	Original papers not obtained. The evaluation of a literature search by Agency for Toxic Substances and Disease Registry (ATSDR)
Borgeest	2002	Ecotoxicity	2	Method in accordance with University of Maryland protocols; controls conducted
Brown et al	1990	Human health	2	Interviews and statistical evaluations. Not an experiment
Chedrese & Feyles	2001	Human health (Reprotoxic effects)	2	Methods referenced, not GLP; controls conducted
Fei, Chung and Taylor	2005	Ecotoxicity	3	Method in accordance with Yale University protocols; controls conducted. Small sample size - 4 per group
Hamdy and Axhar	2013	Human health (Reprotoxic effects)	2	No "accepted" guideline but sufficiently explained. Controls conducted

Author	Year	Adverse Effects	Klimisch Score	Further notes on scoring
Kim et al.	2014	Human health (Carcinogenicity)	2	Conducted using an MTT assay. Controls conducted. Supported by Korean government
Latchoumycandane	2002	Human health (Reprotoxic effects)	2	WHO methodology (1999). Lab Manual for examination of human semen and sperm-cervical mucus interaction. Controls conducted
Masutomi	2003	Human health (Reprotoxic effects)	2	Not GLP. Protocols under National Institute of Health Sciences, Japan
Miller et al.	2006	Ecotoxicity	2	Method in accordance with University of Maryland protocols. Follicle culture assay.
Mills & Yang	2006	Human health (Carcinogenicity)	2	Regression analysis of pesticide use data and breast cancer incidence rates for population from 1988–2000 using CA state cancer registry
Miranda Filho	2009	Ecotoxicity	4	Original paper not obtained.
Ortiz-Zarragoitia & Cajaraville	2005	Ecotoxicity	2	Methods referenced, not GLP; controls conducted
Paulose et al.	2012	Human health (Reprotoxic effects)	2	Method in accordance with University of Maryland protocols. Sample size based on power calculation set to determine if 80% power to identify difference of 10% between control and treatment groups
Stein et al., 1965 as cited in Krieger, 2001	2001	Human health	4	Original paper not obtained.
Sokolowski and Zawilska	1983	Human health	4	Original paper not obtained.
Tomic et al.	2006	Ecotoxicity	2	Method in accordance with University of Maryland protocols. Dosing followed Borgeest et al., 2002
Tomlin	1997	Ecotoxicity	4	Original paper not obtained.
USEPA	2009	Ecotoxicity	1	USEPA/US Fish & Wildlife Service methodology
Zama & Uzumcu	2009	Human health (Reprotoxic effects)	2	Method in accordance with Rutgers University protocols; controls conducted. Only two ovaries collected for control and 20 µg/kg/day groups; three collected for others.
Ziem	1982	Human health	1	Physician's report of a patient with Methoxychlor exposure.

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