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Report of the Persistent Organic Pollutants Review Committee on the work of its twelfth meeting

Addendum

Risk profile on dicofol

At its twelfth meeting, by its decision POPRC-12/1, the Persistent Organic Pollutants Review Committee adopted a risk profile on dicofol on the basis of the draft contained in the note by the Secretariat (UNEP/POPS/POPRC.12/2), as revised during the meeting. The text of the risk profile as adopted is set out in the annex to the present addendum. It has not been formally edited.

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Annex

DICOFOL

RISK PROFILE

September 2016

Table of Contents

Executive summary

1. Dicofol is an organochlorine pesticide consisting of two isomers (*p,p'*-dicofol and *o,p'*-dicofol). Technical dicofol is composed of 80-85% *p,p'*-dicofol and 15-20% *o,p'*-dicofol with a reported variation range of DDT and other impurities. In several countries regulations exist with respect to the ΣDDT content of commercial dicofol. The FAO/WHO Specification 123/TC/S/F (1992) requires ΣDDT to be less than 0.1%. In Australia, Brazil, Canada, Japan, EU, and USA the limit is 0.1%. Dicofol has been sold from the mid-1950s as a miticidal pesticide, and has been used primarily in East and Southeast Asia, the Mediterranean coast, as well as in Northern and Central America. Dicofol is restricted or prohibited in many countries and usage has markedly decreased in the last decade (approximately 80% from the years 2000 to 2012).

2. Although laboratory data indicate that dicofol will not persist in water or sediment under neutral or alkaline conditions because of rapid hydrolysis at these pH values, dicofol is considered persistent under acidic conditions because the *p,p'*-dicofol isomer (the dominant isomer at 80-85%) meets the persistence criterion in sterile water at pH 5 (UNEP, 2014), based on the evidence presented, dicofol is likely a concern for water bodies with naturally acidic conditions. Moreover there is evidence of persistence in soil from a number of soil simulation tests, with some of the results indicating half-lives exceeding 180 days. Field soil dissipation studies from Florida and California reported dissipation half-lives in the range of 7 to 113 days for dicofol (US EPA, 1998). Experimental evidence suggests that abiotic as well as biotic degradation are dependent on the pH value of the receiving environmental compartment with longer degradation half-lives under acidic conditions. Several laboratory studies reported low mineralisation of dicofol (US EPA, 2009). Recent monitoring data show that dicofol is sufficiently persistent to be transported via riverine input to the open sea and dicofol has been detected in deep sediment layers dating back several decades. One study has measured dicofol in remote regions (Zhong et al., 2012).

3. The UN ECE Task Force on POPs under the Convention on Long-range Transboundary Air Pollution concluded that the risk profile provided sufficient information to support that dicofol was persistent with regards to the indicative values of the Executive Body decision 1998/2 based on half-life in water at pH5 or below. The UNECE Task Force concluded that ' *based on persistence, bioaccumulation, toxicity and air monitoring data from the Arctic, there was sufficient information to suggest that the substance was likely to have significant adverse human health and/or environmental effects as a result of LRAT*. The conclusion also contained a dissenting view of one expert. Therefore it is concluded that dicofol is otherwise sufficiently persistent to justify its consideration within the scope of this Convention.

4. Reported log K_{OW} values for dicofol range from 3.5 to 6.06. The bioconcentration potential of dicofol in aquatic organisms is confirmed by experimental data. The reported bioconcentration factors (BCFs) in bluegill sunfish and common carp range between 6,100 and 10,000. If steady state is considered, the BCF in bluegill sunfish is 25,000. In a full life cycle test with the fathead minnow the highest observed BCF value was 43,000. The high BCF steady state values are reflected by slow elimination from fish tissue with a half-life of 33 days. Model estimates indicate that dicofol can accumulate in aquatic species with modelled BCFs >5,000 L/kg ww. Partitioning coefficients between octanol/water and octanol/air, indicators of potential bioaccumulation in terrestrial animals for the screening assessment of POPs, show that bioaccumulation in terrestrial species might occur if metabolism is not considered. For mammals half-lives of approximately 14 days are reported.

5. Degradation products are considered in the risk profile of dicofol. Major degradates of dicofol with a higher persistence than dicofol include DCBP (dichlorobenzophenone), FW-152 (2,2-dichloro-1,1-bis(4-chlorophenyl)ethanol), DCBH (dichlorobenzhydrol), OH-DCBP (3-hydroxy-dichlorobenzophenone) and DCBA (dichlorobenzilic acid). DCBP, FW-152 and DCBH accumulated in a water/sediment study and can be classified as persistent in sediment. US EPA (2009) suggested a half-life of 313 days in soils for *p,p'*-dicofol plus major degradates and 32 days for *p,p'*-dicofol alone under slightly alkaline conditions. Modelled log K_{OW} values for the metabolites are below the screening value of 5. For dicofol metabolites (DCBP, FW-152, DCBH and OH-DCBP), estimated log K_{OW} values ranging from 3.96 to 4.89 (EPISuite v.4.0) are cited in US EPA (2009). Kelly et al. (2007) proposed that the biomagnification in the terrestrial food chain is particularly relevant, because they have a high log K_{OA}. Log K_{OW} values and log K_{OA} values for the metabolites are in the ranges that indicate a high bioaccumulation potential in terrestrial organism according to Kelly et al. (2007) and ECHA (2008). In the absence of experimental data, the estimated bioconcentration potential with one Quantitative Structure-Activity Relationship (QSAR) model for the metabolite *o,p'*-FW-152 is high (BCF 5,888 L/kg for fish). The acute LC50 toxicity values of *p,p'*-DCBP and *p,p'*-FW-152 for rainbow trout are >2.29 mg/L and 0.24 mg/L indicating for *p,p'*-FW-152 high toxicity to fish. The metabolite *p,p'*-DCBP has been shown to reveal potent

antiandrogen activity in vitro. Regarding the overall persistence (Pov), long-range transport potential (LRTP), characteristic travel distance (CTD) and transfer efficiency (TE) of the metabolites it can be concluded that although the metabolites have lower Pov than *p,p'*-DDT, aldrin and endrin, the metabolites have comparable or higher LRTP estimates to these known POPs. Notably metabolite FW-152 fulfills the Annex D criteria for PBT, with dicofol residues including FW-152 likely to fulfill the long-range transport criteria.

6. The potential of dicofol for long-range transport (LRT) has been confirmed by screening information from physical chemical information, estimated degradation half-lives in air, the application of LRT models and monitoring information from remote areas. Atmospheric oxidation by hydroxyl radicals (OH) is a possible removal pathway for dicofol in the atmosphere. Depending on the OH radical concentrations half-lives are between 3.1 to 4.7 days.

7. LRT model results show that dicofol can be transported to remote regions with moderate efficacy and that it has a high modelled capacity for enrichment in the Arctic environment. Though monitoring information from remote areas is limited, transport via air and seawater to the high Arctic demonstrates that dicofol can be detected far from sources due to LRT. No measurements from biota in remote regions were found in the literature. Among other reasons difficulties to analyse dicofol properly could be involved in this observation.

8. In most of the recent environmental monitoring studies dicofol is not directly measured but dicofol application is indicated by the ratio of measured DDT isomers (*o,p'*-DDT/*p,p'*-DDT), leading to the conclusion that dicofol is one source for current DDT pollution at least in regions of dicofol use. The use of isomer ratios for determination of DDT sources (technical DDT or dicofol) is affected by differential degradation of the isomers in various media and differing water solubility and vapour pressure of the two isomers. On this basis the use of ratios to determine source of DDT should be used with caution.

9. Dicofol is classified for environmental hazards according to the Globally Harmonized System as very toxic to aquatic life (H400) and as very toxic to aquatic life with long lasting effects (H410). The lowest observed acute (96h-LC_{50}) and chronic (95d-NOEC) effects for different fish species were 0.012 and 0.0044 mg/L, respectively.

10. Dicofol has shown reproductive effects such as eggshell-thinning and feminization of male embryos in birds. Dicofol, DCBP and FW-152 have been detected in bird eggs indicating maternal transfer to offspring. Dicofol has been detected in a variety of environmental compartments and biota. With regard to the reported chronic and acute laboratory derived effect concentrations of dicofol (e.g. $NOEC_{fish}$ 0.0044 mg/L), the detected environmental concentrations in water bodies in areas of dicofol use (0.0009 – 0.0058 mg/L, Bishnu et al. 2009) indicate the potential for causing adverse effects in wildlife on a local and regional scale.

11. The metabolism of dicofol has been studied in laboratory rodents. After uptake dicofol is distributed preferentially to adipose tissue but also to muscles, lung, testes, liver, kidney, brain and heart and is eliminated mainly in the feces. It has been shown that dicofol retains to a greater extent in adipose tissue of female rodents. In humans, dicofol or its degradation products have been detected in breast milk, blood, colostrum and adipose tissue in the low ng/g and ng/ml range. (Haraguchi et al. 2009, Lessenger & Riley, 1991, Wang et al. 2011, Lucardo et al. 2013b, Wang et al. 2014). The maximum concentration of 559 ng/g was detected in adipose tissue (Wang et al. 2011).

12. Dicofol exhibits moderate acute toxicity in mammals; common signs of toxicity include decreased spontaneous motor activity, ataxia, passiveness, somnolence, prostration, and occasionally tremors. Chronic toxic effects concern the liver, thyroid, adrenals, brain, heart and testes. A number of recent in vitro studies demonstrate interaction with the endocrine system, protein binding activity, enzyme induction and interference with other chemicals. Within Europe a priority list for endocrine disrupting chemicals has been developed to help aid action on those of highest priority. Sub-categories considered were: category 1 (evidence of endocrine disrupting activity in at least one species using intact animals), category 2 (at least some in vitro evidence of biological activity to endocrine disruption) or category 3 (no evidence of endocrine disrupting activity or no data available). Based on the review of available evidence, dicofol was listed in category 2 for wildlife and category 3 for humans. (DHI, 2007). Dicofol was more recently also addressed as an example in a wider assessment of potential EDC substances in Europe by Kortenkamp et al (2012) which alludes to a study by Roberts (2007) on developmental neurotoxicity through endocrine disruption mechanisms for dicofol in children.

13. There is some evidence of neurotoxicity, immune effects, and reproductive effects. The assessment of dicofol by IARC (1998) found that no overall evaluation of the mutagenicity of dicofol

could be made; there is limited evidence that it is carcinogenic to experimental animals and insufficient data to evaluate the carcinogenicity of dicofol to humans. Recent epidemiological studies have shown that dicofol exposure is associated with a greater incidence of prostate cancer. Certain epidemiological studies have noted associations between dicofol exposure and prostate cancer in men and leukemia, Hodgkin's disease and autism disorders in children. Limitations of these studies hinder definitive causal relationships. These epidemiological studies illustrate the concern that adverse effects associated with dicofol exposure might also occur in humans. Risk assessment for consumers has clearly demonstrated exceeding acceptable exposure limits by orders of magnitude (EFSA 2011).

14. Based on its inherent properties, dicofol 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.

1. Introduction

15. In May, 2013 the European Community and its Member States submitted a proposal to list dicofol in Annex A, B and/or C of the Stockholm Convention (UNEP/POPS/POPRC.9/3), which was considered by the Persistent Organic Pollutants Review Committee (POPRC) at its ninth and tenth meetings held in October 2013 and 2014.

16. Dicofol is an organochlorine miticidal pesticide and was introduced commercially in 1955 (WHO 1996). The substance has been used primarily in East and Southeast Asia, the Mediterranean coast, as well as in Northern and Central America (Li et al. 2014a). Intended uses of dicofol cover fruits, vegetables, ornamentals, field crops, cotton, Christmas tree plantations, and non-agricultural outdoor buildings and structures (US EPA 1998, Li et al. 2014a). Concerning the mode of action in target organisms WHO (1996) reported that dicofol produces stimulation of axonal transmission of nerve signals, believed to be related to inhibition of ATPases in the central nervous system (CNS). The signs of toxicity are consistent with CNS depression. However, the Insecticide Resistance Action Committee (IRAC) has classified the mode of action concerning efficacy for dicofol as unknown or uncertain (IRAC 2008 cited in US EPA 2009). Sanchez et al. (2010) reported that dicofol acts as a mitochondrial electron transport inhibitor.

1.1 Chemical identity

17. Dicofol is comprised of two isomers: *p,p'*-dicofol and *o,p'*-dicofol. The technical product (95% pure) is a brown viscous oil and is composed of 80-85% *p,p'*-dicofol and 15-20% *o,p'*-dicofol with up to 18 reported impurities. The purer form is generally >95% dicofol which contains less than 0.1% DDT and related compounds (ΣDDT, i.e. DDT, DDE and DDD) (WHO 1996). Please see Table 1.1-1 and 1.1-2 for the chemical identity of dicofol and the degradation products. Further information on the metabolites of dicofol is also provided in Table 2 of the information document UNEP/POPS/POPRC.11/INF/15.

Table 1.1-1. Chemical identity of dicofol

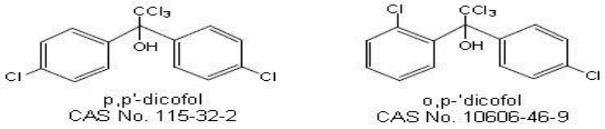
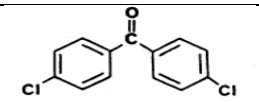
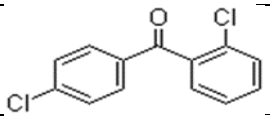
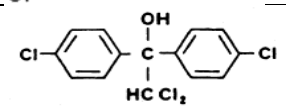
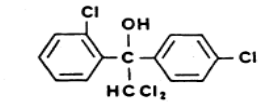
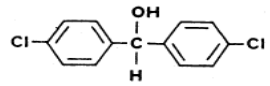
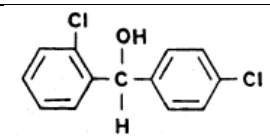
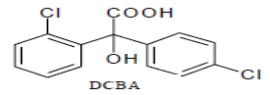
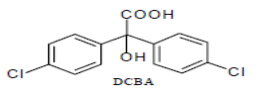
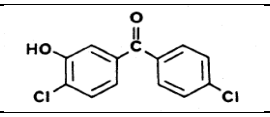
Common name IUPAC Chem. CAS chemical name	Dicofol 2,2,2-trichloro-1,1-bis(4-chlorophenyl)ethanol Benzenemethanol, 4-chloro-α-(4-chlorophenyl)-α-(trichloromethyl)- (CAS Registry)[1] 4-chloro-alpha-(4-chlorophenyl)-α-(trichloromethyl) benzene-methanol (WHO, 1996) 1,1-bis(4'-chlorophenyl)2,2,2-trichloroethanol (UNEP/POPS/POPRC.9/3)
Other names	1,1-bis(4-chlorophenyl)-2,2,2-trichloroethanol and 1-(2-chlorophenyl)-1-(4-chlorophenyl)-2,2,2-trichloroethanol (*p, p'*- and *o,p'*-isomer) (US EPA, 1998)
CAS registry number	115-32-2 (dicofol; *p,p'*-dicofol); 10606-46-9 (*o,p'*-dicofol)
Trade name	1,1-bis(chlorophenyl)-2,2,2-trichloroethanol; 4-chloro-α-(4-chlorophenyl)-α-(trichloromethyl)-; Acarin; Benzenemethanol; Carbax; Cekudifol; CPCA; Decofol; Dicaron; Dichlorokelthane; Dicomite; Difol; DTMC; ENT 23648; FW293; Hilfol; Hilfol 18.5 EC; Kelthane; Kelthanethanol; Kelthane A; Kelthane (DOT); Kelthane Dust Base; Kelthane 35; Milbol; Mitigan; *p,p'*-dicofol; NA2761 (DOT); NCI-C00486 (WHO, 1996).
Molecular formula	$C_{14}H_9Cl_5O$
Molecular weight	370.49
Structural formulas of the isomers	

Table 1.1-2. Chemical identity of environmental degradation products of dicofol (Source: US EPA 2009; Spain 2006; CAS REGISTRY 2015; Chemspider 2015)

Chemical (CAS Number)	Chemical Name	Molecular weight (g/mole)	Structure
p,p'-DCBP (90-98-2)	4,4'-dichlorobenzophenone	251	
o,p'-DCBP (85-29-0)	2,4'-dichlorobenzophenone	251	
p,p'-FW-152	1,1-bis(4-chlorophenyl)-2,2- dichloroethanol	336	
o,p'-FW-152	1-(2-chlorophenyl)-1-(4'-chlorophenyl)-2,2-dichloroethanol	336	
p,p'-DCBH (90-97-1)	4,4'-dichlorobenzhydrol	253	
o,p'-DCBH (43171-49-9)	2,4'-dichlorobenzhydrol	253	
o,p'-DCBA	2,4'-dichlorobenzilic acid	297	
p,p'-DCBA (23851-46-9)	Bis(4-chlorophenyl)(hydroxy)acetic acid, 4,4'-dichlorobenzilic acid	297	
3-OH-*p,p'*-DCBP	3-hydroxy-4,4'-dichlorobenzophenone	267	

[1] http://www.cas.org/content/chemical-substances

Physical and chemical properties

18. Dicofol has a water solubility around 1 mg/L and a low vapor pressure. The Henry's Law constant indicates low volatility from water and volatilization from moist soil surfaces is not expected to be an important fate process (HSDB 2015). However, reported values differ considerably (cf. Table 1.1-2). Zhong et al. (2014) suggested that the low Henry's Law constant and the higher log K_{OA} value of dicofol favor dicofol scavenging from atmosphere, and also dicofol partitioning in seawater. If released to air, a vapor pressure of 5.3 x 10^{-5} at 25 °C indicates that dicofol will exist in both the vapor and particulate phases in the atmosphere (HSDB 2015). Dicofol absorbs light >290 nm (HSDB 2015).

Table 1.1-3. Selected physical and chemical properties

Property	Results	Source
Melting point, ºC	77.5 78.5 - 79.5	Mackay et al. (2006) Tomlin (2001) in Rasenberg (2003)
Boiling point, °C	180 193 225	0.1 mmHg, Mackay et al. (2006) 360 mmHg, tech., Mackay et al. (2006) 665 Pa, UNEP/FAO/RC/CRC.2/14/Add.4
Density, g/cm³	1.45	Tomlin (1994) in Mackay et al. (2006)
Solubility in water, mg/L, at 25°C	0.8 1.32	Mackay et al. (2006) US EPA (2009)
Vapeur Pressure, Pa, at 25ºC	5.3 x 10^{-5} 2.5 x 10^{-4}	Mackay et al. (2006) PPDB (2012) in UNEP/POPS/POPRC.8/INF/13
Henry's Law Constant	5.66 x 10^{-5} Pa m^3/mol (25ºC) 2.45 x 10^{-2} Pa m^3/mol (25ºC) 1.44 x 10^{-7} atm m^2/mol	Mackay et al. (2006) PPDB (2012) cited in UNEP/POPS/POPRC.8/ INF/13, Saito et al. 1993 cited in Zhong et al. (2014) US EPA (1998)
Partition coefficient octanol/water (log K_{OW})	3.5 3.54 – 4.28 4.08 – 5.02 5.02 6.06	Kelly et al. (2007) Mackay et al. (2006) Rasenberg (2003) Li et al (2014a, Supporting Information), measured value recommended by EPI SUITE TM US EPA (2009), measured value
Partition coefficient organic carbon/water (log K_{OC})	3.8	US EPA (2009)
Partition coefficient air/water (log K_{AW})	-5.01	UNEP/POPS/POPRC.8/INF/13 (measured value recommended by EPI Suite v 4.0)
Partition coefficient air/octanol (log K_{OA})	8.9 9.3 10.03	Kelly et al. (2007) UNEP/POPS/POPRC.8/INF/13 (estimated value, EPI Suite v 4.0) Li et al (2014a, Supporting Information)

Table 1.1-4. Selected physical and chemical properties of the degradation products

Name	Water solubility	Log K_{OW}	Log K_{AW}
DCBP	3.8 mg/L at 25°C [b] 7.8 mg/L[b]	4.44[a] 4.62 (experimental)[b]	-5.005[a]
FW-152	1.6 mg/L at 25°C 1.8 mg/L	4.85[a]	-4.436[a]
DCBH	28.3 at 25°C[b] 19.2 mg/L[b]	4.0[a]	-6.404[a]
DCBA	99.7 at 25°C [b] 306.09 mg/L[b]	3.54[b]	-7.903[b]
3-OH DCBP	30.2 mg/L at 25°C (WSKOWv1.42)[c] 235.9 mg/L[c]	3.96[a] 4.15[b]	-8.343[a]

[a] US EPA (2009), maximal value derived in EPIsuite
[b] Chemspider (2015)
[c] EPISUITE (2015)

Analytical method

19. The analysis of dicofol is affected by several difficulties, which have to be considered when evaluating the reliability of study results: it undergoes thermal breakdown during analysis, it can degrade to *p,p'*-dichlorobenzophenone (DCBP) and cannot be distinguished from other DCBP sources if only DCBP is detected noting that *p,p'*-DCBP is also a degradate of chlorobenzilate, chloropropylate, and DDT (US EPA 2009). DCBP can also degrade at high pH (EURL-SRM 2013). While if analysis for dicofol does not include DCBP measurements within the study it may produce results that likely underestimated the concentrations of dicofol present. LC-MS/MS sensitivity for dicofol is very poor and the compound is thus typically analyzed via GC (e.g. using ECD, MSD or MS/MS). GC-analysis is challenging due to the poor reproducibility of dicofol decomposition within the hot GC-inlet and the risk of complete decomposition. The most efficient way to eliminate all the above error-sources is the use of isotope-labeled dicofol (e.g. dicofol-D8) as internal standard (EURL-SRM 2013). A study by Eng et al. (2016) looked to address this issue for air monitoring using a novel method, which provided reliable measurement of dicofol via passive air sampling through a methodology which forces the complete conversion of dicofol into DCBP.

20. The procedures of extraction and clean-up in which water and other solvents, as acetonitrile, are used can lead to degradation of dicofol (Spain, 2006). An alternative method to aid assessment of dicofol for environmental monitoring relates to the use of DDT isomers. Where the ratios of DDT isomers in technical DDT (*o,p'*-DDT/*p,p'*-DDT) and dicofol differ it is possible to make use of DDT isomer monitoring to infer what quantity of release is related to dicofol. However as degradation pathways within soil, sediment and water can vary dependent on the specific environmental conditions, due care is needed in the methodology and interpretation of results. (see section 2.3.1).

1.2 Conclusion of the Review Committee regarding Annex D information

21. The POPs Review Committee evaluated the proposal regarding dicofol (UNEP/POPS/POPRC.9/3) according to the requirements in Annex D of the Stockholm Convention at its ninth and tenth meeting in Rome. In Decision POPRC-10/3 the Committee reached the conclusion that dicofol fulfilled the screening criteria specified in Annex D. The Committee also decided to establish an ad-hoc working group to review the proposal further and prepare a draft risk profile in accordance with Annex E of the Convention. At the eleventh meeting of the POPs Review Committee the draft risk profile was discussed and it was agreed in Decision POPRC-11/2 to defer its decision on the draft risk profile for dicofol to the twelfth meeting of the Committee.

1.3 Data sources

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

(a) Proposal submitted by the European Community and its member States that are Parties to the Convention (UNEP/POPS/POPRC.9/3, UNEP/POPS/POPRC.7/INF/3), 2013;

(b) Decision POPRC-10/3 of the POPs Review Committee, 2014;

(c) Factsheet on dicofol, UNEP/POPS/POPRC.8/INF/13 (http://chm.pops.int/Convention/POPsReviewCommittee/POPRCMeetings/POPRC8/POPRC7WorkingDocuments/tabid/2801/Default.aspx, 2015-01-15);

(d) Information submitted by Parties and observers according to Annex E of the Convention: Albania, China, Ecuador, Japan, Kenya, Mali, Netherlands, Serbia, Sweden, United States of America, International POPs Elimination Network (IPEN) and Pesticide Action Network (PAN); Inuit Circumpolar Council;

(e) This information is available on the Convention's website. (http://chm.pops.int/TheConvention/POPsReviewCommittee/Meetings/POPRC10/POPRC10Followup/Dicofol(AnnexEinformation)/tabid/4293/Default.aspx, 2015-01-15);

(f) International Programme on Chemical Safety, Dicofol, WHO/FAO Data Sheets on Pesticides No. 81 World Health Organization. Geneva, July 1996 (http://www.inchem.org/documents/pds/pds/pest81_e.htm, 2015-01-15);

(g) Ospar Commission, 2002. Hazardous Substances Series, Dicofol. (http://www.ospar.org/v_publications/download.asp?v1=p00150, 2015-01-15);

(h) US EPA, 1998. Reregistration Eligibility Decision (RED), Dicofol (http://envirocancer.cornell.edu/turf/pdf/dicofol_red.pdf, 2015-01-15);

(i) US EPA, 2009. Risks of Dicofol Use to Federally Threatened California Red-legged Frog (*Rana aurora draytonii*) (http://www.epa.gov/espp/litstatus/effects/redleg-frog/dicofol/analysis.pdf, 2015-01-15).

In addition to these information sources, a literature search of public data bases was conducted that focused on recent scientific literature. The following databases were included: ECOTOXicology database, EU plant protection database, EFSA pesticides database, Pubmed, SYRAUSE Environmental Fate DataBase, OECD eChemPortal, TOXNET, The Carcinogenic Potency Database, NITE DataBase, GESTIS, WHOLIS Library and information networks for knowledge database, WHO, IPCS Inchem (International Programme of Chemical Safety), Biocatalysis/Biodegradation databases, PAN pesticide database, Google scientific search, U:search (University search, all e-journals).

1.4 Status of the chemical under international conventions

23. Dicofol is subject to a limited number of international treaties and conventions:

(a) In December 2009 dicofol was proposed to be added to Annex I (prohibition of production and use) of the Aarhus Protocol on Persistent Organic Pollutants (POPs) under the Convention on Long-Range Transboundary Air Pollution. The POPs Task Force (except for one expert) concluded that Dicofol met the indicative numerical values of the Executive Body decision 1998/2. However, no finalized action for dicofol under the LRTAP POPs Protocol was taken pending further consideration under the Stockholm Convention. In December 2013, the Executive Body of LRTAP decided to defer any discussion of dicofol until after COP7 of the Stockholm Convention in 2015[2] (Annex E information 2015 from USA);

(b) The OSPAR Commission included dicofol in the List of Chemicals for Priority Action (by 2004). Further information can be found at http://www.ospar.org/;

(c) In 2012 the Chemical Review Committee (CRC) of the Rotterdam Convention on the Prior Informed Consent Procedure (PIC) for Certain Hazardous Chemicals and Pesticides in International Trade decided that for dicofol a notification from another PIC region is outstanding, therefore at this time dicofol has not been recommended for listing in Annex III of the Convention;

(d) Since 2009 the specific exemptions for DDT listed in Annex B of the Stockholm Convention as intermediate in the production process of dicofol is outdated and no new registrations may be made with respect to such exemptions. However, the production and use of DDT as a closed-system site-limited intermediate that is chemically transformed in the manufacture of other chemicals that, taking into consideration the criteria in paragraph 1 of Annex D, do not exhibit the characteristics of persistent organic pollutants is still allowed upon notification to the Secretariat.

2. Summary information relevant to the risk profile

2.1 Sources

2.1.1 Production, trade, stockpiles

24. Dicofol has been manufactured from technical DDT by hydroxylation of DDT (van de Plassche et al. 2003). In several countries regulations exist with respect to the ΣDDT content of commercial dicofol. The FAO/WHO Specification 123/TC/S/F (1992) requires ΣDDT to be less than 0.1%. In Australia, Brazil, Canada, Japan, EU, and USA the limit is 0.1% (van de Plassche et al. 2003). Qiu et al. (2005) mentioned the legal requirement in China for DDT impurity to be no more than 0.5% of technical dicofol or no more than 0.1% of formulated dicofol by 2003. However, dicofol productions with impurities of ΣDDT above these standards were still available on the Chinese market even after 2003. The authors reported an average contents of *o,p'*-DDT, *p,p'*-Cl-DDT, *o,p'*-DDE, and *p,p'*-DDT in 23 commercially available dicofol formulations of 11.4, 6.9, 4.4, and 1.7 %, respectively. This equals a ΣDDT content of 24.4%. Also Turgut (2009) investigated dicofol formulations on the Turkish market. The ΣDDT content of formulated dicofol was between 0.3% and 14.3%. A content of 3.5% ΣDDT has been reported in dicofol produced in India (van de Plassche et al. 2003).

25. Global production of dicofol between the year 2000 and 2007 was estimated to be 5,500 t/y (tonnes/year), whereas production in USA was estimated at 160 t/y for the years 1999 to 2004 (Hoferkamp et al. 2010). Spain produced approximately 1500 t/y (formulating was conducted in Italy), and use was reported to be 100–150 t in 2000 (van de Plassche et al. 2003). Until 2006 Spain was the major manufacturer and consumer (90 t in 2006) of dicofol in Europe (OSPAR, 2008). Brazil

[2] http://www.unece.org/fileadmin/DAM/env/documents/2013/air/eb/ECE_EB.AIR_122_E.pdf

was manufacturing around 90 tonnes per annum in 2010; however this production rate declined in subsequent years down to 18 tonnes by 2013, and ceased completely in 2014 following agreement between the Brazilian government and producers. Remaining stockpiles in Brazil were expected to have been fully used/destroyed by 2015 (Brazil, 2016).

26. The following notifications were made to the Stockholm Convention's register for closed site limited production/uses (UNEP 2015[3]). In Brazil, dicofol was produced by Nortox (plant capacity was 0.2 tonnes/d), but production ceased in 2003 and 2004 for closed-system site-limited production. In India production and use was 150 t on the date of notification (10/27/2006). Dicofol was produced in a closed system in batches. On the basis of the notification submitted to the Secretariat by India on 10 March 2014, the production and use of DDT as a closed-system site-limited intermediate in the production of dicofol has been extended until 15 May 2024 (UNEP/POPS/COP.7/4/Rev.1). In China production and use were 3,000 -4,000 t on the date of notification (2/2/2005). About 80% of DDT was used as an intermediate in the production of dicofol. There were 6 enterprises with the capability to produce dicofol (UNEP 2015).

27. China was one of the major producers of technical DDT and dicofol, which amounted to approximately 97,000 t of technical DDT between 1988 and 2002. Over half of this amount (approximately 54,000 t) was used to manufacture dicofol (40,000 t) (Qiu et al. 2005). In China, the enterprises registered to produce technical dicofol and its formulations were distributed in 13 provinces and municipalities. In 2013, the last remaining technical dicofol producer in China ceased production of technical dicofol. In 2014, it shut down its production line for technical dicofol. By a letter dated 28 February 2014, China notified the Secretariat that as of May 2014 it had withdrawn the use of DDT as a closed-system site-limited intermediate starting from June 2014 (UNEP/POPS/COP.7/4/Rev.1-Corr.1).

28. In India, the Indian state-owned enterprise and currently the only known producer of dicofol, Hindustan Insecticides Ltd, has a production capacity for dicofol of 150 t/y (company homepage[4]) and still manufactures dicofol with an average annual production output of approximately 50 t (Li et al. 2014a). No data on current production could be found in literature regarding other potential current producers, e.g. Dow AgroSciences and Adama Agricultural Solutions Ltd (formerly Makhteshim Agan Industries Ltd).

29. In 2011 US EPA published an order for the voluntary cancellation of dicofol at the request of the registrant (Makhteshim Agan of North America, Inc). Existing stocks provision allowed the registrant to reformulate it into end-use products and sell it until 2013. Sale and distribution by others was allowed until 2013. A final rule revoking most dicofol residue tolerances was issued in 2012. Import tolerances for tea were maintained pending future decision making (Annex E information, USA, 2015).

2.1.2 Uses

30. Dicofol is used as miticidal pesticide in many countries around the world and reported to be applied to food, feed, and cash crops including apple, citrus, lichi, longan, pear, leafy vegetables, tea, and cotton (Li et al. 2014a). It is also used on ornamentals such as orchids. In Senegal, dicofol is used on onion, watermelon, potato and pimento crops (Jepson et al. 2014). In Mexico, there are 17 registrations for dicofol, which is authorized for the application on aubergine, chilli, strawberry, lime, apple, orange, pear, watermelon, mandarin, grapefruit, vine, citrus fruits, ornamental shrubs, ornamental plants and nursery gardens (comment from Mexico, May 2015, to the POPRC dicofol draft risk profile). In Brazil dicofol was used an acaricide for cotton, citrus and apple crops. However this usage was banned after the registration for use of dicofol as a pesticide was removed in 2015 (Brazil, 2016). It is reported to be restricted or prohibited in most developed countries. In Canada, use has not been permitted since 2011, and in the USA, use will not be permitted after 2016 (Li et al. 2014a; Annex E information, USA, 2015). Dicofol is banned in Benin, Côte d'Ivoire, the European Union, Guinea, Iraq, Indonesia, Japan, Mauritania, Oman, Saudi Arabia, and Switzerland (Annex E information, 2015, comments from Iraq and Côte d'Ivoire, May 2015, to the POPRC dicofol draft risk profile and from Indonesia during the 11th POPRC meeting).

31. Li et al. (2014a) estimated, based on a combination of literature surveys, field surveys and personal communications, a total of 28,200 t (tonnes) of dicofol used globally in a 13 year period from 2000 to 2012, mainly in Asia (21,719 t), followed by North America (1,817 t), Europe (1,745 t), Latin America (1,538), Africa (1,434 t) and Oceania (13 t). The estimated use by continent in 2012 was for Asia 619 t (mainly in China 530 t and India 43 t), North America (USA) 33 t, Latin America

[3] http://chm.pops.int/Implementation/Exemptions/RegisterofSpecificExemptions/tabid/1133/

[4] http://www.hil.gov.in/DICOFOL%20.html

38 t, Africa 36 t, and Oceania around 1 t. Over the period 2000 to 2012, 76.8% of the usage was estimated in Asia, mainly in China (69.1% of total usage). However, between 2000 and 2012 the estimated dicofol usage decreased by 75% in China (from 2,013 t to 530 t), 69% in India (from 145 t to 43 t) and 90% in the USA (from 324 t to 33 t) with most use occurring in California and Florida. The decrease of estimated global use from 2000 (3,350 t) to 2012 (730 t) was approximately 80%. Average application rates were 1.3 kg/ha, 0.44 kg/ha and 0.31-0.45 kg/ha in the USA, Europe and China, respectively (Li et al. 2014a).

32. In Europe dicofol usage was estimated to decrease from 317 t to 32 t between 2000 and 2009 (Li et al. 2015). According to estimated emission data published by van der Gon et al. (2007), the major consuming countries in 2000 were Spain, Italy, Turkey, Romania, and France. In EU countries, the use of dicofol for plant protection products expired by 2010 at the latest according to Commission Decision 2008/764/EC[5]. In addition, all non-agricultural uses are prohibited according to the Biocidal Products Regulation No (EC) 528/2012[6]. In 2010 a dicofol questionnaire for the Water Framework Directive 2000/60/EC was sent to EU Member States. France reported 2.8 tonnes sales in 2008 and 2.3 tonnes in 2009 and Italy 6.8 tonnes in 2008 (Entec UK Limited, 2011).

33. Notice No. 11 of 1997 issued by Ministry of Agriculture of China banned the use of dicofol on tea plants. Ministerial Announcement of Agriculture No. 199 of 2002 re-stressed the ban of dicofol on tea plants. At present, registered use of dicofol in China is to prevent *Tetranychus cinnabarinus*, *Tetranychus viennensis (Zacher)* and *Phyllocoptruta oleivora (Ashmead)* on cotton, citrus and apple trees (Annex E information, China). The market share of dicofol in China`s acaricide market has declined from 27% (in 1999) to less than 8% after 2008 (Li et al. 2014a).

34. In summary the data provided by Li et al. (2014a), together with other above mentioned literature sources; plausibly indicate a decreasing trend of global dicofol usage, which probably is continued after the observed study period (2000-2012). Therefore, it can be estimated, that the current global dicofol use is well below 1,000 t/y, and is most likely closer to the currently only known production of 50 t/y in Asia.

2.1.3 Releases to the environment

35. Principal releases to the environment can occur from the production process, professional or private use and the resulting waste. Li et al. (2014a) estimated via BETR-Global Modelling the realistic global contribution of dicofol and concluded that, of the estimated 28,200t used between 2000 and 2012, 731t remain in the environment. The results from the model also indicates a declining trend in emissions after 2008 due to lower release estimations of 1000 t per year which is more in line with current rates. They also estimated that 1.9 t of dicofol has been deposited in the Arctic, and 2.2 t in the Antarctic as a result of LRT. These are modeled data but not measured in the field.

36. Dicofol is produced in a closed system but releases can result from improper production practices. Li et al. (2014) described DDT, dioxin and furan releases from a closed system dicofol production process in China. The annual amounts of ΣDDT and *p,p'*-DDT directly released to the environment via the use of dicofol were estimated as 9,480 kg and 1,080 kg, respectively. From the PCDD/F distribution patterns, it is suggested that the major pathway for PCDD/F formation involves precursor synthesis during the production of dicofol in the closed-system process, which is estimated to result in an annual release to the environment of 0.17 g I-TEQ (toxicity equivalent value) from this particular company (Li et al. 2014).

2.2 Environmental fate

2.2.1 Persistence

Abiotic degradation

37. Both dicofol isomers are susceptible to aqueous hydrolysis and the hydrolysis degradation rate is pH dependant. *o,p'*-Dicofol hydrolyzed with half-lives of 47 days at pH 5, 8 hours at pH 7, and 9 minutes at pH 9. *p,p'*-Dicofol hydrolyzed with half-lives of 85 days at pH 5, 64 hours at pH 7, and 26 minutes at pH 9 at 25°C (IUCLID cited in Rasenberg, 2003; US EPA 1998). The major degradate in the studies, the *o,p'*- and *p,p'*-isomer of dichlorobenzophenone (DCBP), appeared to resist further degradation (no quantification was provided in US EPA, 1998). Other metabolites for *p,p'*-dicofol were isolated but not identified (US EPA 1998). According to Boethling et al. (2009) the potential for the formation of more persistent degradation products must also be assessed for all POPs.

[5] http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32008D0764

[6] http://eur-lex.europa.eu/legal-content/EN/ALL/?uri=OJ:L:2012:167:TOC

38. At a pH of 5, the half-life of dicofol's main *p,p'*-isomer was 85 days, fulfilling the cut-off value of 60 days for persistence in water (UNEP/POPS/POPRC.10/10). Approximately 680 (14%) out of 4,837 watersheds i.e. lakes and rivers from northern European countries (DK, GB, IE, FI, NO, SE, EE) have a minimum pH value of ≤6 and 139 (3%) watersheds displayed a pH ≤5. The data were extracted from the European Environment Agency (2015) Waterbase databank[7]. Pienitz et al. (2004), Hawes et al. (2002) and Michelutti et al. (2002) reported in addition to neutral and alkaline pH values also acidic pH values in several Arctic lakes and ponds. Black-water rivers found in several areas around the world (Australia, Amazonia, Europe, Indonesia, the Orinoco basin and the northern and southern areas of the United States) typically have a pH of around 5 (Alkhatib et al. 2007), but some black-water rivers can also have higher pH values (Horbe and da Silvia 2009, Rousu 1999). In conclusion, based on the evidence presented, dicofol is likely a concern for water bodies with naturally acidic conditions.

39. Experimental data on aqueous photolysis of dicofol at pH 5 showed photolysis of *o,p'*-dicofol with a DT50 of 14.8 days and *p,p'*-dicofol photodegraded with a half-life of 92.5 days (US EPA, 1998). If corrected for the control samples the DT50 values for *o,p'*-dicofol and *p,p'*-dicofol are 27.5 and 244 days, respectively (US EPA, 2009). US EPA (2009) reported soil photolysis half-lives of 56 and 21 days for *o,p'* and *p,p'*-dicofol, respectively. Photolytic half-lives of 30 days for both isomers were cited in Spain for soil (2006). However the photolysis studies lacked information with regard to the light spectrum and TLC chromatograms. *p,p'*-DDD and DCBH were detected with 4.5% and 20% applied radioactivity respectively (Spain 2006). US EPA (2009) concluded that photodegradation is not expected to be significant route of dissipation of dicofol in the environment.

40. The estimated atmospheric half-life for dicofol based on reaction with hydroxyl (OH) radicals is 3.1 days, using the default atmospheric hydroxyl radical concentration of 1.5×10^6 molecules/cm^3 during sunlight hours in AOPWIN, EPISUITE v4.11TM computer program[8]. Using a lower hydroxyl radical concentration of 5×10^5 molecules/cm^3, which is generally used as a daily (24-hour) average in relatively unpolluted air in the EU (EC 2003), the atmospheric half-life is 4.7 days. It should be noted that hydroxyl radical reaction rates vary spatially and temporally with average daily sunlight, and 5×10^5 molecules/cm^3 may not be typical of northern latitudes since hydroxyl radical concentrations decline with latitude. Moreover AOPWIN estimates the gas-phase reaction rate for the reaction between OH radicals and the chemical at 25°C. However based on the physical chemical properties (cf section 1.1) dicofol can exist in air in the gas and particulate phase. HSDB (2015) reported for dicofol light absorption at wavelengths >290 nm which suggests that photolysis may be an important degradation process in the atmosphere (Chen et al. 1984 cited in HSDB 2015). Rena et al. (2011) studied the theoretical photodegradation mechanisms of dicofol by density functional theory calculations. The authors found that OH radicals attacking the C7-C8 bond and the addition of OH to the C12 atom of dicofol are favorable pathways. Besides one dominant reaction product $(C_6H_4Cl)_2CO$ a precursor for forming PCDD/Fs, C_6H_4ClOH(4-CP) was identified.

Biotic degradation

41. In a ready biodegradability test, conducted according to the OECD 301C Test Guideline dicofol (at a concentration of 100 mg/L which is above the water solubility of 1 mg/L), reached 0% of its theoretical BOD (biological oxygen demand) in 4 weeks using an activated sludge inoculum at 30 mg/L (Japanese NITE database, 2015)[9].

42. The fate and behavior of dicofol during wastewater treatment has been assessed by Oliveira et al. (2012). The authors specifically investigated the biodegradation of dicofol during aerobic wastewater treatment and anaerobic sludge biodigestion using ^{14}C labeled dicofol. Residues of dicofol, and the breakdown product DCBP, were quantified, but the recovery rate for dicofol in wastewater was only about 60%. After seven days of the aerobic process 55%-60% of the applied radioactivity (AR) was associated with the activated sludge (14% dicofol, 41% '*p,p'*-DCBP) and 45% to the wastewater (5% AR dicofol, 40% AR unknown metabolites). After aerobic treatment only 0.1% AR of dicofol was mineralized. After 18 days in the anaerobic process, only 3% of the dicofol and 5% of *p,p'*-DCBP was detected in the sludge with 70% of remaining radioactivity in the sludge associated with other metabolites. This study, therefore, suggests that dicofol can be degraded (in the system studied) to other compounds, but not mineralized. However, sewage treatment plants are not expected to be primary receiving compartments for dicofol; this route of elimination may not be the most relevant to the use-profile for dicofol.

[7] http://www.eea.europa.eu/data-and-maps/data/waterbase-rivers-6

http://www.eea.europa.eu/data-and-maps/data/waterbase-lakes-10

[8] http://www.epa.gov/opptintr/exposure/pubs/episuite.htm

[9] http://www.safe.nite.go.jp/jcheck/detail.action?request_locale=en&cno=115-32-2&mno=4-0226 (Reports: Dicofol (The results of the investigation))

43. In a laboratory water/sediment test with two different water/sediment systems (using approved EU methods detailed in Council Directive 91/414/EEC and Council Directive 95/36/EC; SETAC Environmental Fate protocols, ad Good Laboratory Practice (GLP). Test conditions set at water pH 7.1 and 7.9, 20°C) DT50 degradation values in the whole sediment/water system were between 7 and 13 hours for *p,p'*-dicofol and less than 2 hours for *o,p'*-dicofol. Isomer specific accumulation in sediments of major metabolites at the end of the experiment after 100 days occurred for *p,p'*-DCBP (22% AR), *p,p'*-DCBA (dichlorobenzilic acid, 10% AR) and *o,p'*-DCBH (dichlorobenzhydrol, 40% AR). Other major metabolites >10% AR detected in the studies were: *o,p'*-DCBP, *p,p'*-DCBH, *p,p'*-FW-152 (2,2-dichloro-1,1-bis(4-chlorophenyl)ethanol) and *o,p'*-DCBA (UNEP/POPS/POPRC.8/INF/13, Spain, 2006). A new study with water/sediments at pH <7 has been required for the assessment of the fate of dicofol in the aquatic environment (Spain, 2006 in UNEP/POPS/POPRC.8/INF/13). A study by Wicks (2002) (quoted in Rasenberg, 2003) indicated half-lives in sediment for DCBP, DCBH and DCBA in the range of 7 to 13 days, 197 to 429 days and 24 to 174 days, respectively. Belfroid et al. (2005) indicated that DCBP degrades to the corresponding alcohol or carboxylates molecules (DCBH and DCBA) and these products degrade at different rates in sediment. For DCBA the half-life in sediment is <6 months, while for DCBH the half-life in sediment is >6 months. But no media and also no source is quoted for this finding. According to Annex E submission (2015) from USA, dicofol is expected to partition to sediment based on log K_{OW} of 6.06 and a K_{OC} of 7,060 mL/g. US EPA (2009) stated that anaerobic soil metabolism studies (pH value 7.9) indicate that dicofol will degrade relatively rapidly in sediment with a half-life less than 30 days. Xia (2008) reported enhanced disappearance of dicofol by water hyacinth in a laboratory study, although further studies to confirm reproducibility of the results are not known to exist.

44. In aerobic degradation soil studies under laboratory conditions (20 and 25°C), *o,p'*-dicofol was degraded more rapidly than *p, p'*-dicofol. The data showed that the rate of degradation was fastest in soils with higher pH. In a GLP study carried out according to EU requirements (Council Directive 91/414/EEC Annex II, Point 7.1.1.2.1), reported DT50 values in the soil with a pH of 8.4 were 18 and 204 days for *o,p'*-dicofol and *p,p'*-dicofol at 20°C, respectively. In the other two European soils (pH 4.9 and 6.7), no degradation was observed under the study conditions for *p,p'*-dicofol. DT50 for *o,p'*-dicofol was 468 days in the clay loam (pH 6.79) with no degradation observable in the other soil. Mineralization was low (Spain, 2006 cited in UNEP/POPS/POPRC.8/INF/13). The DT50 of 8.5 and 31.5 days for *o,p'*-dicofol and *o,p'*-dicofol originate from US EPA guideline soil metabolism studies (silt loam silt loam 25°C, pH 7.5 and 7.8, GLP). According to the results of degradation studies in soil and the results of the hydrolysis studies, the degradation of dicofol is pH dependant (Spain, 2006). Many areas especially in northern Europe have a soil pH<7 (Böhner et al. 2008). Data on pH in soils globally can be found in IGBP-DIS (1998). In the Annex E submission (2015) from Sweden referring to an ecotoxicological evaluation in 1988, it was concluded that the commercial dicofol then available had a slow degradation (DT50 of 10 – 205 days) and did not further degrade to reach full mineralization.

45. US EPA (2009) indicated for lab soil simulation studies that *o,p'*-dicofol degraded with a half-life of 8.5 days in a loam soil and the *p,p'*-isomer degraded with a half-life of 32 days in a silt loam soil (pH from 7.5 to 7.9). Major metabolites for the *p,p'*-isomer were *p,p'*-FW-152, *p,p'*-DCBP, and 3-hydroxy-4,4'-dichlorobenzophenone (3-OH-*p,p'*-DCBP). Volatile residues were 21-22% and <4% of the applied and unextractable residues were 10-15% and 57-61% of the applied after 12 months for the *p,p'*- and *o,p'*-dicofol isomer, respectively (US EPA 1998). Parent plus major degradation products of concern (including the *o,p'*- and *p,p'*-isomers of DCBP, FW-152, DCBH, OH-DCBP) degraded with a half-life of 104.5 days and 313 days (pH of 7.5 and 7.8) in two soil metabolism studies for *o,p'*-dicofol and *p,p'*-dicofol, respectively (US EPA 2009). Anaerobic soil metabolism half-lives of 6 and <30 days for the *o,p'*- and *p,p'*-dicofol (pH values 7.9 and 7.8) were determined, respectively (US EPA 2009).

46. US EPA (1998) stated that in ecological monitoring studies conducted in Florida and California, dicofol dissipated from the soil surface with a half-life ranging from 58 to 113 days. In a dissipation study on cotton in California half of dicofol residues dissipated in less than 7 days. In another dissipation study on strawberries in California dissipation DT50s of 22 days for *o,p'*-dicofol and 72 days for *p,p'*-dicofol were measured. Half-lives for the *o,p'*-DCBP and *p,p'*-DCBP in the two studies in California, were between 29 and 45 days, and 55 and 132 days, respectively (US EPA 2009). Kumari and Duhan (2011) carried out a field trial in India to assess the persistence of residues of dicofol on cotton and in soil after spraying. Residues dissipated almost completely from soil in 60 days (dissipation half-life of 9 days). However, the soil was extracted with ammonia and the detection method did not account for analytical losses. Dicofol residues were detected in cotton lint and seed. No degradation products were measured or suggested by the authors. A field trial at 26°C and pH 5.9 reported a (dissipation) half-life of 40 to 50 days (study author Hofmann 1986 Annex E

information, 2015, Sweden). However, no DT50 value could be calculated from this study according to Spain (2006). Rasenberg (2003) provided dissipation half-lives in the range of 3.7 to 62 days for the dicofol isomers. Based on a comparison of applied formulation and soil parameters the studies quoted by Rasenberg (2003) are identical with the studies evaluated by Spain 2006. EFSA (2014) pointed out that there are a number of difficulties in the determination of a reliable degradation rate parameter from field studies e.g. the initial decline of applied substance can be more rapid followed by a slower rate of decline, loss of the substance due to volatilization or leaching, uptake by plants, run-off etc. However, translocation processes did not play a part in the loss or degradation rate of dicofol in the Florida and California studies.

47. US EPA (2009) makes estimates for persistence of dicofol in the environment, with half-lives of less than 90 days in soil, depending upon the specific environmental conditions. However, when dicofol and its major degradates are considered together, conservative estimates provided by US EPA (2009) show that persistence of dicofol and its major degradates could be as high as 313 days (pH 7.8). US EPA (2009) also noted that there is a lack of adequate information to estimate persistence of dicofol degradates in the environment.

Monitoring data

48. Weaver et al. (2012) investigated organochlorine residues in surface soils from the Namoi Valley, Australia. The study aimed to quantify historical residues in soils. Dicofol was measured and detected by a certified Government analytical laboratory in one Vertisol soil sample at 18 ng/g. The pH of this soil was 6.9 ($CaCl_2$) and the detected level was attributed to a historic use (T. Weaver, personal communication, March, 2015). Dicofol was also measured in deeper layers in dated sediment cores from Lake Saint André in northern France by Sabatier and co-workers. Measured residues traced back to the 1940s sediment layers, with highest levels in the 1970s, 1992, and 2000. As dicofol was introduced on the market in 1958, it is likely that dicofol leaching through the soil affected the lower sediment layers; although conclusive proof was not provided by the author to define any specific mechanism. Though no half-lives were calculated the data indicate that dicofol can persist in this environment for several decades (Sabatier et al. 2014). Zhong et al. (2015) measured high dicofol levels in surface sediment samples from the coastal and offshore regions of the Bohai and Yellow seas. The presence of concentrations of dicofol at river estuaries, sea water (pH >7) and sea sediments suggests that dicofol is sufficiently persistent to be distributed to the sea. Mean concentrations of dicofol near the Yangtze River and Yellow River estuaries were seven times higher than those at other sampling sites (Zhong et al. 2015) indicating higher inputs closer to the estuaries. Though data for remote regions are very limited, dicofol has been detected in the Arctic environment in seawater and air (Zhong et al. 2012) suggesting sufficient persistence to be transported to higher latitudes (reported levels from source regions and higher latitudes are reported in section 2.3.1).

Summary on persistence

49. Experimental evidence suggests that abiotic as well as biotic degradation of dicofol are dependent on the pH value of the receiving environmental compartment with longer degradation half-lives under acidic conditions. The dominant dicofol isomer (*p,p'*-dicofol) is persistent under acidic conditions in hydrolysis studies. According to the available laboratory studies dicofol will degrade in aquatic compartments with a pH $\geq$ 7. Experimental primary degradation half-lives for dicofol in soil are variable. Dicofol is not persistent in some soils according to field studies performed in California and Florida. However field studies in colder climates and degradation rates for metabolites are not available. A conservative estimate for persistence of *o,p'*- and *p,p'*-dicofol and major degradates of concern of as high as 104.5 and 313 days in soil (from laboratory studies) was reported. Recent monitoring data have shown that dicofol is sufficiently persistent to be transported via riverine input to the open sea and to be detected in deep sediment layers dated back several decades. One study has measured dicofol in remote regions. The breakdown of dicofol to DCBP during analysis makes it difficult to determine the source of the identified DCBP. In addition, it would be impossible to determine the meaning of non-detections, i.e., non-detections do not mean that dicofol was not present.

2.2.2 Bioaccumulation

Screening assessment based on physical-chemical properties

50. The reported log K_{OW} values for the *p,p'*- and *o,p'*-isomers of dicofol span a wide range from 3.5 to 6.06, respectively (see section 1.1). A maximum measured log K_{OW} value of 6.06 was used for modelling estimates by US EPA (2009). The following log K_{OW} values for dicofol are reported by Li et al. (2014a): 5.02 (measured value recommend by KOWWIN in EPI suite), 4.18 (logarithmic mean of measured values 4.08-4.28) for *p,p'*-dicofol and 4.40 (logarithmic mean of measured values 4.32-4.34) for *o,p'*-dicofol. For dicofol metabolites (DCBP, FW-152, DCBH and OH-DCBP), estimated log K_{OW} values ranging from 3.96 to 4.89 (EPISuite v.4.0) are cited in US EPA (2009). These values indicate a potential for bioconcentration in aquatic organisms for dicofol as well as for its degradation products, although most of them are below the screening trigger of 5 of the Stockholm Convention.

51. The octanol/air partition coefficient (K_{OA}) is mentioned as an indicator of potential bioaccumulation in terrestrial animals for the screening assessment of POPs (UNEP/POPS/POPRC.3/INF/8, 2007). Kelly et al. (2007) proposed that the biomagnification of dicofol in the terrestrial food chain is particularly relevant, because it has a high log K_{OA}. According to two different sources, the proposed log K_{OA} values for dicofol are 8.9 and 10.03 (Kelly et al. 2007; and Li et al., 2014a). Based on a log K_{OW} range of 3.5 to 6.06 and a log K_{OA} range of 8.9 to 10.02, a high bioaccumulation potential in both air-breathing organisms and aquatic organisms can be expected (log K_{OW} higher than 2 and a log K_{OA} higher than 5 according to ECHA 2008). For the degradation products log Koa values were estimated with KOAWIN EPISuite v.4.1. Estimated log K_{OA} values were 8.799 for DCBP, 12.07 for FW-152, and 10.4 for DCBH. Log K_{OW} values and log K_{OA} values for the metabolites are in the ranges that indicate a high bioaccumulation potential in terrestrial organism according to Kelly et al. (2007) and ECHA (2008).

Bioconcentration and bioaccumulation studies in aquatic organisms

52. In a 28-day laboratory BCF study with bluegill sunfish (*Lepomis macrochirus*) exposed to *p,p'*-dicofol, a BCF of 10,000 was observed in whole fish (steady state was not reached), the estimated steady-state BCF for dicofol was 25,000 (US EPA 2009). In this study, parent dicofol represented >94% of the radioactivity measured after the 28-day exposure, suggesting that metabolism of dicofol was minimal in fish. FW-152 and OH-DCBH were detected in tissue samples (each at 4.7% AR) according to US EPA (2009) and UNEP/FAO/RC/CRC.2/14/Add.4 in Annex E information, Netherlands (2015).

53. UNEP/POPS/POPRC.8/INF/13 cited the same BCF of 25,000 for dicofol (*p,p'*-isomer) in fish with a slow clearance time and a estimated depuration rate (CT_{90}) of 110 days. No further information is given on the fish species used or BCF calculation details.

54. In an early life stage test with the aquatic invertebrate, *Hyalella azteca* and the fathead minnow (*Pimephales promelas*), mean 28-day BCF values of 10,000 (±3000) and 3,700 (±800), respectively, were observed. As the duration of this study was insufficient to allow the test organisms to reach steady-state, it is expected that if the duration had been extended, observed BCF values would have increased, according to US EPA (2009). In another study quoted in US EPA (2009), a full life cycle test (US EPA 40 CFR Part 158 Guideline 72-5, GLP, flow-through conditions) with the fathead minnow, the highest observed BCF value was 43,000, which was observed in F_0 females after 296 days of exposure to dicofol. The BCFs (based on total ^{14}C activity; range of 11,000 to 43,000) from this study indicated that dicofol tends to concentrate in the tissues of fish at all growth stages (Spain, 2006).

55. Studies according to the OECD 305 Test Guideline resulted in BCF values of 8,200 and 6,100, obtained for common carp exposed to 0.1 and 1 µg/L (Japanese NITE database, 2015[10]). A recent bioaccumulation test based on the use of zebrafish eleutheroembryos as an alternative to adult-individuals indicate that the BCF was highest for dicofol compared to chlorpyrifos and atrazine. Zebrafish eleutheroembryos (72 h after hatch) were exposed to 0.1 and 1 µg/L dicofol for a period of 48 hours. Steady state was not reached. The log BCF was 3.9 (=7,943 L/kg) calculated with two toxicokinetic models assuming steady state (El-Amrani et al. 2012). Based on analytical challenges to measure dicofol accumulated residues might also include breakdown products in the above cited studies.

[10] http://www.safe.nite.go.jp/jcheck/detail.action?request_locale=en&cno=115-32-2&mno=4-0226 (Reports: Dicofol (The results of the investigation))

Toxicokinetic and metabolism studies

56. Metabolism and toxicokinetics are well described in WHO (1992), US EPA (1998) and JMPR (2011). Single doses of 25 mg/kg were administered to male mice. Approximately 60% of the administered dose was eliminated within 4 days primarily in the feces. Fecal excretion accounted for 40% of the administered dose whereas urinary excretion accounted for 20%. Peak tissue concentrations were reached within 24-48 h. The highest concentrations of the radiolabel led compound were found in adipose tissue followed by liver, kidney, lung, heart, blood plasma, brain, whole blood, and spleen Concentrations dropped rapidly over 4 days except in adipose tissue (Kaneshima et al., 1980). Metabolism studies in rats were performed with radiolabelled dicofol with administration of high (50 mg,/kg bw single treatment) and low (0.5 mg/kg bw for 16 days) doses. The dicofol was eliminated mainly with the feces, or stored in adipose tissue. The metabolic pathways for dicofol were deduced, with the major one involving reductive halogenation to dichlorodicofol and oxidation to dichlorobenzophenone, dichlorobenzoic acid, and dichlorobenzil. The analysis of metabolites revealed at most 0.2% of the radioactive residue was DDE which could be contributed by the presence of DDT (0.2%) and DDE (0.01%) in the test material. The data indicated that dicofol metabolized differently from that of DDT, which is metabolized to the purported carcinogen, DDE (US EPA 1998). In an ADME (adsorption, distribution, metabolism, excretion) study in rats dicofol distributed preferentially to adipose tissue and was eliminated mainly in the feces. Essentially the entire dicofol dose was excreted within 8 days (IPCS Inchem 1992). For repeated exposure elimination half-lives were estimated to be 6-14 days for dicofol (Steigerwalt et al. 1984b cited in IPCS Inchem 1992).

57. Dietary feeding for 12 weeks (32 ppm) of rats demonstrated; that after 8 weeks an equilibrium in fat (at 25 ppm for males and 70 ppm for females) was reached. After 12 weeks dicofol was withdrawn and concentrations declined; whereas in males it was zero after 14 weeks, it remained at about 6 ppm in females. Also higher and lower levels in the diet were stored to a higher extent in females than in males (IPCS, 1992).

58. In bluegill sunfish elimination was slow with minimal metabolism. The estimated depuration half-life was 33 days (US EPA 1998, US EPA 2009). Brown and Casida (1987) provide details of a study on metabolism of both dicofol and separately DDT as an impurity to dicofol. Preparations were administered to male mice at 30mg/kg bw and also incubated with rat livers. Results indicated that dicofol is dechlorinated to dechlorodicofol (DCD), with both dicofol and DCD metabolized to DCBP and dichlorobenzhydrol. Brown and Casida (1987) suggest that in vivo metabolic pathways for dicofol will likely involve a reduced porphyrin (porphyrin is a liver enzyme required for healthy metabolic function) in liver microsomes. In vitro exposure of bovine and rat microsome indicates that formation of DCBP is not dependent on enzymatic activity but rather results from inorganic mechanisms, primarily via OH-catalyzed elimination of a trichloromethyl anion (Thiel et al, 2011).

Assessment of bioconcentration and biomagnification models and monitoring data

59. Based on governmental assessment reports (US EPA 1998, US EPA 2009, Spain 2006) and the conducted literature search no empirical information on bioaccumulation, biomagnification and trophic magnification in food webs is available for dicofol.

60. However, Malik et al. (2011) examined the potential persistence and bioaccumulation for dicofol across three heronries based on the rivers Chenab, Ravi and the Rawal Lake Reservoir in the Punjab region of Pakistan. Samples of surface sediment (n=15, to a depth of 3-8 cm) along with prey item (e.g. insects, toads, fishes) (n=150) and egret eggs (n=30, one egg from each nest) from within the heronries were collected during the summer months of 2007. Sediment mean concentration from Chenab and Ravi were 12.5±18.4 and 11.3±16.2 ng/g, respectively. The key finding is that, in all cases, the greatest concentrations of dicofol from the three locations were found within egg samples (10±21.3, 38.4±50.2 and 48.3±53.3 ng/g, mean values) compared to prey (not detected, 21.6±30.6 ng/g and 10.3±14.5 ng/g, mean values), suggesting bioaccumulation in all three heronries. However, results were not lipid corrected, so the values may not fully explain if there was in fact biomagnification to higher order species.

61. Estimated BCF values for dicofol with the KABAM model[11] ranged from about 28,000 L/kg for filter feeders to about 55,000 L/kg for phytoplankton (USA, Annex E submission, 2015). Estimates of FW-152 residues in fish were highest among the model results for metabolites (US EPA 2009).

[11] http://www.epa.gov/oppefed1/models/water/kabam/kabam_user_guide_appendix_d.html

62. QSAR (Quantitative Structure Activity Relationship) estimates for the log BCF values of the metabolites *p,p'*-DCBP, *p,p'*-DCBP, *p,p'*-FW-152, *o,p'*-FW-152 and *p,p'*-DCBH, *p,p'*-DCBH was calculated using VEGA[12]. VEGA is an open source platform that contains three BCF tools including one read across model. Read across, in this case, means that unknown values (in this case log BCF) of a target compound(s) are estimated based on the known values for structurally related substances. For FW-152 isomers a log BCF of 3.77 (5,904 L/kg) was calculated with the BCF read across model.

63. Kelly et al. (2007) calculated (assuming a log K_{OW} of 3.5) high biomagnification factors (BMFs) in terrestrial species ranging from 6.1 in reptiles to 76 in humans. However, metabolic transformation can reduce or eliminate the anticipated biomagnification potential, but only if the metabolic transformation rate is sufficiently high, in which cases, the bioaccumulating behavior of resulting metabolites should also be considered.

Summary on bioaccumulation

64. Dicofol has a high bioconcentration potential as demonstrated by experimental derived BCF values in fish that range from 6,100 to 43,000 and an experimental calculated depuration half-life of 33 days in bluegill sunfish. Model calculation indicates high biomagnification factors for terrestrial species, which may be reduced if metabolic transformation was considered. For dicofol measured log K_{OW} values are from 4.08 to 6.06, for metabolites estimated log K_{OW} values are from 3.54 to 4.89, as well as the log K_{OA} values for dicofol and its metabolites indicate that a high bioaccumulation potential might occur based on this screening information (without the consideration of metabolism). In addition a QSAR model calculation identified a high bioconcentration potential for FW-152. One monitoring study indicated bioaccumulation in heron eggs, but the results were not lipid corrected, so the values may not fully explain if there was in fact biomagnification within the food chain.

2.2.3 Potential for long-range environmental transport

Screening of physical-chemical properties

65. Under Annex D, an atmospheric half-life >2 days is recognized as a criterion for long-range transport potential (LRTP). Calculated half-lives in air at 25°C in the gas phase for dicofol are between 3.1 and 4.7 days (cf. section 2.2.1). Taking into account the much lower temperatures of the troposphere, the half-life of dicofol under real situations is likely to be longer. The degradation rate constant is temperature dependant (cf. Aktinson 1989). Based on the vapor pressure combined with the propensity of the compound to sorb to particles (see section 1.1), dicofol is expected to partition between the gas and particle phases in the atmosphere. The average half-life for particles is estimated to be about 3.5 - 10 days, with full degradation of particles estimated to be about 5 - 15 days (Atkinson et al. cited in Rasenberg 2003).

LRT model predictions

66. Several models have been developed for estimating the LRT potential of POP candidates. The MSCE (Meteorological Synthesizing Centre East) POP model (Vulykh et al. 2005), a multicompartment chemistry transport model, uses a benchmark approach to overcome model dependency of numerical values. Benzo(a)pyrene (*B[a]P*) is a listed POP in the UN ECE POPs Protocol and was selected as a benchmark substance because of its high travel distance of approximately 2,400 km, its environmental half-life of approximately 75 days. For their model, they assume dicofol half-lives of 3, 30 and 60 days in air, water and soil, respectively. The model predicts an atmospheric travel distance (TD; the distance after which the concentration has fallen beneath l/1000 of that at the source) of 1,650 km. The estimated environmental half life of dicofol was 20 days. The ranking of dicofol and *B[a]P* with respect to environmental half life shows that dicofol is less persistent than *B[a]P*. According to the model calculations of TD, LRT potential of dicofol is slightly less than that of *B[a]P*.

67. US EPA (2009) estimated the overall persistence (Pov) and LRTP of dicofol and its breakdown products with the OECD "Pov and LRTP Screening Tool". Pov metrics combines estimates of single-media half-lives with the multi-media partitioning of a chemical and do not rely on the single-media half-lives as persistence criteria. Pov takes into account the environmental media a chemical is likely to partition to, and weigh the single-media half-lives with the chemical's fractions in the individual media (Wegmann, 2009). The characteristic travel distance (CTD) represents the potential of a chemical to be transported over long distances in air or water (distance at which the concentration of chemical decrease to 37% due to transport). The transfer efficiency (TE) is a dimensionless metric of potential for atmospheric transport and deposition of parent compound in terrestrial and aquatic environments of a remote region. The OECD Tool requires estimated

[12] http://www.vega-qsar.eu/index.php

degradation half lives in soil, water and air, and log K_{AW} and log K_{OW} as chemical-specific input parameters. In order to characterize the long range transport potential (LRTP) of dicofol, the US EPA used the OECD P_{OV} and LRTP screening tool. Three chemicals known to move via long range transport, DDT, aldrin and endrin, were also modeled to provide context for dicofol estimated LRTP. According to the US EPA (2009) there are considerable uncertainties in the environmental fate properties (input values) of the selected chemicals under consideration. The results indicate that, while dicofol and its breakdown products have lower P_{OV} than other chemicals, it has comparable or higher LRTP estimates. *p,p'*-DDT, aldrin and endrin display a Pov of 1010, 225 and 1556 days, a CTD of 2530, 206 and 515 km and a TE of 5.17, 0.003 and 0.04%. The Pov, CTD and TE for *o,p'*-dicofol and *p,p'*-dicofol were 37 and 138 days, 2142 and 1467 km and 9.45 and 3.39%, respectively. For the metabolites model predictions for DCBP, FW-152 and DCBH were 172, 516 and 108 days for Pov, 1381, 504 and 238 km for CTD and 2.24, 2.15 and 0.66% for TE.

68. The most recent LRT potential was assessed by Li et al. (2014a) with the Globo-POP model. Li et al. (2014a) summarized that dicofol, relative to other Arctic contaminants, exhibits a moderate 'absolute Arctic Contamination Potential' ($eACP^{air}_{10}$) and the highest 'relative Arctic Contamination Potential' ($mACP^{air}_{10}$), indicating that it can be transported from source locations to the Arctic environment with moderate efficiency, that its persistence is more influenced by temperature with cold temperatures in the Arctic favoring slow degradation and relative enrichment, whereas warm temperatures near the equator favor fast degradation. Based on the simulated total dicofol mass that resides in the Arctic surface media (M_{Arctic}) after a decade of continuous emission, $eACP^{air}_{10}$ is defined as the percentage of M_{Arctic} in the cumulative global emission. $mACP^{air}_{10}$ is defined as the percentage of M_{Arctic} in the total dicofol mass remaining in the entire global environment by end of the tenth year. Dicofol has a similar $eACP^{air}_{10}$ (0.06%) compared with HBCD (0.05%) or aldrin (0.04%). The $mACP^{air}_{10}$ for dicofol (3.7%) was higher than lindane (3.39%) and DDT (2-3%). The modelled rate of decline of dicofol concentration in the Arctic lags behind the rate of decline in global dicofol usage, indicating modelled accumulation in the Arctic as a result of slowed temperature-dependent degradation (Li et al. 2014a).

Confirmation based on measurements in remote areas

69. Zhong et al. (2012) provides evidence of dicofol in environmental media remote from sources, based on a study carried out on surface seawater and marine boundary layer air data collected during a cruise from the East China Sea (33.2°N) to the high Arctic (84.5°N). Dicofol was detected in air (predominantly gas phase) and in seawater (cf. section 2.3.1).

Summary of long-range environmental transport

70. Dicofol has a calculated half-life between 3.1 and 4.7 days that is a screening indicator for LRT. Model results showed that dicofol and its metabolites can be transported to remote regions and displayed LRT properties similar to those of several known POPs. Limited monitoring evidence of dicofol in environmental media from remote sources (two studies, Zhong et al, 2015 – East China Sea and Jantunen, 2015 – Canadian Arctic) is available.

2.3 Exposure

2.3.1 Environmental monitoring data

Remote areas

71. In a large scale study from East Asia to the high Arctic Ocean, dicofol was abundantly found along with the already listed POP α-endosulfan and detected in average levels of 14 ± 29(SD) pg/m³ in air and 9 ± 23(SD) pg/L seawater (Zhong et al. 2012). Concentrations decreased from ~25 pg/m^3 and 87 pg/L at 35°N to 0.9-2.5 pg/m^3 and <0.2-2 pg/L at 66-80°N latitude in air and seawater, respectively. The authors used the data to calculate air-water fugacity ratios at each of the sampling locations which provide information on the likely net direction of chemical transfer. It was suggested that air was the dominant mode of transport, with dicofol being carried from original source and deposited into surface water at all points along the cruise, although deposition rates were highest close to potential source regions. Zhong et al. (2012) performed a polar extract of the samples and a GC injection technique (pulsed splitless) that helps to prevent thermal breakdown of dicofol. Moreover, they used an internal dicofol standard and an isotope labeled surrogate (but not dicofol-D8). Therefore, and supported by discussions with experts and clarification by the authors (G. Zhong, personal communication, April, 2015), the study results seem to be plausible, based on the applied analytical method.

72. Levels of dicofol and DCBP (could not be separated analytically) in Canadian archipelago Arctic air were ~2 pg/m^3 during ArcticNet cruises in 2011-2013 (L. Jantunen, Environment Canada, personal communication, 2015). Hoferkamp et al. (2010) were unable to find any results for dicofol in Arctic environmental media. Muir and de Wit (2010) stated that there were no direct measurements of dicofol in the Arctic. Among other reasons the analytical problems of dicofol could be involved in this observation. Kucklick (J. Kucklick, personal communication, November, 2013) mentioned for example the difficulties of detecting dicofol in seal samples.

Regional and local scale

73. In air and seawater of the Bohai and Yellow Seas, China, dicofol was frequently detected. Gas phase atmospheric concentrations averaged 3.8±2.3 pg/m^3, whilst particulate concentrations were lower averaging 0.68 pg/m^3 (Zhong et al. 2014). Concentrations of dicofol dissolved in seawater averaged 63±65 pg/L with highest concentrations up to approximately 240 pg/L. Zhong et al. (2015) analyzed dicofol in 72 surface sediment samples from the coastal and offshore regions of the Bohai and Yellow seas, which border on regions of high pesticides consumption and production and are exposed to huge amounts of runoff and sediment load of several rivers. Dicofol was detected in 60% of the samples and dominated the concentration profile with 90% of the reported concentrations greater than 0.1 ng/g dw, an average concentration of 1.3±2.5 ng/g dw and a highest concentration of 18 ng/g dw. Concentrations generally reflected those measured in air and water with higher values closer to estuaries indicating on-going riverine sources (Zhong et al. 2015) including inputs from local areas of production (Jiangsu and Shandong provinces were the first and second largest pesticide producers in China (2011), accounting for 29 and 20% of the total production, respectively (Zhong et al. 2015).

74. Eng et al. (2016) carried out an air monitoring programme in India using passive air sampling equipment to take 23 samples (plus an additional three blank trials) from rural and urban areas. The samples were then analyzed by GC/MS using a similar pulsed splitless method as to that used by Zhong (2012), with further amendment to fully convert all dicofol into DCBP during analysis. This reportedly provided a complete and robust set of data with less loss of dicofol during analysis. The results indicated air concentrations of 1-2 ng/m^3 in rural areas, 2 ng/m^3 in urban areas, and 0.4 ng/m^3 in an area expected to represent natural background concentrations.

75. In sediments in California's Central Valley, dicofol was found in 75% of the 28 tested samples up to 250 ng/g dw (Weston et al. 2013). In an earlier publication (Wang et al. 2010) dicofol was detected in five out of 12 sediment samples from California's Central Valley with reported concentrations of 36±207 (mean±SD) ng/g dw. In lower regions of Yangtze River, Tang et al. (2013) detected dicofol levels of 0.46±1.38 (mean±SD) ng/g dw in the sediment, whereas the dicofol levels in the surface water where below the detection limit (<0.28 ng/L).

76. In a national survey in France, dicofol was not detected in any of 154 sediment sampling points (Vulliet et al., 2014). This observation is in line with the findings of Thomas et al. (2012), where dicofol was not detected in freshwater fish and sediments from fish ponds in north-eastern France.

77. In a vineyard watershed in France, Sabatier et al. (2014) reconstructed the long term levels of dicofol in lake sediment. Concentrations showed peaks in 1970, 1992 and 2000 reaching fluxes of approximately 4.5, 8.0, 6.0 ng/cm²/y, respectively. In transboundary aquifers in North-eastern Greece, dicofol was detected in one out of 37 wells above the EC drinking water quality standards limit of 0.1 µg/L at a level of 0.153 µg/L (Vryzas et al. 2012). Papadakis et al. (2015) examined 416 water samples from six rivers and ten lakes in the main cultivation areas of Greece (collected from Sep. 1999 to Feb. 2001) and calculated annual average concentrations for dicofol in surface water bodies of 0.01 µg/L, which exceeds the annual average for EU Environmental Quality Standard for dicofol (0.0013 µg/L) according to Directive 2013/39/EC.[13]

78. Bishnu et al. (2009) detected dicofol in the water bodies in tea gardens in the Doars region of West Bengal, India, in April, at a mean level of 3.6 (range 0.9–5.8) µg/L. In a South Florida Water Management District study of samples collected regularly from 27 surface water sites between 1988 and 1993, dicofol was not detected (above detection limits generally ranging from 2 to 180 µg/l) in any of the samples (US EPA 1998). Domagalski (1996, cited in US EPA 2009) reported for an analysis of water samples from San Joaquin River (California) and its tributaries that all samples collected between March and June 1993 were below detection limits but in June to September 33 samples were found above the detection limit (0.05 µg/L) with max concentrations of 2.5 µg/L. From 1990-2006, 618 samples from surface waters were analysed for dicofol in the California Department of Pesticide Regulation (CDPR) database. Of these, dicofol was detected in 11 (1.8%) of

[13] http://eur-lex.europa.eu/legal-content/EN/ALL/?uri=CELEX:32013L0039

the samples, with a maximum concentration of 0.27 µg/L (US EPA 2009). The Pesticides in Ground Water Data Base (US EPA 1992, cited in US EPA 2009) showed no detections of dicofol in limited sampling in several States, including California (1634 wells sampled between 1979 and 1991).

79. Syed and Malik (2011) detected dicofol in surrounding surface soils of an industrial site in Pakistan in 69% of 36 samples at a mean level of 10.75 ng/g, although it is not quite clear to what extent these levels originate from industrial production processes (including waste dumping) or from agricultural use in this area.

80. Weaver et al. (2012) found dicofol in surface soil (one sample was analyzed for dicofol measuring 18 µg/kg) from the Namoi Valley, Australia. Dicofol was measured at up to 53.2 pg/m^3 in urban air in Spain (Coscolla et al. 2011).

81. Dicofol levels (highest mean concentrations) in biota in crop areas with historical dicofol use have been reported by the US EPA (2009) for small mammals (up to 1.4 µg/g, Florida), terrestrial invertebrates (up to 3.9 µg/g, California) and reptiles/amphibians (up to 3.8 µg/g, Florida). In non-crop areas the highest mean concentrations of dicofol were 0.3 µg/g for small mammals, 0.76 µg/g for terrestrial invertebrates, 0.38 µg/g for reptiles/amphibians, 0.9 µg/g in birds and 0.26 µg/g for fish. Empirical data were not available for exposure of aquatic animals to dicofol's major degradates (DCBP, FW-152, DCBH, OH-DCBP and CBA) alone, i.e. separate from exposure to parent dicofol (US EPA 2009). Therefore, the US EPA (2009) used quantitative structure-activity relationships (ECOSAR) to predict relative toxicity of dicofol degradates to fish and invertebrates. In New York dicofol was detected in earthworms at a level of 1-2 µg/g (US EPA 2009). In eggs collected from thirteen avian species in California, Florida and New York, the yearly mean levels for dicofol, *p,p'*-FW 152 and *p,p'*-DCBP ranged from 0.003 - 0.46, 0.002 - 0.218, and 0.004 – 0.165 µg/g, respectively (US EPA 2009). The dicofol levels found by Malik et al. (2011) in eggs of cattle egret, prey samples and sediment in Pakistan are described in section 2.2.2. Dicofol was also frequently detected in liver samples from six species of predatory birds of the Canary Island, Spain with concentrations ranging from 0.001 to 0.0095 µg/g ww (Luzardo et al. 2014).

82. In animal feed samples in India, dicofol was found at mean concentration ranging from 0.03 to 0.34 µg/g (Nag & Raikwar 2011). Dicofol has been shown to accumulate in cows' fat and milk (Shaffer 1987, unpublished): 0.5 µg/g of *p,p'*-dicofol in the fat after 29 days of 10 µg/g in food. In mutton bird in New Zealand, dicofol was not found in any of the analyzed samples (Bekhit et al. 2011). However, if DCBP is not reported, dicofol measurements may be likely underestimated due to the breakdown of dicofol to DCBP during sample analysis.

DDT and related compounds from dicofol production and use

83. Dicofol can contain DDT and related compounds depending on the manufacturing method (UNEP/POP/POPRC.10/4). The ratio of *o,p'*-DDT/*p,p'*-DDT can indicate dicofol as source of DDT (use of dicofol or DDT). For ΣDDT originating from technical DDT a ratio of 0.2 to 0.3 is typical, whereas a ratio of 1.3 or higher (mean ratio 7) indicates technical dicofol as source (Qiu et al. 2005; Qiu and Zhu 2010). The following discussion below focuses on data pertaining to the use of technical dicofol.

84. The ratio of *o,p'*-/ *p,p'*-DDT has been used in literature to distinguish between DDT and dicofol as source of ΣDDT. But to use isomer ratios for the estimation of their emission source, the environmental fate of the two isomers should also be taken into consideration (e.g. differing volatility from soil to air, stability in soil, air water fluxes and bioaccumulation). However, Ricking and Schwarzbauer (2012) claim that the potential to follow the environmental fate of ΣDDT via isomer composition has not been realized accurately so far and, consequently, has not been well established in the field of environmental chemistry. In case of the ratio of *o,p'*-/ *p,p'*-DDT the 4.7-fold higher water solubility and 7.5-fold higher vapor pressure of the *o,p'*-than the *p,p'*-isomer (Ricking and Schwarzbauer, 2012) have to be considered in terms of what that might mean for environmental fate and concentrations present in the environment. Regarding the half-life of the isomers further studies are needed (Qiu et al. 2005). A faster metabolization of *o,p'*-DDT in the environment is reported by Martin et al. (1993, in Li et al. 2006). Bidleman et al. (2013) reported a decreasing proportion of *p,p'*-DDT to *o,p'*-DDT in air from the years 1994-2006 at the Norwegian arctic station Zeppelin Mountain (which was not observed at the Canadian arctic station Alert). For the findings at Zeppelin Mountain, the authors suggested an increase atmospheric transport of dicofol-type DDT vs. technical DDT over time or a preferential degradation of *p,p'*-DDT versus *o,p'*-DDT in source media of soil emissions. Hence, source correlations have to be interpreted cautiously. Eng et al, 2016 showed that for the 'near zone' within a study in India that the DDT isomers found were based on fresh uses of DDT and not dicofol. On the other hand the fact that dicofol is one source of current DDT pollution cannot be ignored.

85. A study by Liu et al (2015) looked at soil contamination for production sites of DDT and dicofol in China. For the sites under investigation soil cores were taken and analyzed for both DDT and dicofol. Soil concentrations for the dicofol production site ranged from 0.6 – 6071 mg/kg for DDT and 0.5 – 1400 mg/kg for dicofol. For the DDT production site concentrations were lower with DDT ranging from 0.01 – 664 mg/kg and concentrations of dicofol less than 0.1 mg/kg.

86. Dicofol as source for ΣDDT was suggested by the authors for sediments from Yangtze River Estuary and the adjacent East China (Zhou et al. 2014) where isomer ratios ranged from 0.26-2.84 (mean average of 1.2), and for surface sediments in Pakistan (Syed et al. 2014) where an isomer ratio of 1.4 was calculated. Equally, samples from an Eurasian Eagle owl population from south-eastern Spain (Gomez-Ramirez et al. 2012) produced isomer ratios of 1.02, 1.3 and 0.75. In a study based on mussels collected from a Spanish estuary (Suarez et al. 2013) isomer ratios of 0.07 – 1.58 were determined based on 36 samples; this included two samples with higher isomer ratios of 2.41 and 10.53, than the core data-set.

87. In more remote areas ΣDDT possibly originating from dicofol exposure was found in air in a mountain of the Tibetan Plateau of China (Zhu et al. 2014) where results suggest environmental levels of DDT are present from the use of both technical DDT and dicofol. The analysis of an extensive database of organochlorine (OC) pesticide concentrations measured at the Norwegian Arctic monitoring station at Svalbard revealed an increasing trend in *o,p'*-DDT/*p,p'*-DDT ratios in the Arctic atmosphere, which may indicate a shift from use of technical DDT to dicofol (Becker et al. 2012).

88. In contrast to the findings above, there are also studies existing, which state that the DDT residue ratios are indicating technical DDT as the source rather than dicofol (Qu et al. 2015, Yu et al. 2014, Ding et al. 2009). Monitoring results from the Portuguese coast showed no predominance of *o,p'*-DDT and therefore Mizukawa et al. (2013) estimated no dicofol induced DDT pollution for this region. The ratios of *o,p'*-DDT/*p,p'*-DDT in marine fish from the South China Sea were <1, suggesting that dicofol was unlikely the source of DDT (Hao et al. 2014). Monitoring of soil, lichen, conifer needles and bark of the Southeast Tibetan Plateau produced isomer ratios indicative of technical DDT rather than dicofol (Yang et al 2013), while sampling in the Kara Sea (Russian Arctic) possibly originating from the Ob and Yenisei Rivers also indicated technical DDT only (Carroll et al 2008). In their recent study measuring dicofol (in the form of DCBP) in air at several sites in India, Eng et al. (2016) also measured *o,p'*-DDT/*p,p'*-DDT isomers. The authors found that DDT isomers had an average ratio of 0.3 and therefore indicated that the source of DDT detected in the samples was not associated with dicofol use but the additional ongoing use of technical DDT (Eng et al. 2016).

2.3.2 Human Exposure

89. Dicofol has been measured in breast milk in China (geometric mean = 9.63 ng/g lipid; max = 64 ng/g), Korea (mean =1.87 ng/g lipid, max =2.96 ng/g) and Japan (mean = 0.32 ng/g lipid; max = 2.65 ng/g) (Fujii et al. 2011); and in adipose tissue in 75-95% of people tested in 3 regions of China, with a maximum value of 559 ng/g lipid and means of 9.06, 2.91, and 4.82 ng/g lipid (Wang et al. 2011). Elevated ratios of *o,p'*-DDT to *p,p'*-DDT in breast milk in China is suggested to result from dicofol exposure (Haraguchi et al. 2009, Wang et al. 2014). In Spain dicofol was detected in 27.8% of 18 colostrum samples with concentrations ranging between 0.12 and 0.59 µg/L (median 0.35 µg/L). but was not detected in 13 major human milk samples from the Canary Islands (Luzardo et al. 2013b).

90. Chen et al (2014) analyzed 10 human milk samples collected from anonymous donors in 2010-2011, 10 cow milk samples and 10 baby formula samples purchased from local stores in USA. In all analyzed samples, *p,p'*-dicofol was found. Detected *p,p'*-dicofol concentrations ranged between 0.033 and 0.230 ng/ml (median 0.091 ng/ml) in cow milk, 0.029 and 1.115 ng/ml (median 0.109 ng/ml) in human milk, and 0.029 and 0.096 ng/ml (median 0.047 ng/ml) in baby formula.

91. The concentration of organochlorine residues was measured in pasteurized milk from Mato Grosso do Sul, Brazil. Of the 100 composite samples analyzed, dicofol was detected in 14% in the range of 2.75–9.61ng/g lipid with a mean concentrations of 5.11ng/g lipid (Avancini et al. 2013).

92. Luzardo et al. (2013a) investigated the presence of organochlorines in locally produced eggs from different production sites (conventional, free-run and organic; n=12 each) collected in 2012 from supermarkets and stores for organic food in the Canary Islands (Spain). All analyzed samples contained low but quantifiable levels of organochlorine pesticides based on limits of detection (0.15 ppb / 0.15 µg/kg). Dicofol was present in 75% of eggs from conventional production (range: n.d.-8.42 ng/g fat; median: 0.93 ng/g), in 41.7% of eggs from free-run production (n.d.-1.08 ng/g fat; 0.57 ng/g fat), and in 58.3% of eggs from organic production (n.d.-2.31 ng/g fat; 1.07 ng/g fat).

93. Wang et al. (2013) examined pesticide residues including 33 different pesticides in market vegetables (n=285) in Shaanxi Province of China by GC and ECD detector in a multi-residue method.

Dicofol was detected in 1.05% of the samples in both green pepper and chives samples. In Bangladesh 210 samples of 8 types of vegetables collected in 2009-2012 were analyzed for 19 agricultural pesticides. Dicofol was detected only in one sample (cucumber) at a concentration of 0.14 mg/kg ww (Chowdhury et al. 2013). Yan et al. (2014) detected dicofol in four of nine celery samples in local markets of Baoding, Korea at levels of 3.6, 2.5, 2.5, and 3.4 ng/g ww.

94. According to European Food Safety Authority (EFSA) 2011 appropriate analytical methods for the detection of dicofol were lacking, which may result in underreporting of residues. They suggested measurements e.g. in plant commodities: *o,p'*-dicofol, *p,p'*-dicofol and their corresponding DCBP, for milk from ruminants sum of dicofol (sum of *o,p'*- and *p,p'*-isomers) and FW-152. A new analytical method was published from the European laboratories for residues of pesticides in 2013 (EURL-SRM, 2013). Therefore, data reported before 2011 might be less sensitive and negative results in these studies might not be an indication of lack of exposure. In processed commodities the major degradation product seemed to be the corresponding DCBP, but formation of chloroform under boiling and sterilization conditions cannot be excluded (EFSA 2011).

95. The 2013 European Union report on pesticide residues in food of EFSA documented dicofol detections in 0.15% of the samples. Highest mean concentrations have been found in mandarins with 0.02 mg/kg ww. Highest concentrations were detected in strawberries with 0.04 mg/kg ww (EFSA 2015).

96. Lozowicka (2015a) investigated 696 samples of Polish apples in the period of 2005–2013 (182 samples for pesticides). Dicofol was detected in 4 samples and the median of the four residue levels (above the LOQ) was 300% higher than the maximum allowable residue level. The highest measured value was 0.156 mg/kg ww (EFSA 2013).

Consumer Exposure and Risk Assessment

97. In 2011 EFSA reviewed maximum residue levels for dicofol (EFSA 2011). As dicofol is no longer registered in the EU, only the Codex limits (CXLs) were considered in the calculations of the consumer exposure. Assuming the toxicological reference values, the highest chronic exposure was calculated for the Dutch children, representing 1379% of the acceptable daily intake (ADI of 0.002 mg/kg bw). Exceedances of the acute reference dose (ARfD of 0.15 mg/kg bw) were also identified for the existing CXLs in oranges, grapefruits, mandarins, table grapes, lemons and peaches. Excluding CXLs for these commodities and those not sufficiently supported by data from the calculation, the highest chronic exposure still represented 258.1% of the ADI for the French population. When only considering the CXL for tea (50 mg/kg), the highest chronic exposure declined to 95.7% of the ADI for Irish adults; the highest acute exposure is then calculated for tea, representing 30.7% of the ARfD. It has been stated that CXLs considered for consumer risk assessment were actually based on European uses of dicofol that are no longer authorized, except for tea, for which the notifier made a specific request (EFSA 2011). In Brazil the consumer profile developed by the Brazilian Government (POF/IGBE, 2009 – Brazilian Institute of Geography and Statistics) indicated that the median exposure for the population was 249% of the ADI, with highest exposure in the Rio Grande at 397% of the ADI (Brazil, 2016).

98. Diop et al (2016) provide details of a sampling programme for fresh fruit and vegetables in Senegal, where 175 samples were taken from farms where pesticides, including dicofol, were in use. The results indicated that dicofol was one of the most prevalent pesticides detected, being present in 35% of all samples. Diop et al (2016) did question however if the farmers used the best practice for use of pesticides. Another study by Lozowicka et al (2015b) assessed the presence of pesticides within cucumbers and tomatoes in Kazakhstan, based on 82 samples. Concentrations of dicofol were found to range between 0.06 and 0.08 mg/kg.

Summary of human exposure

99. Due to the chemical instability of dicofol in solution as well as limitations in analytical methods reported dicofol measurement values may result in underreporting. However, dicofol and/or its metabolites have been detected in milk, baby formula, eggs, fruits, vegetables, human breast milk, colostrum and blood. Exposure calculations based on Codex limits revealed up to 1379% above the TDI limits for the population group with the highest exposure.

2.4 Hazard assessment for endpoints of concern

Adverse effects on aquatic organisms

100. Dicofol is highly toxic to aquatic animals as defined in the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) (UNEP/POPS/POPRC.10/10). It is classified as aquatic acute and chronic category 1 in the European Union's regulation on the classification, labelling

and packing of substances and mixtures (Regulation (EC) No. 1272/2008). According to OSPAR (2002) the lowest LC50 for fish is 0.012 mg/L; the lowest value for crustaceans is 0.08 mg/L, and the no observed effect concentration (NOEC) in a 300-d chronic exposure of fish was 0.0045 mg/L. US EPA (1998) cites effects on the reproductive physiology of the fathead minnow from concentrations as low as 0.0055 mg/L.

101. Dicofol acute toxicity ranges from very highly toxic to highly toxic to freshwater fish and invertebrates under acute exposure conditions (Annex E information, USA, 2015). The LC_{50} values for seven species of fish range from approximately 0.05 to 0.6 mg/L, whereas for invertebrates (*Daphnia magna*) an EC_{50} of 0.14 mg/L was observed (US EPA, 2009). Chronic exposure to freshwater animals resulted in adverse effects on growth and reproduction in multiple fish species with a no observed adverse effect concentration (NOAEC) of approximately 0.004 mg/L (95d-NOEC= 0.0044 mg/L) and on survival in amphipod with a NOAEC of 0.019 mg/L (US EPA 2009). For rotifers the 11d-NOEC for growth rate was 0.2 mg/L, and for the maximum population density in correlation with the food density 0.1 mg/L and 0.2 mg/L for the lower and the higher food amount, respectively (Xu et al. 2014).

102. In a comparative analysis between fish and mice (Grisolia 2002) erythrocyte micronuclei assays, injection of the dicofol formulation Kelthane 480 CE induced a significant increased micronucleus frequency in the fish *Tilapia rendalli* (from 25 mg/kg), but not in mice (up to 200 mg/kg).

103. Regarding the acute toxicity values of dicofol metabolites, the 96h-LC_{50} values for rainbow trout are >2.29 and 0.24 mg/L for *p,p'*-DCBP, and *p,p'*-FW-152, respectively (Spain, 2006). The 96h-LC_{50} of *p,p'*-FW-152 is in the range of those reported for dicofol.

Adverse effects on terrestrial organisms

104. In terrestrial species, dicofol induced chronic effects. Studies completed on rats (via the diet) identified impairment of sperm motility and effects on hormone levels, and issues for developing ovarian follicles, with a NOAEL of 0.4 mg/kg bw/day (IPCS Inchem (1992). Jadaramkunti (1999) detected affects on the estrous cycle for albino rats when dicofol formulations were administered orally at doses of >30 mg/kg bw per day. Dicofol is classified as practically non-toxic to the adult honey bee on an acute exposure basis (LD50 > 0.05 mg/bee) (US EPA 2009). However, task-dependent behavioral effects on learning have been observed in honeybees when exposed to sublethal concentrations of dicofol (Stone et al. 1997). For earthworms (*Eisenia foetida)* a LC50 of >354 mg/kg dw was reported (UNEP/POPS/POPRC.8/INF/13).

105. Wiemeyer et al. (2001) provides details of a study on American Kestrels (*Falco Sparverius*) using commercial Kelthane. Diets containing 1,3,10 and 30 µg/g (wet weight) were fed to the birds and then analysis completed on eggs and carcasses. Concentrations of dicofol and DCBP increased within carcasses and eggs with increasing dose concentration. The lowest observed dietary effect for concentration on eggshell thinning was 3 µg/g (wet weight), whereas the 1 µg/g (wet weight) exhibited no visible effects. A two-generation study of reproductive and morphological effects of *o,p'*-dicofol on captive American kestrels by MacLellan et al. (1996) showed for females exposed to 5 and 20 mg/kg bw significantly thinner egg shells at 20 mg/kg of *o,p'*-dicofol. Male embryos from females dosed with 5 and 20 mg/kg bw of *o,p'*-dicofol had gonads that were significantly ($p<0.05$) different from those of control chicks, indicating feminization by the presence of primordial germ cells. US EPA (2009) carried out assessments for the effects of dicofol on a number of avian species including American Kestrel (*Falco Sparverius*), Easten Screech Owls (*Otus Asio*), Mallard Duck (*Anas Platyrhynchos*), Ring Dove (*Streptopelia Risoria*) and Northern Bobwhite Quail (*Colinus Virgianus*). In all, cases except for the Bobwhite Quail, effects were observed, with the American Kestrel being the most sensitive endpoint. From this study the US EPA (2009) reported the LOAEC of 3 mg/kg diet and NOAEC of 1 mg/kg diet) based on decreased egg shell thickness in kestrels. According to the OSPAR document on dicofol (OSPAR 2002), the pattern and magnitude of eggshell thinning due to dicofol (0.0334 mg/g, <0.1% ΣDDT) was similar to that observed with *p,p'*-DDE. Schwarzbach et al. (1988, cited in OSPAR 2002), showed that dicofol was not metabolized to DDE in ring-neck doves and therefore concluded that the adverse effect (egg shells became progressively thinner with increasing time of exposure) was caused by dicofol itself. In contrast to the findings above Frank et al. 1986 (cited in USEPA 1998) reported no significant effects of dicofol concerning the number of eggs laid, cracked eggs, shell thickness, eggs set, viable embryos, hatchlings, and 14-day survivors in a one generation study (19-week-exposure) with bobwhite quail exposed to dicofol concentrations of 30 and 120 mg/kg diet. Furthermore the study date of 1986 may indicate that formulations of dicofol used would have contained greater impurity of DDT than more modern formulations. Spain (2006) concluded that for the two one-generation reproduction studies

conducted with bobwhite quail and mallard duck, mallard duck was the most sensitive species and effects on eggshell quality was the most sensitive parameter. Accordingly, the no-observed-effect concentration (NOEC) for mallard exposed to dicofol was 2.5 mg a.s./kg feed which was equivalent to a daily dietary dose 0.26 mg a.s./kg bw/day (Spain 2006).

106. In embryonic livers of *Gallus domesticus*, a formulation of dicofol (Colonel-S® 18.5%) applied as solution in which the eggs were immersed for 60 min on day 0 and 4 of incubation at concentrations of 250, 500 and 1000 mg/L induced severe biochemical and histological alterations (e.g. extensive cell degeneration and necrosis with enlarged blood sinusoids, cytoplasmic vacuolization, and leucocyte infiltrations with congestion or dilation of central vein, decrease in the levels of total protein, glycogen, and glutathione content and an increase in alkaline phosphatase activity) (Bhaskar et al. 2014). The survival rate of chick embryo was reduced and the number of malformations was exhibited by a formulation of dicofol (18.5% Emulsifiable Concentrate (EC)) applied at concentrations of 250, 500 and 1000 mg/L (Nitu et al., 2012). In both studies concentrations were selected in correlation to the recommended application rate (500 mg/L) for the products used in plant protection practice and indicate adverse effects of short time exposure of eggs to dicofol, although it is unlikely that this exposure scenario (immersion for 60 min in a dicofol solution) would occur during direct overspray in the field. In-ovo exposure to *o,p'*-dicofol resulted in damage of Japanese quail reproduction, mainly through eggshell thinning in dosages of 0.0003, 0.001 and 0.003 mg/g of egg (Kamata et al. 2010).

107. According to the US EPA (2009) risk assessment on dicofol, risks to aquatic invertebrates, fish, aquatic-phase amphibians, terrestrial-phase amphibians and mammals were identified. An indirect risk due to effects on habitat was identified for the federally threatened California red-legged frog (*Rana aurora draytonii*).

Summary of ecotoxicological effects

108. Dicofol is highly toxic to aquatic animals ($NOEC_{fish}$= 0.0044 mg/L) and can severely affect the reproduction in birds (e.g. eggshell thinning and feminization of male embryos). The dicofol metabolites *p,p'*-DCBP and *p,p'*-FW-152 are shown to be toxic or highly toxic to fish (96h-LC_{50}_fish = >2.29 and 0.24 mg/L, respectively) . Endocrine related effects have been observed in a broad range of tests with cells originating from a variety of different animal species.

Adverse effects on human health

109. The toxicity of dicofol was assessed by WHO 1996, 2009, EPA 1998, IARC, 1998, the European Union in the frame of the assessment of active substances in plant protection products, 2006, JMPR, 2011. An acceptable daily intake (ADI) of 0.002 mg/kg has been derived (JMPR 2011). A chronic reference dose of 0.0004 mg/kg bw/day has been established by US EPA (1998). An acute reference dose of 0.15 mg/kg has been established by Spain, based on neurotoxicity in rats (Spain 2006, EFSA 2011). EPA established an acute reference dose of 0.05 mg/kg bw (US EPA, 1998). Several toxicity studies on dicofol had been published before 1980, with a dicofol preparation with lower purity degree (below 95 % containing more than 0.1 % DDT relating impurities) and therefore may not be currently marketed any more (WHO 1996). However, as depicted in section 2.1.1 this might not be true for all countries. The DDT contaminant could have been contributed to the effects seen in the older studies.

110. Classification and labelling: Dicofol is classified for its hazards to human health according to the Globally Harmonized System as acute toxic, category 4, H302 (harmful if swallowed) acute toxic, category 4, H332 (harmful if inhaled) skin irritant, category 2, H315 (causes skin irritation) and sensitizing to skin, category 1, H 317 (may cause an allergic skin reaction) (EC 2015).

111. Main adverse effects observed in short term dietary studies with laboratory rodents were on the liver, adrenals and the thyroid. The NOAEL in rats was 0.07 mg/kg bw/day and in mice 1.6 mg/kg bw/day. In dogs, target organs for dicofol toxicity were the adrenals, liver, heart and testes. The NOAEL in a three month study on dogs was 0.29 mg/kg b.w./day. Cortisol response to adenocorticotropic hormone (ACTH) was reduced; the LOAEL for these effects (decrease in Cortisol release and oligospermatogenesis) was 3.3 mg/kg bw/day. (WHO, 1996). A 1-year dietary study in dogs (was reported with a NOAEL of 0.12/0.13 mg/kg bw/day (males/females) based on inhibition in ACTH stimulated cortisol release at 0.82 mg/kg bw/day. Dermal application in short term tests in rabbits (4 weeks/6 hours/day, 5 days/week) resulted in a NOAEL of 4 mg/kg bw/day (based on decrease in body weight) and in rats (13 weeks 6 hours/day, 5 days/week) of 4 mg/kg, based on liver hypertrophy (US EPA 1998).

112. Jadaramkunti et al. (2002) reported toxicity on testes and accessory reproductive organs in rats at doses of 400 mg/kg of a dicofol formulation administered by gavage for 30 days. Chan et al. (2009) examined the ability of dicofol to induce cytochrome P450 and affect phenobarbital-induced sleeping

time by treating 6-weeks old male Wistar rats with 1, 10 and 25 mg of dicofol/kg intraperitoneally for four days Thus, results of the study demonstrated that dicofol induces CYP1A1, CYP2B, CYP2E1 and CYP3A in rat liver and increases phenobarbital metabolism and CCl4 toxicity in rats at 10 and 25 mg/kg bw with a dose dependent increase.

113. The genotoxicity of dicofol was tested in a series of in vitro and in vivo tests. Negative results were obtained from gene mutation assays; however some limitations due to negative results of the positive control and the purity of the test substance were reported. Dicofol was also negative in *in vitro* and *in vivo* chromosome aberration and unscheduled DNA synthesis tests (WHO 1996, 2006). According to testing information of the NTP for dicofol dosed-feed over a two year test cycle, positive results in mouse lymphoma assays were found (NTP 2015).

114. Dicofol was cytotoxic to human lymphoid cells at a concentration of 10^{-4} to 10^{-6} M (molar). In cultures incubated with 10^{-4} M dicofol, M1 metaphases were as high as 13% compared to less than 1% in controls indicating an effect on cell cycle kinetics. Statistically significant increases in sister chromatid exchange frequency was seen in cells exposed to dicofol at 10^{-5} and 10^{-6} M (Sobti et al. 1983).

115. The European, US and IARC reports are in agreement that the dietary carcinogenicity studies performed with dicofol are negative in rats but positive in male mice at the highest dose (Spain, 2006, US EPA 1998, IARC, 1998). A bioassay for possible carcinogenicity carried out by the National Cancer Institute in the US reported statistically significant increases in hepatocellular carcinomas in dosed male mice, and the Institute concluded that dicofol was carcinogenic in male mice (NTP, 1978). Hepatocellular adenomas and carcinomas were observed at doses of 39.6 and 79.2 mg/kg bw/day treated for 45 weeks in males. No tumors were observed in females treated with 18.3 or 36.5 mg/kg/day (NTP 1978, US EPA 1998). This resulted so far in no EU GHS classification, an US group C, possible human carcinogen classification and an IARC conclusion that the available data are insufficient to evaluate the carcinogenicity of dicofol to humans. From the long term study in rats a NOAEL of 5 ppm corresponding to 0.22 mg/kg bw/day in males and 0.27 mg/kg in females was based on decreased food consumption, decreased body weight gain, reduced triglyceride levels, and increased hepatic mixed function oxidase activity, seen at or before 12 months. Histological changes were observed in the liver (centrilobular hepatocyte hypertrophy, vacuolation, and areas of necrosis in 50 and 250 ppm males and females), and the adrenal glands (cortical cell vacuolation in 250 ppm males and females). (US EPA 1998). The reproductive toxicity was assessed in rats and rabbits. In a two generation reproduction study in rats a NOAEL of 0.4 mg/kg/day was established based on ovarian vacuolation in the F1 generation at 1.9/2.1 mg/kg/day in M/F; the NOAEL for offspring was 1.9 mg/kg bw/day based on reduced viability at 9.5/10.5 mg/kg bw M/F. The NOAEL for parental toxicity was 0.4 mg/kg/day; the LOAEL based on liver hypertrophy in both generations was 1.9/2.1 mg/kg/day in M/F. In a one generation postnatal toxicity study in rats a NOAEL of 1.7/2.0 mg/kg bw/day M/F for parents and offspring based on liver pathology seen at the LOAEL at 8.7/9.8 mg/kg bw/day M/F was derived. In a study in rabbits a NOAEL of 4 mg/kg bw/day for maternal and developmental toxicity was observed; the LOAEL was 40 mg/kg/day, based on an increased incidence of abortions in the does. A rat developmental toxicity study established a maternal NOAEL of 0.25 mg/kg bw/day, maternal effects were detected at 2.5 mg/kg bw/day whereas no developmental toxicity was observed at the highest dose of 25 mg/kg bw/day (US EPA, 1998). Toxic effects in offspring were not observed at maternal non-toxic doses, which would be indication for reprotoxicity. Exposure to dicofol at 2.5 mg/kg for eight weeks significantly reduced sperm motility in male Lewis rats. Sperm morphology, daily sperm production, sperm transit time through the epididymis, hormonal levels, and histopathological evaluation of testis and epididymis did not differ significantly. A mixture of dicofol and other pesticides at their NOEL also changed sperm motility (Perobelli et al. 2010).

116. Shahani et al. (2013) investigated the teratogenicity of the pesticide Colonel-S, a commercial formulation containing 18.5% dicofol in Swiss Albino mice. The pesticide formulation was orally administrated in a low and a high dose (resulting in a dicofol concentration of 4 and 16 mg/kg bw, respectively) to pregnant female mice during the entire organogenetic period of gestation (day 5-14). Mice were sacrificed on day 18 of gestation for uteri examination for teratological changes. Treatment showed maternal toxicity (as evidenced by reduced maternal weight gain). A dose related decline in live litter size and rise in percentage of resorbed fetus was shown (low dose: 52.48% high dose 40.74%). In the high dose group, the percentage of alive fetuses was greatly reduced. However, mice from the low dose group did not exhibit significant alterations. The authors conclude that the tested formulation is a developmental toxicant in a dose-dependent manner.

117. Liu et al. (2012b) studied the interaction of dicofol with the globular protein trypsin in aqueous medium. Dicofol was shown to form spontaneously a complex with trypsin mainly by hydrogen bond

with one binding site. The change in trypsin conformation was proved. The results indicated that dicofol had potential effects on structure as well as activity of trypsin and that the effects enhanced with increasing dicofol concentration (concentration range 2-10x10^{-5}Mol/L). The results indicate that dicofol has deleterious effects on the frame conformation of proteins and disturbs their physiological function in vitro.

118. Liu et al. (2012a) examined the interaction between dicofol and serum protease α-chymotrypsin (α-CT) in aqueous medium. Three aspects including conformational change, interaction mechanisms and functional change were investigated. Dicofol bonded to α-CT and formed a stable complex unfolding the protein structure and increasing the exposure to chromophore groups in the internal hydrophobic region. Thus, dicofol exposure can lead to conformational changes of α-CT, which can lead to disturbed function and activities of enzymes. The effects enhanced with the increasing concentration of DCF (concentration range 1-5x10^{-5} Mol/L).

119. A screen for nongenotoxic carcinogens identified dicofol as a compound that significantly stimulated phospholipid-dependent protein kinase C (PKC) in the absence of calcium at concentrations of 100 to 1000 µM. PKC plays a central role in the signal transduction pathway in cells, and thus is used as a potential marker that could be affected by carcinogens that act via non-genotoxic modes (Rotenberg, 1991). Dicofol was found to be a potent inhibitor of gap junction intercellular communication in *in vitro* assays (Flodström, 1990). According to the WHO dicofol was found to induce rat liver mixed function oxidase activity and ranked after heptachlor, DDT chlorfenson and dieldrin (WHO 1996).

120. Neurotoxicity was assessed in an acute and a subchronic study in rats. From the acute study a NOAEL of 15 mg/kg bw was established and the LOAEL was 75 mg/kg/day (based on body weights and reduced food consumptions). At the highest dose observed, 350 mg/kg an increase in the incidence of ataxia and of uncoordinated landing was observed in females. From the subchronic study, the NOAEL was 0.3 mg/kg bw/day and the LOAEL was 5.6 mg/kg bw/day, based on decreased motor activity and increased liver weights. A significant decrease in brain weight was seen in males at 27.8 mg/kg bw/day (US EPA 1998).

Epidemiological studies

121. Settimi et al. (2003) investigated the association between different types of pesticides and prostate cancer in a case control study. They documented an increased risk among farmers exposed to organochlorine insecticides and acaricides (OR=2.5, 95% CI=1.4–4.2), more specifically to the often contemporary used compounds DDT (OR=2.1, 95% CI=1.2–3.8), and dicofol with tetradifon (OR=2.8, 95% CI=1.5–5.0), whose effects could not be well separated. In general odds ratios (OR) of >1 mean that the respective exposure is associated with a higher odds of outcome. Until confirmed by other studies of prostate cancer in relation to past exposure to DDT and dicofol, the present results may be considered statistical artefacts arising from multiple comparisons. Nevertheless, these types of exposures could contribute to the excess of prostate cancer frequently reported among farmers, especially in view of some specific mechanisms of action reported for DDT.

122. Reynolds et al. (2005a) examined in a population-based case-control study early childhood cancer among California children aged 0-4 years who were born between 1990 and 1997 and the residential proximity to agricultural applications of pesticides of the mothers at the time of child birth. Two investigated pesticides were associated with a higher risk for leukemia when comparing the highest and lowest categories including dicofol (OR: 1-49th percentile 0.75 (0.36–1.55 CI); ≥50th - percentile 1.83; 1.05-3.22 CI). Although they observed elevated risk for leukemia in highest areas of use of dicofol, some limitations of the study were described; e.g. most children included in the study lived in areas with no or very low agricultural pesticide use; therefore the odds ratios for the highest exposure categories were based on small numbers.

123. In a case control study, Reynolds et al. (2005b) also evaluated associations between rates of lympho proliferative malignancies among children from areas of intensive agricultural pesticide use in California, USA. Seven individual pesticides, ranked highest for toxicity and usage (dicofol among others) were separately analyzed. Among the investigated study population, children with Hodgkin's disease (n=258) were slightly elevated in areas with highest use of dicofol 1^{st}-74^{th} percentile OR: 0.77 (0.41–1.45 CI) versus ≥74^{th} percentile OR: 1.43 (0.70–2.95 CI). The authors described limitations as well, e.g. the suitability of proximity as indicator of exposure and the small number of cases may have resulted in the association not being statistically significant.

124. Roberts et al. (2007) evaluated the hypothesis of the association between the maternal residence near agricultural pesticide applications during key periods of gestation and the development of autism spectrum disorders (ASD) in a case control study in children. Comparisons between children of

mothers living within 500 meters of field sites with the highest nonzero quartile of organochloride use (endosulfan and dicofol) and children of mothers not living near field sites by multivariate a posteriori models suggested an Odds Ratio for ASD of 6.1 (95%CI 2.4-15.3). The risk for ASD increased with the percentage of organochlorine applied and decreased with increasing distance from field sites. Study authors noted this finding was not statistically significant and was based on a relatively small number of cases. Also it is noted that the RR was not increased for leukemia. Although taking into account that the proportion of mothers living in proximity to pesticide applications during the defined time periods of interest was small in the study the possible connection between gestational exposure to dicofol and ASD gives reason for concern.

125. A recent review suggests that the cause of autism spectrum disorders may involve, at least in a subset of children, complex interactions between genetic factors and certain environmental toxicants, including organochlorine pesticides, that may act synergistically or in parallel during critical periods of neurodevelopment, in a manner that increases the likelihood of developing autism spectrum disorders (Rossignol et al, 2014).

Neurotoxicity in humans

126. Several case reports on accidental exposure to dicofol describe effects of nausea, dizziness, weakness and vomiting. One case of poisoning of a 12 year old boy who was accidentally exposed to dicofol when he fell into a puddle of spilled undiluted dicofol formulation has been published. Initial symptoms were nausea, dizziness, disorientation, confusion, lethargy, and headache. The patient demonstrated horizontal nystagmus and impaired balance. These symptoms resolved within three weeks. Eight months after exposure impairment of certain cognitive functions including auditory attention, immediate memory, and ability to selectively inhibit inappropriate responses were shown (Lessenger and Riley 1991).

Immunotoxicity

127. Ohnishi et al. (2008) investigated Kelthane, a commercial formulation of dicofol in a study with a mouse macrophage cell line to evaluate the influence on innate immune function of macrophages. It could be demonstrated that lipopolysaccharide-induced activation of the interferon IFN-ß promoter was inhibited. This indicates that dicofol may influence the development of infectious diseases.

Endocrine Disruption

128. Dicofol has been identified as a substance with at least some *in vitro* evidence of biological activity related to endocrine disruption (EC 2015). Effects on ovarian vacuolation have been detected at 2.1 mg/kg/day in a two generation study in rats (US EPA 1998). Endocrine disrupting effects have also been detected in a series of in vitro assays using different cell lines from various species. According to the WHO, endocrine disrupting effects are endocrine system related and not necessarily species dependent. Effects shown in wildlife or experimental animals may also occur in humans if they are exposed to EDCs at a vulnerable time and at concentrations leading to alterations of endocrine regulation. Of special concern are effects on early development of both humans and wildlife, as these effects are often irreversible and may not become evident until later in life (WHO 2012).

129. In their discussion of the need for a postnatal developmental neurotoxicity study with dicofol, EPA notes in their 1998 RED that “endocrine toxicity (adrenal and thyroid) was seen throughout the database”. Dicofol was issued Tier 1 Endocrine Disruptor Screening Program (EDSP) test orders in 2009; however, the registrant ultimately opted to cancel the technical registration. The issuance of EDSP test orders was based on exposure potential and did not imply any conclusions regarding potential endocrine interaction (Annex E submissions, 2015, USA).

130. The OSPAR Commission listed dicofol as a potential endocrine disruptor in 1998. OSPAR (2002) states: “There is a lot of evidence of the toxic properties of dicofol and of its effects as an endocrine disrupter.” The OSPAR Commission advised that the presence of dicofol in fresh water, even in very small quantities, for most of the growing season may have implications that there will be endocrine disruption of aquatic organisms.

131. One indication for endocrine disruption was a spill of Kelthane (dicofol), which contained DDT at concentrations as high as 15%, and DDT’s metabolites, DDD, DDE, and chloro-DDT into Lake Apopka, Florida. Studies at Lake Apopka spanned two decades, and identified a number of endocrine-disrupting effects on reproductive development in Lake Apopka alligators, in comparison to the less contaminated reference site. Observations on alligators included a high mortality rate in embryos and neonates, and a higher ratio of estradiol to testosterone in neonates which lead to histological differences in gonads. The effects seen could not be attributed to dicofol

only but were rather mixture related (Guillette et al. 1994; US EPA 1998). A subsequent study on dicofol and other chemicals found in Lake Apopka determined that a mixture of DDT, DDT breakdown products, and dicofol reduced binding to alligator estrogen receptor by 40%. Dicofol alone reduced binding to alligator progesterone receptor by 40%, identifying potential routes by which dicofol, alone or in combination with other chemicals present in the lake, might elicit the endocrine-disrupting effects observed in Lake Apopka (Vonier et al. 1996).

132. Endocrine toxicity was seen also in rats and dogs; affecting the adrenals, the thyroid and ovaries (US EPA 1998; Jadarmkunti & Kaliwal, 1999). An increase of uterine weight in mice was reported by Zhao et al. (2000) as well as proliferation in the human breast cancer cell line MCF7 (Du & Xu, 2001).

133. In carp liver microsomes testosterone glucuronidation was significantly inhibited by dicofol (Lavado et al., 2004). Further it was shown that the synthesis of sex hormones in fish microsomes was influenced by dicofol (Thibaut & Porte 2004).

134. A series of in vitro studies with yeast or cell lines of different origin (e.g. human, hamster, alligator, frog, fish, chicken) have demonstrated that dicofol is able to bind to estrogen receptors from various species and enhances transcriptional activity. The dicofol metabolite, DCBP showed potent antiandrogenic properties (Thiel et al. 2011). In a competitive binding assay *p,p'*-dicofol displaced up to 83% of 17 ß-estradiol from alligator estrogen receptor alpha (ERα) and was an equivocal binder to human ERα, displacing a maximum of 58% 17 ß-estradiol (Rider et al. 2010). Several studies have demonstrated that dicofol also interacts with the thyroid hormone receptor and related effects. Dicofol was a powerful inhibitor of the 3,5,3'-triiodothyronine (T3)-uptake system on the plasma membrane inhibiting more than 80% of the saturable initial uptake and significantly depressing the T3 response (Shimada & Yamauchi 2004). Dicofol exhibited a biphasic, nonmonotonic effect on thyroid hormone binding to transthyretins and inhibited T3 binding (Ishihara et al. 2003). It had strong T3- antagonist activity (Sugiyama et al. 2005) and exhibited relatively strong interference with the T4 binding site of transthyretin (van den Berg et al. 1991).An overview of endocrine related effects is provided in an information document to the risk profile (see cf POPRC.11/INF.15).

Summary of adverse effects on human health

135. Dicofol is classified for its hazards to human health according to the Globally Harmonized System as acute toxic, category 4, H302 (harmful if swallowed) acute toxic, category 4, H332 (harmful if inhaled), skin irritant, category 2, H315 (causes skin irritation) and sensitizing to skin, category 1, H 317 (may cause an allergic skin reaction). Target organs in short term toxicity tests were the liver, adrenals, the thyroid, heart and testes and the nervous system. Tumors have been observed in male mice at higher dose levels (39.6 and 79.2 mg/kg bw/day). Dicofol is classified as an US group C, possible human carcinogen and an IARC conclusion that the available data are insufficient to evaluate the carcinogenicity of dicofol to humans meant that a group 3 (not classifiable as to its carcinogenicity to humans) was applied. Endocrine disruption has been observed in *in-vitro* studies and endocrine toxicity in *in vivo* studies. Reprotoxic and developmental effects were observed at maternal toxic doses. A NOAEL of 0.22 mg/kg bw has been established based on neurotoxic effects observed in a two year toxicity and carcinogenicity study on rats leading to an ADI of 0.002 mg/kg derived by JMPR. The NOAEL of 0.12 mg/kg in dogs based on inhibition of adrenal cortical trophic hormone stimulated release of cortisol in both sexes of dogs was used to establish a chronic reference dose of 0.0004 mg/kg bw/day from US EPA. In vitro assays demonstrate interference with e.g. confirmation and function of proteins, inhibition of gap junction intercellular communication and immune reactions. Several epidemiological studies have noted associations between dicofol exposure and prostate cancer in men and leukemia, Hodgkin's disease and autism disorders in children. Although limitations of these studies hinder causal associations they illustrate the concern that adverse effects associated with dicofol exposure might also occur in humans. Further mixture toxicity of dicofol and other organochlorine compounds may be of concern.

3. Synthesis of information

136. The estimated global dicofol usage decreased from 3,350 t in 2000 to 730 t in 2012. In total 28,200 t dicofol were estimated to be consumed worldwide during this period. Asia was the biggest consumer, accounting for 76.8% (21,700 t). China, by far the largest consumer during this period (19,500 t), showed a reduction of about 75% in its annual domestic usage from 2000 to 2012. In 2013, the last remaining technical dicofol producer in China ceased production of technical dicofol. In India, the annual dicofol consumption decreased from 145 t to 45 t during this period. An Indian state-owned enterprise still manufactures dicofol with an average annual production output of approximately 50 t. There is evidence that, although dicofol is being produced in closed systems, improper production

practices can result in direct release of DDT to the environment, as can DDT contamination in dicofol. Ongoing dicofol production and usage can be sources of PCDD/Fs contamination (see section 2.1.3)

137. *o,p'*-Dicofol and *p,p'*-dicofol hydrolyze relatively quickly at neutral and alkaline pH values as shown by experimental data. However, the dominant isomer (*p,p'*-dicofol) has a half-life (85 days at pH 5) that is persistent under acidic conditions. While laboratory conditions provide useful data, it is important to recognize the complexity of the natural environment which can alter results. The hydrolytic stability of dicofol at pH 5 under laboratory conditions does not necessarily imply within the natural environment that it will be persist. This is because other processes such as biodegradation by microorganisms in environmental media may occur. Equally however, fast hydrolysis rates at alkaline pH conditions in laboratory settings cannot alone lead to conclude that a substance is not persistent according to ECHA. Again this is due to other environmental processes such as particulate in water bodies providing shielding from hydrolysis (2014).

138. Photodegradation is not expected to be a significant route of dissipation of dicofol in the environment. Dicofol is not readily biodegradable under acidic conditions. Dicofol degrades rapidly in water/sediment systems with a pH >7. No data for water/sediment systems at pH<7 were reported. Experimental evidence suggests that abiotic as well as biotic degradation are dependent on the pH value of the receiving environmental compartment with longer degradation half-lives under acidic conditions. Several laboratory studies reported low mineralization of dicofol. In laboratory soil simulation tests DT50 values >180 days (n=3) have been reported for some soils, however also degradation half-lives of 8.5 and 32 days for *o,p'*- and *p,p'*-dicofol indicate that dicofol is not expected to persist in soils. Field trials conducted in Florida and California indicated a range of dissipation half-lives of a few days up to 72 days with one reported value of 113 days, depending upon the specific environmental conditions. Based on the physical chemical data the volatilization and leaching potential of dicofol is considered to be low. No field studies from other locations or colder climates are available.

139. A conservative estimate for persistence of *p,p'*-dicofol and its major degradates, as high as 313 days versus 32 days for *p,p'*-isomer alone in soil (pH 7.8), was reported by a regulatory body. The UN ECE Task Force on POPs concluded that dicofol is persistent in water at a pH of 5 or below and meets the persistency indicative numerical value of EB decision 1998/2 (UN ECE, 2009). In aquatic ecosystems with pH values below 6, it can be anticipated that dicofol and/or its degradation products will persist longer in these ecosystems. Recent monitoring data have shown that dicofol is sufficiently persistent to be transported via riverine input to the open sea and two studies have measured dicofol in remote regions. Modelled data indicate that the persistence of dicofol in the environment is lower or comparable to benchmark substances and known POPs.

140. The reported log K_{OW} values for dicofol range between 3.5 and 6.06. Based on a screening approach for bioaccumulation potential, a log K_{OW} range of 3.5 to 6.06 and a log K_{OA} range of 8.9 to 10.02, indicates a high bioaccumulation potential of dicofol in both air-breathing organisms and aquatic organisms.

141. In three laboratory BCF studies with bluegill sunfish and common carp, BCF values are 6,100, 8,200 and 10,000 (steady-state calculated BCF of 25,000). Metabolism of dicofol was minimal in bluegill sunfish with an estimated elimination half-life of 33 days. In a full life cycle test the highest observed BCF value was 43,000. Experimental evidence of high bioaccumulation (BCF of 10,000) in invertebrates during 28 days of exposure was shown. Based on experimental studies in fish species dicofol has a high bioaccumulation potential (BCF >5,000). Model predictions for dicofol also suggest biomagnification in terrestrial species; although metabolic transformation was not taken into consideration. Recent monitoring data in heron eggs showed elevated levels compared to prey items, however values were not lipid corrected and therefore no conclusion on biomagnification can be made.

142. If released to air, a vapor pressure and the partitioning coefficients indicate that dicofol will exist in both the vapor and particulate phases in the atmosphere. Atmospheric oxidation by hydroxyl radicals is a possible removal pathway for dicofol in the atmosphere with half-lives of 3.1 to 4.7 days. Model results concerning LRT for dicofol depend on the model used. Whereas the MSCE POP model indicated a lower travel distance and environmental persistence than the benchmark chemical Benzo(a)pyrene, the OECD Pov and LRT tool indicated a characteristic travel distance and transfer efficiency comparable to already identified POPs. The most recent modelling assessment showed that the Arctic contamination potential of dicofol is comparable to known POPs: dicofol can be transported to remote regions with moderate efficacy and results in high calculated enrichment in the Arctic environment. Though monitoring information from remote regions for dicofol is limited, transport via air (mainly in the gas phase but also on airborne particle) and seawater to the high Arctic has been demonstrated in two studies. No measurements from biota in remote regions were available. It should

be noted that for chlordecone, a substance listed in the Stockholm Convention, the assessment for LRT was based on physical-chemical properties and modelling data (UNEP/POPS/POPRC.2-17 Add.2). Analytical determination of dicofol is made difficult by the thermal degradation of dicofol to DCBP during analysis. This may provide one possible explanation for the more limited availability of monitoring data in remote locations. However viable data for the regional scale (areas of use) does exist, which may reflect that limited monitoring data found in remote areas such as the Arctic may compounded by lower environmental concentrations.

143. Degradation products can be considered in the hazard profile of dicofol. This has been applied in practice in the UNEP POP assessments of PCP and decaBDE. Major degradates of dicofol with a higher persistence than dicofol include DCBP, FW-152, DCBH, OH-DCBP and DCBA. DCBP, FW-152 and DCBH accumulated in a water/sediment study and can be classified as persistent in sediment. Modelled log K_{OW} values for the metabolites are below the screening value of 5 but according to high log K_{OA} values high bioaccumulation in terrestrial organisms may occur (no metabolism is considered). The estimated bioaccumulation potential for the metabolite FW-152 indicated a BCF >5,000 for fish. The acute LC50 toxicity values of *p,p'*-DCBP and *p,p'*-FW-152 for rainbow trout are >2.29 and 0.24 mg/L, the latter indicating high toxicity to fish. The metabolite *p,p'*-DCBP has been shown to reveal potent antiandrogen activity *in vitro*.

144. Dicofol is classified according to the Globally Harmonized System as hazardous for the aquatic environment: aquatic acute H400 (very toxic to aquatic life) and aquatic chronic H410 (very toxic to aquatic life with long lasting effects). The acute toxicity values of dicofol, *p,p'*-DCBP, and *p,p'*-FW-152 for rainbow trout (96h-LC50) are 0.053, >2.29 and 0.24 mg/L. The lowest chronic effect concentration of dicofol (95d-NOEC) for fish is 0.0044 mg/L. Among terrestrial species dicofol has a NOAEC for chronic effects in birds and a NOAEL in mammals of 1 mg/kg and 0.4 mg/kg bw/day, respectively.

145. Dicofol has been detected in environmental compartments like seawater, surface waters, air, sediment and soil and in a variety of biota, including fish, mollusks, cattle and birds. But as there are analytical difficulties in the detection of dicofol (e.g. thermal breakdown during analysis, degradation to DCBP and the inability of differentiation from other DCBP sources if only DCBP is detected and degradation at high pH) and these problems may have not been sufficiently addressed, results have to be assessed carefully and reviewed in context with the wider data available. In several studies dicofol is indirectly detected via the ratio of *o,p'*-/*p,p'*-DDT, but especially in areas with no dicofol use and remote areas, the use of isomer ratios for the estimation of their emission source has to be utilized cautiously.

146. Dicofol levels in biota in crop areas have been reported for small mammals (up to 1.4 mg/kg), terrestrial invertebrates (up to 3.9 mg/kg) and reptiles/amphibians (up to 3.8 mg/kg). In non-crop areas detected values were in earthworms (up to 2 mg/kg), fish (0.26 mg/kg), birds (0.9 mg/kg) and in eggs (annual mean: 0.03-0.46 mg/kg). The detected dicofol levels in fish are well above the laboratory derived acute and chronic effect levels. According to US EPA (2009) risk assessment of dicofol use, risks to aquatic invertebrates, fish, aquatic-phase amphibians,
terrestrial-phase amphibians and mammals were identified.

147. The available data demonstrate interactions with the endocrine system in a multitude of different tests and test systems, including disruption and toxicity. Findings from animal experiments show also adverse effects in endocrine organs and hormonal imbalances. Mixtures of pesticides including dicofol at their NOAEL and LOAEL administered to rats via the diet lead to impairment of sperm motility (Perobelli et al, 2010). While other studies on dicofol and/or dicofol formulations administered orally demonstrated effects on the estrous cycle (Jadaramkunti et al, 1999), hormone levels, and development of ovarian follicles (increase in the size and/or number of vacuoles in the cytoplasm of ovarian stromal cells) (US EPA, 1998). Evidence for mixture toxicity has also been derived from an accidental spill of Kelthane (a dicofol formulation, which contained DDT at concentrations as high as 15%, and DDT's metabolites, DDD, DDE, and chloro-DDT) leading to histological differences in gonads and a high mortality rate in embryos and neonates of alligators at the contaminated lake. A dramatic decline in the alligator population has been observed in the years after the spill. Therefore the toxicity of dicofol and ΣDDT concentrations within commercial dicofol might cause concern for humans and wildlife

148. Subchronic and chronic toxicity studies of dicofol lead to toxic effects in target organs (liver, thyroid, adrenals, brain, heart, testes) of mammals at low concentrations (NOAEL 0.22 mg/kg). Neurotoxicity has been demonstrated in acute and subchronic studies. A series of mechanistic in vitro studies on endocrine disruption, enzyme induction intercellular communication, signal transduction and protein binding support evidence for adverse effects, which may lead to tumor promotion. Risk

assessment for consumers with regard to fresh fruit and vegetables, details a number of studies where ADIs have been exceeded (EFSA, 2011; Diop et al, 2016; Lozowicka et al 2015a and 2015b). Several epidemiological studies have noted associations between dicofol exposure and prostate cancer in men and leukemia, Hodgkin's disease and autism disorders in children. Although limitations of these studies hinder causal associations they illustrate the concern that adverse effects associated with dicofol exposure might also occur in humans.

4. Concluding statement

149. Dicofol is restricted or prohibited in many countries and generally usage as a pesticide has markedly decreased in the last decade and was below 1,000 tonnes in 2012.

150. Dicofol and/or its transformation products can be atmospherically transported to areas far from local sources, including Arctic and subarctic regions based on environmental modeling and limited monitoring data. Due to the chemical instability of dicofol in solution as well as limitations in analytical methods, detections of dicofol may be underreported. Dicofol is persistent in the environment and fulfils the persistence criterion of Annex D (under acidic conditions). Equally the transformation products have been shown to meet some of the Annex D criteria for persistence, bioaccumulation, toxicity and LRT. Dicofol fulfils the bioaccumulation criterion of Annex D based on high BCF values in aquatic species.

151. Dicofol is toxic for reproduction in birds and dicofol and its metabolites, notably FW-152 are highly toxic to the aquatic environment. Dicofol has been shown to be neurotoxic in mammals; it further affects the thyroid, the liver and the adrenals. There is evidence of its presence in human tissues and accordingly, and there are concern for adverse effects in humans. Endocrine disruption and toxicity were reported in a series of in vitro assays. Indications from animal experiments showing adverse effects in endocrine organs, reproductive development and hormonal imbalances. An unrefined risk assessment based on exposure scenarios in various countries demonstrates a risk for consumers (up to 1379% of ADI). Further the toxicity of mixtures of dicofol, DDT and other organochlorines may be of concern for humans and wildlife.

152. Based on its inherent properties, dicofol 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.

5. References

Alkhatib, M, Jennerjahn, TC, Samiaji, J (2007): Biogeochemistry of the Dumai River estuary, Sumatra, Indonesia, a tropical black-water river. Limnol. Oceanogr., 52(6): 2410–2417.

Aktinson, R (1989): Kinetics and mechanisms of the gas-phase reactions of the hydroxyl radical with organic compounds. J. Phys. Chem. Ref. Data, Monograph 1.

Avancini, RM, Silva, IS, Rosa, ACS, de Novaes Sarcinelli, P, de Mesquita, SA (2013): Organochloride compounds in bovine milk from the state of Mato Grosso do Sul – Brazil. Chemosphere, 90: 2408-2413.

Bhaskar N, Shahania L, Bhatnagara P (2014): Biochemical and histological alterations induced by a formulation of dicofol in the embryonic liver of Gallus domesticus, Toxicological & Environmental Chemistry, 2014, http://dx.doi.org/10.1080/02772248.2014.950267.

Becker S, Halsall CJ, Tych W, Kallenborn R, Schlabach M, Mano S. (2012). Changing sources and environmental factors reduce the rates of decline of organochlorine pesticides in the Arctic atmosphere. Atmospheric Chemistry and Physics 12:4033–4044.

Bekhit LC, Al-Amer S, El-Din A, Mason SL, Gooneratne R, Osman KA Clucas L (2011): Concentrations of trace elementals and organochlorines in Muttonbird (*Puffinus griseus*), Ecotoxicology & Environmental Safety 74 (2011) 1742–1746.

Belfroid A, H. Blok H, Balk F (2005): Addendum to the risk profile of Dicofol, 2 December 2005, Final Report 9R5744.01. (http://www.unece.org/fileadmin/DAM/env/lrtap/TaskForce/popsxg/2008/Dicofol_Addendum%20to%20RA%20dossier_proposal%20for%20submission%20to%20UNECE%20POP%20protocol.pdf, 2015-01-16)

Bidleman TF, Kurt-Karakus PH, Wong F, Alegria HA, Jantunen L, Hung H (2013): Is There Still "New" DDT in North America? An Investigation Using Proportions of DDT Compounds. Chapter 8, pp 153–181. In: L.L. McConnell, J. Dachs, C.J. Haperman (eds) Occurrence, Fate and Impact of Atmospheric Pollutants on Environmental and Human Health. ACS Symposium Series, 1149.

Bishnu A, Chakrabrati K, Chakraborty A, Saha T (2009): Pesticide residues in tea ecosystems of Hill and Doars regions of West Bengal, India. Environ Monit Assess 149:457-64.

Boethling R, Fenner K, Howard P, Klecka G, Madsen T, Snape, JR Whelan MJ (2009): Environmental Persistence of Organic Pollutants: Guidance for Development and Review of POP Risk Profiles, Integrated Environmental Assessment and Management, 5: 4 pp. 539–556.

Böhner J, Blaschke T, Montanarella L. (Eds.) (2008): SAGA – Seconds Out. Hamburger Beiträge zur Physischen Geographie und Landschaftsökologie, Vol.19, 113pp.

Brazil (2016) Further information on dicofol provided by the Brazilian government following the requirements of Annex E request for information.

Brown and Casida, (1987): Metabolism of a dicofol impurity alpha-chloro-DDT, but not dicofol or dechlorodicofol, to DDE in mice and a liver microsomal system. Xenobiotica. 1987;17(10):1169-74.

Chan W-H, Liao J-W, Chou C-P, Chan P-K, Wei C-F, Ueng T-. (2009): Induction of CYP1A1, 2B, 2E1 and 3A in rat liver by organochlorine pesticide dicofol. Toxicology Letters 190, 150-155.

CAS REGISTRY (2015): Chemical Abstracts Service. (Assessed via http://www.stn-international.de/fileadmin/be_user/STN/pdf/database_details/STN_Database_Clusters.pdf, 2015-10-29).

Chen X, Panuwet P, Hunter RE, Riederer AM, Bernoudy GC, Barr DB, Ryan PB (2014): Method for the quantification of current use and persistent pesticides in cow milk, human milk and baby formula using gas chromatography tandem mass spectrometry. Journal of Chromatography B 970, 121-130.

Chemspider (2015): ChemSpider database (Assessed, http://www.chemspider.com/About.aspx 2016-01-10).

Chowdhury MA, Fakhruddin ANM, Islam MN, Moniruzzaman M, Gan SH, Alam MK (2013): Detection of the residues of nineteen pesticides in fresh vegetable samples using gas chromatography–mass spectrometry. Food Control 34, 457-465.

Coscollà C, Castillo M, Pastor A, Yusàa V (2011): Determination of 40 currently used pesticides in airborne particulate matter (PM 10) by microwave-assisted extraction and gas chromatography coupled to triple quadrupole mass spectrometry. Analytica Chimica Acta 693:72–81.

Ding, X; Wang XM, Wang QY, Xie ZQ, Xiang CH, Mai BX, Sun LG.(2009): Atmospheric DDTs over the North Pacific Ocean and the adjacent Arctic region: spatial distribution, congener patterns and source implication. Atmos Environment 43:4319–4326.

Diop A, Diop YM, Thiare DD, Cazier F, Sarr SO, Kasprowiak A, Landy D, Delattre F (2016) Monitoring survey of the use patterns and pesticide residues on vegetables in the Niayes zone, Senegal, Chemosphere 144:1715-1721.

DHI (2007) Study on enhancing the Endocrine Disrupter priority list with a focus on low production volume chemicals. DHI Water and Environment. Revised report to DG Environment. (http://ec.europa.eu/environment/chemicals/endocrine/pdf/final_report_2007.pdf) Ding X, Wang XM, Wang QY, Xie ZQ, Xiang CH, Mai BX, Sun LG (2009): Atmospheric DDTs over the North Pacific Ocean and the adjacent Arctic region: spatial distribution, congener patterns and source implication. Atmos Environment 43:4319–4326.

Du K, Xu X (2001): Dicofol stimulation of cell proliferation. Bulletin of Environmental Contamination and Toxicology 67(6):0795–99.

FAO/WHO (1992): Dicofol. In: Pesticide residues in food: 1992 evaluations. Part II — Toxicology.Geneva, Food and Agriculture Organization of the United Nations and World Health Organization (WHO/PCS/93.34; http://www.inchem.org/documents/jmpr/jmpmono/v92pr08.htm).

ECHA (2008): Guidance on information requirements and chemical safety assessment, Chapter R.7c: Endpoint specific guidance, European Chemicals Agency. (http://echa.europa.eu/documents/10162/17224/information_requirements_r7c_en.pdf, 2015-01-22).

ECHA (2014): Guidance on information requirements and chemical safety assessment, Chapter R.11: PBT Assessment, European Chemicals Agency. (http://echa.europa.eu/de/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment, 2015-01-22).

EFSA (2011): Review of the existing maximum residue levels (MRLs) for dicofol according to Article 12 of Regulation (EC) No 396/20051. European Food Safety Authority Reasoned opinion. EFSA Journal 2011;9(8):2337.

EFSA (2013): The 2010 European Union Report on Pesticide Residues in Food. Scientific report of EFSA. European Food Safety Authority. EFSA Journal 2013;11(3):3130.

EFSA (2014): EFSA Guidance Document for evaluating laboratory and field dissipation studies to obtain DegT50 values of active substances of plant protection products and transformation products of these active substances in soil, European Food Safety Authority, EFSA Journal 2014;12(5):3662 (http://www.efsa.europa.eu/de/efsajournal/doc/3662.pdf, 2015-03-12).

EFSA (2015): The 2013 European Union Report on Pesticide Residues in Food. Scientific report of EFSA. European Food Safety Authority. EFSA Journal 2015;13(3):4038.

El-Amrani S, Pena-Abaurrea M, Sanz-Landaluze J, Ramos L, Guinea J, Cámara C. (2012): Bioconcentration of pesticides in zebrafish eleutheroembryos (Danio rerio). Sci Total Environ. 2012 May 15; 425:184-90.

Eng et al (2016): Assessing Dicofol concentrations in Air: Retrospective analysis of global atmospheric passive sampling network samples from agricultural sites in India, Environmental Science and Technology Letters, Vol 3, pp150-155.

Entec UK Limited (2011): Technical Support for the Impact Assessment of the Review of Priority Substances under Directive 2000/60/EC. Substance Assessment: Dicofol. Report for European Commission Unit D.1 Water. (https://circabc.europa.eu/webdav/CircaBC/env/wfd/Library/framework_directive/thematic_documents/priority_substances/supporting_substances/substance_impacts/Dicofol.pdf; Assessed 2016.01.07)

EPISUITE (2015): Estimation Programs Interface Suite™ for Microsoft® Windows, v 4.11. United States Environmental Protection Agency, Washington, DC, USA.

European Commission (2003a): Technical Guidance Document on Risk Assessment, Part II, European Commission.

European Commission (2003b): Technical Guidance Document in support of Commission Directive 93/67/EEC on Risk Assessment for new notified substances Commission Regulation (EC) No

1488/94 on Risk Assessment for existing substances Directive 98/8/EC of the European Parliament and of the Council concerning the placing of biocidal products on the market, Part III, European Commission, 2003.

European Commission (2015): CLP Inventory, ECHA. (http://echa.europa.eu/information-on-chemicals/cl-inventory-database/-/cl-inventory/view-notification-summary/110026, 2015-04-12).

EU – European Union (2002): European Commission DG ENV Endocrine Disrupting Substances (man-made chemicals) B4-3040/2001/325850/MAR/C2. RPS BKH Project number: M0355037 Report: Endocrine disrupters: study on gathering information on 435 substances with insufficient data. Final report by BKH consulting engineers.

EU – European Union (2015): Endocrine Disrupters: Database. (http://ec.europa.eu/environment/chemicals/endocrine/strategy/being_en.htm; Assessed: 2015.03.13).

EURL –SRM (2013): Analysis of dicofol via QuECHERS - use of isotope labelled dicofol to improve precision. EU Reference Laboratory for Pesticides Requiring Single Residue Methods, CVUA Stuttgart, Germany,Version 1 (last update: 23.04.2013). (http://www.eurl-pesticides.eu/library/docs/srm/EurlSrm_Observations_dicofol.pdf).

Finger JW, Gogal RM (2013): Endocrine-disrupting chemical exposure and the American alligator: a review of the potential role of environmental estrogens on the immune system of a top trophic carnivore. Archives of Environmental Contamination and Toxicology 65(4):704-714.

Flodström S, Hemming H, Wärngård L, Ahlborg UG. 1990. Promotion of altered hepatic foci development in rat liver, cytochrome P450 enzyme induction and inhibition of cell-cell communication by DDT and some structurally related organohalogen pesticides. Carcinogenesis 11(8):1413-1417.

Fujii Y, Haraguchi K, Harada KH, Hitomi T Inoue K, Itoh Y, Watanabe T (2011): Detection of dicofol and related pesticides in human breast milk from China, Korea and Japan. Chemosphere 82(1):25–31.

Gómez-Ramírez P, Martínez-López E-, García-Fernández AJ, Zweers AJ, van den Brink NW (2012): Organohalogen exposure in a Eurasian Eagle owl (Bubo bubo) population from Southeastern Spain: temporal–spatial trends and risk assessment. Chemosphere;88: 903–11.

Grisolia CK (2002): A comparison between mouse and fish micronucleus test using cyclophosphamide, mitomycin C and various pesticides. *Mutation Research* 518:145–150.

Guillette LJ, Gross TS, Masson GR, Matter JM, Percival HF, Woodward AR (1994): "Developmental Abnormalities of the Reproductive System of Alligators (Alligator mississippiensis) from Contaminated and Control Lakes in Florida." Env. Health Perspectives, 102 (8): 680-688.

Hao Q, Sun YX, Xu XR, Yao ZW, Wang YS, Zhang ZW, Luo XJ, Mai BX (2014): Occurrence of persistent organic pollutants in marine fish from the Natuna Island, South China Sea. Mar. Pollut. Bull., 85(1): 274-9.

Haraguchi K, Koizumi A, Inoue K, Harada KH, Hitomi T, Minata M, Tanabe M, Kato Y, Nishimura E, Yamamoto Y, Watanabe T, Takenaka K, Uehara S, Yang HR, Kim MY, Moon CS, Kim HS, Wang P, Liu A, Nguyen Ngoc Hung NN. (2009): Levels and regional trends of persistent organochlorines and polybrominated diphenyl ethers in Asian breast milk demonstrate POPs signatures unique to individual countries. Environment International 35:1072-1079.

Hawes I, Andersen DT, Pollard WH (2002): Submerged Aquatic Bryophytes in Colour Lake, a Naturally Acidic Polar Lake with Occasional Year-Round Ice-Cover. Arctic, 55,(4): 380–388.

Hindustan Insecticide Ltd. Annual Report on the business and operations of the Hindustan Insecticide Ltd.; 2006−2012. (www.hil.gov.in).

Hoferkamp L, Hermanson MH, Muir DC. (2010): Current use pesticides in Arctic media; 2000-2007. Science of the Total Environment 408(15):2985-94.

Horbe MC, da Silva AG. (2009): Chemical composition of black-watered rivers in the western Amazon Region (Brazil) J. Braz. Chem. Soc. 20 (6): 1119-1126 (http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0103-50532009000600018, 2016-01-07).

HSDB (2015): U.S. National Library of Medicine: Hazardous Substance Database (http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB).

Ishihara A, Sawatsubashi S, Yamauchi K. (2003): Endocrine disrupting chemicals: interference of thyroid hormone binding to transthyretins and to thyroid hormone receptors. *Molecular and Cellular Endocrinology* 199(1-2):105-17.

IGBP-DIS (1998): SoilData(V.0) A program for creating global soil-property databases, IGBP Global Soils Data Task, France.
(http://www.sage.wisc.edu/atlas/maps.php?datasetid=20&includerelatedlinks=1&dataset=20 od. http://www.isric.org/content/data).

IPCS Inchem (1992): International Programme of Chemical Safety Dicofol (Pesticide residues in food: 1992 evaluations Part II Toxicology)
(http://www.inchem.org/documents/jmpr/jmpmono/v92pr08.htm).

Jadaramkunti UC, Kaliwal BB (1999): Effect of dicofol formulation on estrous cycle and follicular dynamics in albino rats. Journal of Basic Clinical Physiology and Pharmacology 10(4):305-14.

Jadaramkunti UC, Kaliwal BB (2002): Dicofol formulation induced toxicity on testes and accessory reproductive organs in albino rats. Bulletin of Environmental Contamination and Toxicology 69(5):741-8.

Japanese NITE database (2015) (http://www.safe.nite.go.jp/english/db.html, 2015-01-016).

JMPR (2011) Joint FAO/WHO Meeting on Pesticide Residues: (2011) Pesticide residues in food. FAO Plant protection paper. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Core Assessment Group on Pesticide Residues Geneva, Switzerland, 20–29 September 2011.

Kamata R, Shiraishi F, Nakajima D, Takahashi S, Shimizu A (2010): Evaluation of the impact of in-ovo exposure to dicofol on avian reproduction. Environ Toxicol Chem. 2010 Oct;29(10):2316-22.

Kelly BC, Ikonomou MG, Blair JD, Morin AE, Gobas FAPC (2007): Food web-specific biomagnification of persistent organic pollutants. Science 317:236-9.

Kortenkamp A, Evans R, Olwenn M, McKinlay R, Orton F, Rosivatz E: (2012) State of the art assessment of endocrine disrupters. Summary of the state of the science. Final Report. Annex 1 (http://ec.europa.eu/environment/chemicals/endocrine/pdf/annex1_summary_state_of_science.pdf).

Kumari B, Duhan, A (2011): Persistence of dicofol residues in cotton lint seed, and soil. Environ Monit Assess (2011) 182:129–132.

Lavado R, Thibaut R, Raldu'a D, Martı'n R, Porte C (2004): First evidence of endocrine disruption in feral carp from the Ebro River. Toxicology and Applied Pharmacology 196, 247– 257.

Lessenger JE & Riley N (1991): Neurotoxicities and behavioural changes in a 12-year-old male exposed to dicofol, an organochlorin pesticide. Journal of Toxicology and Envrionmental Health, 33: 255-26.

Li J, Zhang G, Qi S, Li X, Peng X (2006): Concentrations, enantiomeric compositions, and sources of HCH, DDT and chlordane in soils from the Pearl River Delta, south China. Science of the Total Environment, 372: 215-224.

Li L, Liu J, Hu J (2014a): Global inventory, long-range transport and environmental distribution of dicofol. Environmental Science and Technology, 49, 212-222.

Li S, Tian Y, Ding Q, Liu W (2014b): The release of persistent organic pollutants from a closed system dicofol production process. Chemosphere 94:164-168.

Liu Y, Liu R (2012a): The interaction of α-chymotrypsin with one persistent organic pollutant (dicofol): Spectroscope and molecular modelling identification. Food and Chemical Toxicology 50, 3298-3305.

Liu Y, Cao R, Qin P, Liu R (2012b): Assessing the potential toxic effect of one persistent organic pollutant: Non-covalent interaction of dicofol with the enzyme trypsin. Spectrochimica Acta Part A 89, 210-215.

Liu L, Bai L, Man C, Liang W, Li F, Meng X (2015) DDT vertical migration and formation of accumulation layer in pesticide-producing sites, Environ Sci Technol 49:9084-9091.

Lozowicka B (2015a): Health risk for children and adults consuming apples with pesticide residue. Science of the Total Environment 502, 184-198.

Lozowicka B, Abzeitova E, Sagitov A, Kacznski P, Toleubayev K, Li A (2015b) Study of pesticide residues in tomatoes and cucumbers from Kazzkhstan and the associated health risks, Environ Monit Assess 187:609.

Luzardo OP, Rodríguez-Hernández A, Quesada-Tacoronte Y, Ruiz-Suárez N, Almeida-González M, Henríquez-Hernández LA, Zumbado M, Boada L. (2013a): Influence of the method of production of eggs on the daily intake of polycyclic aromatic hydrocarbons and organochlorine contaminants: An independent study on the Canary Islands (Spain). Food and Chemical Toxicology 60, 455-462.

Luzardo OP, Ruiz-Suárez N, Almeida-González M, Henríquez-Hernández LA, Zumbado M, Boada LD (2013b): Multi-residue method for the determination of 57 Persistent Organic Pollutants in human milk and colostrum using a QuEChERS-based extraction procedure. Analytical and Bioanalytical Chemistry 405, 9523-9536.

Luzardo OP, Ruiz-Suárez N, Henríquez-Hernández LA, Valerón PF, Camacho M, Zumbado M, Boada LD (2014): Assessment of the exposure to organochlorine pesticides, PCBs and PAHs in six species of predatory birds of the Canary Islands, Spain. Sci Total Environ. 2014 Feb 15;472:146-53.

MacLellan KNM, Bird DM, Fry DM, Cowles JL (1996): Reproductive and morphological effects of *o,p'*-dicofol on two generations of captive American kestrels. Arch Environ. Contam. Toxicol., 30: 364–372.

Mackay, Donald (2006). Handbook of Physical-chemical Properties and Environmental Fate for Organic Chemicals. CRC Press. ISBN 1-56670-687-4.

Malik RN, Rauf S, Mohammad A, Shah Eqani Syed-Ali-Musstjab-Akber, Ahad K (2011): Organochlorine residual concentrations in cattle egret from the Punjab Province, Pakistan, Published in Environmental Monitoring Assessment (2011) volume 173 pages :325–341.

Michelutti et al. (2002): Limnological Characteristics of 38 Lakes and Ponds on Axel Heiberg Island, High Arctic Canada. Internat. Rev. Hydrobiol. 87(4), 385–399.

Mizukawa K, Takada H, Ito M, Geok YB, Hosoda J, Yamashita R, Saha M, Suzuki S, Miguez C, Frias J, Antunes JC, Sobral P, Santos I, Micaelo C, Ferreira AM. (2013): Monitoring of a wide range of organic micropollutants on the Portuguese coast using plastic resin pellets. Mar Pollut Bull. 2013 May 15;70(1-2):296-302.

Muir DCG, de Wit CA (2010): Trends of legacy and new persistent organic pollutants in the circumpolar arctic: Overview, conclusion, and recommendations. Science of Total Environment, 408: 3044-3051.

Nag SK, Raikwar MK (2011): Persistent organochloride pesticide residues in animal feed. Environmental Monitoring and Assessment 174, 327-335.

Netherlands (2015): Submission of information specified in Annex E to the Stockholm Convention pursuant to Article 8 of the Convention. (http://chm.pops.int/TheConvention/POPsReviewCommittee/Meetings/POPRC10/POPRC10Followup/Dicofol(AnnexEinformation)/tabid/4293/Default.aspx).

Nitu K, Shahani L, Taparia N and Bhatnagar P (2012): Teratogenic and biochemical effects of a formulation containing dicofol in the chick embryo. Toxicological and Environmental Chemistry, 94 (7), 1411-1421.

NTP National Toxicology Programme (1978): Bioassay of dicofol for possible carcinogenicity. CAS Nr 115-32-2. NCI-CG-TR-90. US Department of Health, Education and Welfare. Public Health Service. National Institutes of Health.

NTP National Toxicology Programme (2015): Dicofol. V10835 NCI-CG-TR-90. US Department of Health, Education and Welfare. Public Health Service. National Institutes of Health. (http://ntp.niehs.nih.gov/testing/status/agents/ts-10835-v.html; May,2015).

Okubo T, Yokoyama Y, Kano K, Soya Y, Kano I. (2004): Estimation of estrogenic and antiestrogenic activities of selected pesticides by MCF-7 cell proliferation assay. Archives of Environmental Contamination and Toxicology 46(4):445-453.

Ohnishi T, Yoshida T, Igarashi A, Muroi M, Tanamoto K (2008): Effects of possible endocrine disruptors on MyD88-independent TLR4 signaling. FEMS Immunology and Medical Microbiology 52(2):293-295.

Oliveira J da M, Silva D, Martins E, Langenbach T, Dezotti M (2012): Biodegradation of C-14-dicofol in wastewater aerobic treatment and sludge anaerobic biodigestion. Environmental Technology, 33, 695-701.

OSPAR (2002): Ospar Commission, 2002. Hazardous Substances Series, Dicofol. (http://www.ospar.org/v_publications/download.asp?v1=p00150, 2015-01-15).

OSPAR (2008): Towards the cessation target: Emissions, discharges and losses of OSPAR chemicals identified for priority action, available at: www.ospar.org.

Papadakis, EM, Vryzas Z, Kintzikoglou K, Makris KC, Papadopoulou-Mourkidou E (2015): A pesticide monitoring survey in rivers and lakes of northern Greece and its human and ecotoxicological risk assessment. Ecotoxicology and Environmental safety, 116: 1-9.

Pienitz R, Douglas MSV, Smol JP (éd.) (2004): Long-term environmental change in Arctic and Antarctic lakes. Developments in Paleoenvironmental Research (DPER), vol. 8, Springer Publishers, 562 p.

Perobelli JE, Martinez MF, da Silva A, Franchi C, Dal Bianco Fernandez, C, Viana de Camargo J, De Grava Kempinas W (2010): Decreased Sperm Motility in Rats Orally Exposed to Single or Mixed Pesticides. Journal of Toxicology and Environmental Health Part A 73, 991-1002.

Qiu X, Zhu T, Yao B, Hu J, Hu S (2005): Contribution of dicofol to the current DDT pollution in China. Environ Sci Technol. 2005 Jun 15;39(12):4385-90.

Qiu, X, Zhu, T (2010): Using the *o,p'*-DDT/*p,p'*-DDT ratio to identify DDT sources in China. Chemosphere, 81: 1033-1038.

Qu C, Qi S, Yang D, Huang H, Zhang J, Chen W, Yohannes HK, Sandy EH, Yang J and Xing X (2015): Risk assessment and influence factors of organochlorine pesticides (OCPs) in agricultural soils of the hill region: A case study from Ningde, southeast China. Journal of Geochemical Exploration 149 43–51.

Rasenberg MHC (2003): Risk Profile and Summary Report for Dicofol, Dossier prepared for the UNECE Convention on Long-range Transboundary Air Pollution's Expert Group on POPs, Ministry of VROM/DGM, (http://www.unece.org/fileadmin/DAM/env/lrtap/TaskForce/popsxg/2008/Dicofol_RA%20dossier_proposal%20for%20submission%20to%20UNECE%20POP%20protocol.pdf, 2015-01-16).

Rossignol DA, Genuis SJ Frye RE (2014) Environmental toxicants and autism spectrum disorders: a systematic review Translational Psychiatry 4, e360; doi:10.1038/tp.2014.4.

Rousu R. (1999): Comperison of water quality in the Blackwater River & Henderson creek of south Florida (http://keckgeology.org/files/pdf/symvol/13th/Florida/rousu.pdf, 2016-01-07).

REGULATION (EC) No 1272/2008 of the European parliament and pf the council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006.

Ren X, Sun Y, Zhu L, Cuia Z, (2011): Theoretical studies on the OH-initiated photodegradation mechanism of dicofol, Computational and Theoretical Chemistry, Volume 963, Issues 2–3, February 2011, Pages 365–370.

Reynolds P, Von Behren J, Gunier RB, Goldberg DE, Harnly M, Hertz A (2005a): Agricultural Pesticide Use and Childhood Cancer in California. Epidemiology 16:1, 93-100.

Reynolds P, Von Behren J, Gunier RB, Goldberg DE, Harnly M, Hertz A (2005b): Agricultural pesticides and lymphoproliferative childhood cancer in California. Scand J Work Environ Health 31, 46-54.

Ricking M, Schwarzbauer J (2012): DDT isomers and metabolites in the environment: an overview. Environ Chem Lett, 10: 317-323.

Rider CV, Hartig PC, Cardon MC, Lambright CR, Bobseine KL, Guillette Jr LJ, Gray Jr LE, Wilson VS (2010): Differences in Sensitivity but not Selectivity of Xenoestrogen Binding to Alligator Versus Human Estrogen Receptor Alpha. Environmental Toxicology and Chemistry 29:9, 2064-2071.

Roberts EM, English PB, Grether JK, Windham GC, Somberg L, Wolff C (2007): Maternal Residence Near Agricultural Pesticide Applications and Autism Spectrum Disorders among Children in the California Central Valley. Environmental Health Perspectives 115, 1482-1489.

Sánchez AI, Hernando DM, Vaquero J (2010): Hazard Assessment of Alternatives to Dicofol, Journal of Environmental Protection, (1), 231-241.

Shaffer, S. R. 1987. Residue analysis of dairy cow milk and tissues for dicofol and its metabolites. Supplement to MRID No. 40042030. Rohm and Haas Report No. 34C-88-19. Unpublished. In JMPR Evaluation (026), Dicofol.

(http://www.fao.org/fileadmin/templates/agphome/documents/Pests_Pesticides/JMPR/Evaluation94/dicofol.pdf).

Sweden (2015): Submission of information specified in Annex E to the Stockholm Convention pursuant to Article 8 of the Convention, (http://chm.pops.int/TheConvention/POPsReviewCommittee/Meetings/POPRC10/POPRC10Followup/Dicofol(AnnexEinformation)/tabid/4293/Default.aspx).

Sabatier P, Poulenard J, Fanget B, Reyss J-L, Develle A-L, Wilhelm B, Ployon E, Pignol C, Naffrechoux E, Dorioz J-M, Montuelle B, and Arnaud F (2014): Long-term relationships among pesticide applications, mobility, and soil erosion in a vineyard. Proc. Nat. Ac. Sci. USA (PNAS), 111(44): 15647-15652.

Settimi L, Masina A, Andrion A, Axelson O (2003): Prostate Cancer and Exposure to Pesticides in Agricultural Settings. International Journal of Cancer 104, 458-461.

Shahani L, Patel T, Bhaskar N (2013): Developmental Toxicity of Dicofol Containing Formulation Colonel-S in Swiss Albino Mice. International Journal of Current Pharmaceutical Review and Research 4(4), 102-109.

Shimada N, Yamauchi K (2004): Characteristics of 3,5,3'-triiodothyronine (T3)-uptake system of tadpole red blood cells: effect of endocrine-disrupting chemicals on cellular T3 response. Journal of Endocrinology 183:627–637.

Sobti RC, Krishan A, Davies J (1983): Cytokinetic and cytogenic effect of agricultural chemicals on human lymphoid cells in vitro. II Organochlorine pesticides. Archives of Toxicology 52:221-231.

Spain (2006): Draft Monograph prepared in the context of the inclusion of the following active substance in Annex I of the Council Directive 91/414/EEC, July 2006.

Stone JC, Abramson CI, Price JM (1997): Task-dependent effects of dicofol (Kelthane) on learning in the honey bee (*Apis melliflera*). Bull.Environ. Contam. Toxicol, 58: 177-183.

Suárez P, Ruiz Y, Alonso A, San Juan F (2013): Organochlorine compounds in mussels cultured in the Ría of Vigo: accumulation and origin. Chemosphere. 2013 Jan;90(1):7-19.

Sugiyama S, Shimada N, Miyoshi H, Yamauchi K (2005): Detection of Thyroid System-Disrupting Chemicals Using in Vitro and in Vivo Screening Assays in Xenopus laevis. Toxicological Sciences 88:2, 367-374.

Syed JH, Malik RN (2011): Occurrence and source identification of organochlorine pesticides in the surrounding surface soils of the Ittehad Chemical Industries Kalashah Kaku, Pakistan, Environ Earth Sci, 62: 1311–1321.

Syed JH, Malik RN, Li J, Chaemfa C, Zhang G, Jones KC (2014): Status, distribution and ecological risk of organochlorines (OCs) in the surface sediments from the Ravi River, Pakistan. Sci Total Environ., 472: 204-211.

Tang Z, Huang Q, Yang Y, Zhu X, Fu H. (2013): Organochlorine pesticides in the lower reaches of Yangtze River: occurrence, ecological risk and temporal trends. Ecotoxicol Environ Saf., 87: 89-97.

Thibaut R, Porte C (2004): Effects of endocrine disrupters on sex steroid synthesis and metabolism pathways in fish. J. Steroid Biochem Mol Biol. 92(5):485-94.

Thiel A, Guth S, Böhm S, Eisenbrand G (2011): Dicifol degradation to *p,p'*-dichlorobenzophenone – A potential antiandrogen. Toxicology 282, 88-93.

Thomas M, Lazartigues A, Banas D, Brun-Bellut J, Feidt C (2012): Organochlorine pesticides and polychlorinated biphenyls in sediments and fish from freshwater cultured fish ponds in different agricultural contexts in north-eastern France. Ecotoxicol Environ Saf. 2012 Mar;77:35-44.

Turgut C, Gokbulut C, Cutright T (2009): Contents and sources of DDT impurities in dicofol formulations in Turkey. Environmental Science and Pollution Research, 16, 214-217.

UN ECE (2009): Report by the Co-chairs of the Task Force on Persistent Organic Pollutants, ECE/EB.AIR/WG.5/2009/7, (http://www.unece.org/fileadmin/DAM/env/documents/2009/EB/wg5/wgsr45/ece.eb.air.wg.5.2009.7.e.pdf 2012-04-16).

UNEP/POPS/COP.7/4/Rev.1 (2015): Conference of the Parties to the Stockholm Convention on Persistent Organic Pollutants, Seventh meeting, Geneva, 4–15 May 2015, Specific exemptions and acceptable purposes under the Stockholm Convention. Note by the Secretariat, 11 March 2015.

UNEP/POPS/COP.7/4/Rev.1-Corr.1 (2015): Conference of the Parties to the Stockholm Convention on Persistent Organic Pollutants, Seventh meeting, Geneva, 4–15 May 2015, Specific exemptions and acceptable purposes under the Stockholm Convention. Note by the Secretariat. Corrigendum, 29 May 2015.

UNEP/POPS/POPRC.3/INF/8 (2007): Additional information related to assessment of bioaccumulation data under Annex D of the Convention, POPR .3, 2007.

UNEP/POPS/POPRC.10/10 (2014): Report of the Persistent Organic Pollutant Review Committee on the work of its tenth meeting. Annex to POPRC-10/3, POPRC 10, 2014.

UNEP/POPS/POPRC.8/INF/13 (2012): Fact sheets on chemical alternatives to endosulfan and DDT, POPRC 8, 2012.

UNEP/POPS/POPRC.2-17 Add.2 (2006): Risk profile on chlordecone, POPRC 2, 2006.

UNEP (2015): The Register of Specific Exemptions (http://chm.pops.int/Implementation/Exemptions/RegisterofSpecificExemptions/tabid/1133/).

USA (2015): Submission of information specified in Annex E to the Stockholm Convention pursuant to Article 8 of the Convention, (http://chm.pops.int/TheConvention/POPsReviewCommittee/Meetings/POPRC10/POPRC10Followup/Dicofol(AnnexEinformation)/tabid/4293/Default.aspx).

US EPA (1998) RED: Reregistration Eligibility Decision Dicofol (http://www.epa.gov/pesticides/reregistration/REDs/0021red.pdf, 2012-04-16).

US EPA (2009): Risks of Dicofol Use to Federally Threatened California Red-legged Frog (Rana aurora draytonii), Pesticide Effects Determination Environmental Fate and Effects Division Office of Pesticide Programs Washington, D.C. 20460, June 15, 2009 (http://www.epa.gov/espp/litstatus/effects/redleg-frog/dicofol/analysis.pdf, 2012-04-16).

Van den Berg KJ, van Raaij JA, Bragt PC, Notten WR (1991): Interactions of halogenated industrial chemicals with transthyretin and effects on thyroid hormone levels in vivo. Archives of Toxicology 65(1):15-19.

Van de Plassche EJ, Schwegler M, Rasenberg M, Schouten G (2003): DDT in Dicofol. UN-ECE report. (http://www.unece.org/fileadmin/DAM/env/lrtap/TaskForce/popsxg/2000-2003/ddt in dicofol.pdf, 2015-02-18).

Van der Gon HD, Bolscher M, Visschedijk A, Zandveld A (2007): Emissions of persistent organic pollutants and eight candidate POPs from UNECE–Europe in 2000, 2010 and 2020 and the emission reduction resulting from the implementation of the UNECE POP protocol, Atmospheric Environment 41 (2007) 9245–9261.

Vonier PM, Crain DA, McLachlan JA, Guillette LJ, Arnold SF. (1996): Interaction of environmental chemicals with the estrogen and progesterone receptors from the oviduct of the American alligator. Environmental Health Perspectives 104(12):1318–1322.

Vulliet E, Berlioz-Barbier A, Lafay F, Baudot R, Wiest L, Vauchez A, Lestremau F, Botta F, Cren-Olivé C (2014): A national reconnaissance for selected organic micropollutants in sediments on French territory. Environ Sci Pollut Res Int. 2014 Oct;21(19):11370-9.

Vryzas Z, Papadakis EN, Vassiliou G, Papadopoulou-Mourkidou E (2012): Occurrence of pesticides in transboundary aquifers of North-eastern Greece. Sci Total Environ. 2012 Dec 15;441:41-8.

Vulykh N, Dutchak S, Mantseva E, Shatalov V (2005): EMEP contribution to the preparatory work for the review of the CLRTAP protocol on persistent organic pollutants. Meteorological Synthesizing Centre – East 2005.

Wang D, Weston DP, Ding Y, Lydy MJ (2010): Development of a sample preparation method for the analysis of current-use pesticides in sediment using gas chromatography. Archives of Environmental Contamination and Toxicology, 58: 255–267.

Wang N, Shi L, Kong D, Cai D, Cao Y, Liu Y, Pang G, Yu R (2011): Accumulation levels and characteristics of some pesticides in human adipose tissue samples from Southeast China. Chemosphere 84, 964-971.

Wang S, Wang Z, Zhang Y, Wang J, Guo R (2013): Pesticide residues in market foods in Shaanxi Province of China in 2010. Food Chemistry 138, 2016-2025.

Wang J, Yu X, Fang L (2014): Organochlorine pesticide content and distribution in coastal seafoods in Zhoushan, Zhejiang Province. Marine Pollution Bulletin 80: 288–292.

Wang YQ, Wang Y, Huo X, Zhu Y (2015): Why some restricted pesticides are still chosen by some farmers in China? Empirical evidence from a survey of vegetable and apple growers. Food Control doi: 51:417-24.

Weaver TB, Ghadiri H, Hulugalle NR, Harden S (2012): Organochlorine pesticides in soil under irrigated cotton farming systems in Vertisols of the Namoi Valley, north-western New South Wales, Australia. Chemosphere, 88: 336–343.

Wegmann F (2009): The OECD POV and LRTP Screening Tool, Version 2.21 (http://www.oecd.org/chemicalsafety/risk-assessment/oecdpovandlrtpscreeningtool.htm, 2015-02-4).

Weston DP, Ding Y, Zhang M, Lydy MJ (2013): Identifying the cause of sediment toxicity in agricultural sediments: The role of pyrethroids and nine seldom-measured hydrophobic pesticides. Chemosphere, 90: 958-964.

WHO (1992): The WHO recommended classification of pesticides by hazard and guidelines to classification 1992–1993. Geneva, World Health Organization, International Programme on Chemical Safety (WHO/PCS/92.14).

WHO (1996): International Programme on Chemical Safety, Dicofol, WHO/FAO Data Sheets on Pesticides No. 81 World Health Organization. Geneva, July 1996 (http://www.inchem.org/documents/pds/pds/pest81_e.htm, 2015-01-15).

WHO (2012): State of the science of endocrine disrupting chemicals – 2012 An assessment of the state of the science of endocrine disruptors prepared by a group of experts for the United Nations Environment Programme (UNEP) and WHO (World Health Organisation). ISBN: 978 92 4 150503 1.

Wiemeyer SN, Clark DR J, Spann JW, Belisle AA, Bunck CM (2001): Dicofol residues in eggs and carcasses of captive American kestrels. Environ Toxicol Chem., 20(12): 2848-51.

Wicks RJ (2002): Degradation and fate of dicofol in two water-sediment systems. Huntingdon Life Sciences Ltd. Study Sponsor: Dow AgroSciences. Study Report: DOS/259.

Xia H (2008): Enhanced disappearance of dicofol by water hyacinth in water. Environmental Technology, 29(3), 297-302.

Xu XP, Xi YL, Chu ZX, Xiang XL. (2014): Effects of DDT and dicofol on population growth of *Brachionus calyciflorus* under different algal *(Scenedesmus obliquus*) densities. J Environ Biol. 35(5): 907-16.

Yan H, Yang C, Sun Y, Row KH (2014): Ionic liquid molecularly imprinted polymers for application in pipette-tip solid-phase extraction coupled with gas chromatography for rapid screening of dicofol in celery. Journal of Chromatography A 1361, 53-59.

Yang R, Zhang, S, Li A, Jiang G, Jing C (2013): Altitudinal and spatial signature of persistent organic pollutants in soil, lichen, conifer needles, and bark of the southeast Tibetan Plateau: implications for sources and environmental cycling. Environmental science and technology 47(22): 12736-43.

Zhao BS, Zou JC, Chu SG, Xu XB, Du KJ (2000): Bioassay of estrogenic effect of dicofol using uterine weight method in mice. Environmental Science. Acta Scientiae Circumstantiae 20:244-248. In Chinese, Cited in Du et al 2001.

Zhou S, Yang H, Zhang A, Li YF, Liu W (2014): Distribution of organochlorine pesticides in sediments from Yangtze River Estuary and the adjacent East China Sea: implication of transport, sources and trends. Chemosphere, 114: 26-34.

Zhong GC, Xie ZY, Cai M H, Möller A, Sturm R, Tang JH, Zhang G, He JF, Ebinghaus R (2012): Distribution and air-sea exchange of current-use pesticides (CUPs) from East Asia to the high Arctic Ocean, Environ. Sci. Technol., 46(1), 259–267.

Zhong G, Tang J, Xie Z, Möller A, Zhao Z, Sturm R, Chen Y, Tian C, Pan X., Qin W, Zhang G, Ebinghaus R (2014): Selected current-use and historic use pesticides in air and seawater of the Bohai and Yellow Seas, China. J. Geophys. Res. Atmos., 119, 1073-1086.

Zhong, G., Tang, J., Xie, Z., Mi, W., Chen, Y., Möller, A., Sturm, R., Zhang, G. and Ebinghaus, R. (2015): Selected current-use pesticides (CUPs) in coastal and offshore sediments of Bohai and Yellow seas. Environ. Sci. Pollut. Res Environ Sci Pollut Res, 22:1653–1661.

Zhu N, Schramm KW, Wang T, Henkelmann B, Zheng X, Fu J, Gao Y, Wang Y, Jiang G (2014): Environmental fate and behavior of persistent organic pollutants in Shergyla Mountain, southeast of the Tibetan Plateau of China. Environ Pollut. 2014 Aug; 191:166-74.