

**Stockholm Convention
on Persistent Organic
Pollutants****Persistent Organic Pollutants Review Committee****Ninth meeting**

Rome, 14–18 October 2013

Item 7 (b) of the provisional agenda*

**Consideration of chemicals newly proposed for inclusion
in Annexes A, B and/or C to the Convention: dicofol****Proposal to list dicofol in Annexes A, B and/or C to the
Stockholm Convention on Persistent Organic Pollutants****Note by the Secretariat**

1. The annex to the present note contains a proposal submitted by the European Union to list dicofol in Annexes A, B and/or C to the Convention pursuant to paragraph 1 of Article 8 of the Convention. The proposal is being circulated as submitted and has not been formally edited. The Secretariat's verification of whether the proposal contains the information specified in Annex D is discussed in document UNEP/POPS/POPRC.9/INF/8.

Possible action by the Committee

2. The Committee may wish:

- (a) To consider the information provided in the present note;
- (b) To decide whether it is satisfied that the proposal fulfils the requirements of Article 8 of and Annex D to the Convention;
- (c) To develop and agree on, if it decides that the proposal fulfils the requirements referred to in paragraph 2 (b) above, a workplan for preparing a draft risk profile pursuant to paragraph 6 of Article 8.

* UNEP/POPS/POPRC.9/1.

Annex

Proposal to list dicofol in Annexes A, B and/or C to the Stockholm Convention on Persistent Organic Pollutants

1. Introduction

1. Dicofol is an organochlorine pesticide that is chemically related to DDT. The substance is a miticidal pesticide and acaricide used in many countries around the world on a wide variety of fruit, vegetables, ornamental and field crops.

2. This dossier focuses solely on the information required under paragraphs 1 and 2 of Annex D of the Stockholm Convention and it is mainly based on the following documents:

(a) The Risk Profile and Summary Report for dicofol from April 2002, prepared for UNECE by Rasenberg et al. 2003 as well as its Addenda from December 2005 and February 2009 ;

(b) The documents developed under the screening assessment performed by the persistent Organic Pollutants Review Committee POPRC related to the alternatives to endosulfan [UNEP/POPS/POPRC.8/8, UNEP/POPS/POPRC.8/INF/13] classifying dicofol as substance likely to meet Annex D;

(c) Additional sources of scientific information included reports by US EPA, AMAP and OSPAR, as well as recent scientific publications, investigated on a screening basis for relevant information on dicofol.

2. Identification of the chemicals

2.1 Names and registry numbers

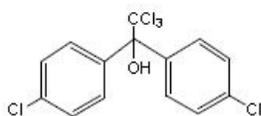
CAS number: 115-32-2

CAS chemical name: 1,1-bis(4'-chlorophenyl)2,2,2-trichloroethanol

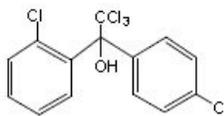
IUPAC name: 2,2,2-trichloro-1,1-bis(4-chlorophenyl)ethanol

Synonyms and Trade Names: Kelthane, Benzenemethanol,4-chloro- α -(4-chlorophenyl)- α -(trichloromethyl)-; acarin; 1,1-bis(chlorophenyl)-2,2,2-trichloroethanol; carbox; cekudifol; dichlorokelthane; hilfol; kelthane; kelthane 35; milbol; CPCA; Decofol; Dicaron; Dicomite; Difol, Mitigan, p,p-dicofol, kelthanethanol

2.2 Structures



p,p'-dicofol
CAS No. 115-32-2



o,p'-dicofol
CAS No. 10606-46-9

Chemical formula: C₁₄H₉Cl₅O

3. Dicofol is comprised of two isomers: p,p'-dicofol and o,p'-dicofol. The typical isomer content in existing technical material is approximately 80% of p,p'-isomer and 20% of the o,p'-isomer.

3. Persistence

4. According to the Japanese NITE database dicofol is characterised as non-biodegradable

5. Degradation in water is primarily by hydrolysis. The rate is strongly pH dependent. For the main p,p'-isomer of dicofol the half life in water has been reported as 85 days at pH 5, 4 days at pH 7 and 0.02 days at pH 9. For the o,p'-isomer of dicofol reported half lifes are 47 days at pH 5, 0.3 days at pH 5 and 0.0006 days at pH 5.

6. This implies that for water bodies with a pH value of 5 or less the half life of dicofol is expected to be > 2 months.

7. Many northern countries have surface waters with pH of 5. In a survey from 1995 the 10th percentile of lake pH values in Denmark, Finland, Iceland, Norway and Sweden were 5.98, 5.68, 6.56, 5.07 and 5.76, respectively.

8. The main hydrolysis products of dicofol are the corresponding dichlorobenzophenones (DCBP), which appear to be resistant to further degradation in water.
9. Photodegradation of *p, p'*-dicofol was reported to show half-lives of 4 and 92.5 d for sensitized and non-sensitized conditions, respectively. Degradation in soil depends on the type of soil and on aerobic conditions. The rate of degradation was fastest in soils with higher pH. *o, p'*-dicofol degraded faster than *p, p'*-dicofol.
10. Dissipation studies from soil were conducted in New York, Florida and California after application on strawberry and cotton, citrus grove and apple orchards. Neither dicofol nor its residues moved below 6 inches and volatilisation could be excluded. The half-life for the parent ranged up to 2 months. The overall half lives of dicofol residues in soils varied between 2 – 4 months.
11. Major degradates of dicofol are the *o, p'*- and *p, p'* isomers of DCBP; 1,1-(*p*-chlorophenyl-) 2,2-dichloroethanol (FW-152); dichlorobenzhydrol (DCBH); hydroxyl-dichlorobenzophenone (OH-DCBP); and chlorobenzoic acid (CBA). DCBP was identified in the hydrolysis, photolysis and metabolism studies while the other degradates were only present in metabolism studies. There are currently no submitted studies addressing the environmental fate and transport of these major degradates. However, the studies submitted in support of the aerobic soil metabolism indicate a large difference between half lives for dicofol alone (8.5 and 32 days for *o, p'*- and *p, p'*-dicofol, respectively) and the half lives for dicofol plus its degradates (186 and 313 days for total *o, p'*- and *p, p'*-dicofol, respectively) (US EPA 2009)¹.
12. A degradation and fate study of dicofol in two water-sediment systems showed that the half life of *p, p'* dicofol is 0.31-0.54 day and 0.05-0.06 day for *o, p'*-dicofol. The pH values of the water phase of the systems were 7.61 and 7.83. The main degradation products are DCBP, DCBA (dichlorobenzilic acid) and DCBH. Half lives of these substances were 7-13 days for DCPB, 24-174 days for DCBA and 197-429 days for DCBH. Levels of carbon dioxide increased slowly throughout the study and accounted for circa 4-6% of applied radioactivity at the end of study, i.e. 100 days. Due to its high *K_{oc}* value, dicofol will be removed from water by adsorption to sediment.

4. Bioaccumulation

13. Measured log *K_{ow}* values vary from 4.08 to 5.02. A high log *K_{ow}* of 6.06 has been reported in US EPA RED (1998).
14. There is strong evidence from several fish studies indicating that BCFs are above the threshold of 5000. One study carried out with the technical Kelthane, resulted in BCF values ranging from 8050 to 13500 with no equilibrium reached within 28 d². Another study with *p, p'*-dicofol in bluegill sunfish (*Lepomis macrochirus*) over 28 d resulted in factors of 6600, 17000 and 10000 for fillet, viscera, and whole fish, respectively.³ A third study with fathead minnows (*Pimephales promelas*) after 296 days of exposure to dicofol and based on measured radio-labeled tissue residues, led to BCF values as high as 43000. (UNECE, 2009). BCF values available in the Japanese METI-NITE database of 8200 (log BCF 3.91) and 6100 (log BCF 3.78) obtained for common carp exposed at 1 µg/l and 0.1 µg/l, respectively, which were in the same range as the BCF values found in their own study with zebra fish eleutheroembryos⁴.
15. Comparison with BCF values obtained from QSAR models showed good agreement with those obtained in their study.

5. Potential for long-range environmental transport

16. There is some evidence for dicofol contamination in remote sites and long-range transport of dicofol, although the levels are not high.
17. As reported in AMAP (2009)⁵, dicofol has been detected in Arctic air samples, whereas a chemical signature of DDT contamination indicates dicofol products from China as the source.

¹ <http://www.epa.gov/espp/litstatus/effects/redleg-frog/dicofol/analysis.pdf>

² Eaton G.J. *et al.* 1982. Effects of suspended clay on bioconcentration of Kelthane in Fathead Minnows. Arch. Environ. Contam. Toxicol. 12, 439-445.

³ Tillman, A. M. 1986. The bioconcentration, elimination and metabolism of 14C-dicofol by bluegill sunfish (*Lepomis microchirus*). Report No. 310-86-17, prepared and submitted by Rohm and Haas Company, Philadelphia, PA.

⁴ El-Amrani S. *et al.* (2012). Bioconcentration of pesticides in Zebrafish eleutheroembryos. Science of the Total Environment, 425: 184-190.

⁵ Arctic Monitoring and Assessment Programme (AMAP), Arctic Pollution 2009, Oslo 2009

18. Zhong et al. (2012)⁶ collected surface seawater and marine boundary layer air samples from the East China Sea to the high Arctic, measured an average contamination of 14 pg/m³ in air and identified contamination in seawater. As assumed by Zhong et al. detection of dicofol in the Arctic is not only due to atmospheric deposition, but also due to input from riverine freshwater, since high levels of dicofol-related DDT have been reported in river water samples from the Russian Arctic in 2003 and 2005 (Carroll et al., 2008)⁷.
19. Information on remote contamination associated to dicofol has been reported via DDT/DDE levels that occur as impurity of technical dicofol. DDT is used as an intermediate in the production of the pesticide dicofol and may occur as a major impurity in the final product.
20. The analysis of 23 commercial dicofol formulation from 7 producers revealed average concentrations for o,p'-DDT, p,p'-Cl-DDT, o,p'-DDE, and p,p'-DDT of 11.4, 6.9, 4.4, and 1.7 %, respectively (Qiu et al., 2005)⁸.
21. Coscollà et al. (2011)⁹, determined dicofol in airborne particulate matter samples from a rural station in Valencia, Spain (median dicofol concentration: 0.016 µg/m³). Hart et al. (2012)¹⁰, analysed PM10 from ambient air samples at one remote, one urban and three rural sites in Valencia Region, Spain (average dicofol concentration: 0.025 µg/m³; range: 0.02-0.03 µg/m³).
22. The residence time of dicofol in the atmosphere (t_{1/2} in air) estimated on the basis of model calculations of its atmospheric transport totals to 3 days (UNECE, 2005). The vapour pressure of dicofol is low, being 5.3 * 10⁻⁵ Pa.
23. Based on the vapour pressure combined with the propensity of the compound to sorb to particles (K_d range 8.4 - 82.8 ml/g, K_{OC} range 5868 - 8383 ml/g_{OC}) dicofol is expected to partition between the gas and particle phases in the atmosphere and is likely to exist largely associated with suspended particulate matter in the atmosphere.
24. The average half-life time for particles is estimated to be about 3.5 - 10 days and the average life time for particles is estimated to be about 5 - 15 days. (UNECE, 2009)
25. The calculated transport distance in Europe is 1650 km for dicofol (UNECE, 2005) on the basis of a multi-compartment transport model for the evaluation of long-range atmospheric transport and deposition of POPs.

6. Adverse effects

Toxicity

26. There is evidence for reproductive effects on birds, and study results indicating effects in rats and dogs. The primary effects observed after long term dietary exposure of laboratory animals to dicofol are liver enlargement and enzyme induction, and other changes in the liver, kidney adrenal gland and urinary bladder.
27. Dicofol has been tested on several animals, i.e. rats, mice, rabbits and guinea pigs. The substance may be absorbed through ingestion, inhalation or skin contact. Most of the studies indicate that the substance is moderately toxic to animals with results ranging from 420 mg/kg and 4365 mg/kg for oral LD₅₀, and 1000 - 5000 mg/kg for dermal LD₅₀.
28. (Sub)chronic studies performed with rats, mice and dogs, showed liver enlargement and enzyme induction as primary effects observed after long term dietary exposure. In a 2-year study with rats, liver, growth, enzyme induction and other changes in the liver, adrenal gland and urinary bladder were observed at doses of 2.5 mg/kg/day. In another two-year study on hormonal effects in dogs a

⁶ Zhong G. *et al.* (2012). Distribution and Air-Sea Exchange of Current-Use Pesticides (CUPs) from East Asia to the High Arctic Ocean. *Environmental Science & Technology*, 46: 259-267.

⁷ Carroll *et al.* (2008). PCBs, PBDEs and pesticides released to the Arctic Ocean by the Russian Rivers Ob and Yenisei. *Environmental Science & Technology*, 42: 69-74.

⁸ Qiu, X. *et al.* (2005). Contribution of Dicofol to the current DDT pollution in China. *Environ Sci Technol* 39: 4385-4390.

⁹ Coscollà C. *et al.* (2011). Determination of 40 currently used pesticides in airborne particulate matter (PM10) by microwave-assisted extraction and gas chromatography coupled to triple quadrupole mass spectrometry. *Analytica Chimica Acta*, 693: 72-81.

¹⁰ Hart E. *et al.* (2012). GC-MS characterization of contemporary pesticides in PM10 of Valencia Region, Spain. *Atmospheric Environment*, 62: 118-129.

NOAEL of 0.22 mg/kg/day has been determined leading to a RfD of 0.0004 mg/kg/day (US EPA RED 1998)¹¹.

29. Effects on the liver, kidney and adrenals and reduced body weights were observed in a 3-months dietary study with mice at doses of 6.25 mg/kg/day. A NOAEL of 2.1 mg/kg/day has been derived for mice in a 3 months study after oral exposure. A dermal study with rabbits resulted in a NOAEL of 4.1 mg/kg/day after an exposure during 4 weeks (6 hours/day, 5 days/week).

30. UNEP/POPS/POPRC.8/INF/13 concluded that based on available data there is no evidence for carcinogenicity of Dicofol. In a recent study by Liu et al. (2012) however, the interaction mechanism at molecular level between dicofol and one of the serine proteases α -chymotrypsin in aqueous medium was investigated. The results indicate that dicofol has deleterious effects on the frame conformation of proteins, disturbs the physiological function, and might raise the risk of cancer incidence.

31. Reproductive effects in rats have been observed only at doses high enough to also cause toxic effects on livers, ovaries and feeding behaviour of the parents. A dietary concentration of 7 mg/kg dicofol fed to mice for 3 generations produced defects in 12 days old offspring of the third generation. These results were not confirmed in a subsequent study in mice fed diets containing 7-500 mg/kg dicofol.

32. In a study with rabbits, the animals were exposed to 0.4 mg/kg/day during day 7-19 of the gestation. No adverse effects were shown.

Ecotoxicity

33. UNEP/POPS/POPRC.8/INF/13 listed LC50 value for fish 0.1 – 2.29 mg/l; 96h as well as NOECs for chronic exposure of 0.009 mg/L - 0.0045 mg/L. The US EPA RED (1998) cites an acceptable life-cycle study in the fathead minnow, where dicofol was shown to affect the reproductive physiology of the fathead minnow at levels as low as 0.005 mg/l (mean hatching success).

34. The NOEC in a 60d- fish early life stage test was 4.4 μ g/l. The NOEC in a test on the survival and reproduction of daphnia magna was 125 μ g/l (Rasenberg *et al.* 2003).

35. Available data from several acute toxicity studies suggest that dicofol is slightly to moderately toxic to birds on an acute exposure basis. The lowest LD50 in mg/kg is 265 mg/kg.

36. Sánchez et al. (2010)¹² identified metabolites have similar toxic effects for aquatic organism based on range-finding studies and (QSAR) model estimations.

37. In rats dicofol and DCBP were found in fat and skeletal muscle after a single i.p. dose of 230 mg/kg bw or after repeated oral administration. The parent compound and DCBP were excreted predominantly via the faeces. After acute exposure, dicofol and DCBP accumulated initially in the liver declining after day 15.¹³

Endocrine disruption

38. Avian studies indicate that dicofol can affect reproductive parameters such as shell strength, shell thickness and egg production although it should be stated that the testing material may have contained more than the amount of DDT nowdays present in dicofol of less than 0.1%. In a multi-year, multi-crop field study in California, New York and Florida no effects could be observed in 13 bird species except for the 'New York robin' where residues of p,p'-dicofol were higher in unsuccessful nests compared to successful nests. Yearly mean residues in eggs were highest in New York and varied from 0.01 to 0.46 mg/kg (US EPA RED,1998).

39. Long-term effects are eggshell thinning, with effects on reproduction (Van Rijn et al., 1995)¹⁴. In ducks, effects on eggshell strength were found in dietary studies (126 days) starting from 2.5 mg/kg dicofol. At 40 mg/kg a slight decrease in hatchability, reduction in eggshell thickness and increase of percentage of cracked eggs was observed.

¹¹ <http://www.epa.gov/pesticides/reregistration/REDS/0021red.pdf>

¹² Sánchez A.I. *et al.* (2010). Hazard Assessment of Alternatives to Dicofol. Journal of Environmental Protection, 1: 231-241.

¹³ <http://www.inchem.org/documents/jmpr/jmpmono/v92pr08.htm>

¹⁴ Van Rijn J.P *et al.* (1995). Handboek Bestrijdingsmiddelen, gebruik en milieueffecten. VU Uitgeverij, Amsterdam (in Dutch).

40. A two generation study was conducted by MacLellan et al. (1996)¹⁵ on a captive population of American kestrels to investigate the reproductive and teratogenic effects of dicofol. Females dosed with 20 mg/kg of dicofol laid eggs with shells that were significantly thinner than those of the control birds. Male embryos from females dosed with 5 and 20 mg/kg of dicofol had gonads that were significantly different from the control chicks. Wiemeyer et al (2001)¹⁶ reported the lowest observed dietary effect concentration for eggshell thinning was 3 mg/kg and the no/observed adverse effect concentration was 1 µg/g.
41. Dicofol was shown to possess an estrogenic activity in an in vitro test with the α - and β -estrogenic receptor (Kojima et al 2004)¹⁷.
42. Lavado et al (2004)¹⁸ showed that dicofol can inhibit testosterone glucuronidation in an in vitro test system (carp liver microsomes) in the same manner as tributyltin. Thibaut and Porte (2004)¹⁹ concluded that dicofol interfered with the synthesis of sex hormones in fish microsomes.
43. Haeba et al. (2008)²⁰ demonstrated in daphnia that sublethal concentrations of dicofol resulted in a significant shift of the sex ratio in favour of males at the highest concentration tested (0.1 mg/L).
44. Hoekstra et al. (2006)²¹ reported enantiomer-specific differences in the estrogenic activity of dicofol indicating that the estrogenic activity of dicofol is primarily associated with the achiral p,p'-isomer and (-)-o,p'-substituted enantiomer.
45. Thiel et al. (2011)²² investigated the degradation of dicofol with special emphasis on generation of p,p'-DCBP as well as its anti-androgenic effects. The results indicate that the degradation of dicofol to DCBP is primarily an abiotic process. Microsomal metabolism does not appear to play a major role in the degradation of dicofol. In addition DCBP showed potent antiandrogenic efficacy. This finding was confirmed by further studies in T47D human mammary carcinoma cells.

7. Statement of the reasons for concern

46. The evaluation of existing information indicated that there is reason of concern, due to clear evidence that dicofol does meet the criterion for bioaccumulation due to its BCF > 5000, its potential for long-range environmental transport, and its very high toxicity to aquatic organism in addition to other health hazards including a potential endocrine disrupting property with reprotoxic effects have been identified. Furthermore concerns are caused by some evidence for dicofol contamination in remote sites, persistency of dicofol in acidic waters and suggested persistence of the major metabolites in water, soil and sediment.
47. In addition, dicofol can contain DDT depending on the manufacturing method.
48. Placing on the market and use of dicofol has been prohibited or restricted in several countries representing different regions of the world. However, it is still produced in some countries and it continues to be used in many countries. As these substances can move far from their sources, single countries or groups of countries alone cannot abate the pollution caused by them. Due to the harmful POP properties and risks related to their production and use, international action is warranted to control this pollution.

¹⁵ MacLellan K. et al. (1995). Reproductive and morphological effects of o,p'-dicofol on two generations of captive American Kestrels. Arch. Environ. Contam. Toxicol. 30, 364-372.

¹⁶ Wiemeyer et al., (2001). Dicofol residues in eggs and carcasses of captive american kestrels. Environ. Toxicol Chem 20: 2848-2851.

¹⁷ Kojima, H *et al.* (2004). Screening for estrogen and androgen receptor activities in 200 pesticides by in vitro receptor gene assays using Chinese Hamster ovary cells. Environ Health Perspect 2004: 112: 524-531

¹⁸ Lavado et al (2004). Toxicol Appl Pharmacol. 2004 Apr 15;196(2):247-57.

¹⁹ Thibaut R, Porte C.; Effects of endocrine disruptors on sex steroid synthesis and metabolism pathways in fish. J Steroid Biochem Mol Biol. 2004 Dec;92(5):485-94.

²⁰ Haeba M.H. *et al.* (2008). Selected Endocrine Disrupting Compounds (Vinclozolin, Flutamide, Ketoconazole and Dicofol): Effects on Survival, Occurrence of Males, Growth, Molting and Reproduction of Daphnia magna. Environmental Science and Pollution Research, 15 (3): 222-227

²¹ Hoekstra P.F. *et al.* (2006). Estrogenic activity of dicofol with the human estrogen receptor: Isomer- and enantiomer-specific implications. Chemosphere, 64: 174-177

²² Thiel A. *et al.* (2011). Dicofol degradation to p,p'-dichlorobenzophenone – A potential antiandrogen. Toxicology, 282: 88-93