Return to Content of Annexes

Annex 12

Scientific evidence used in the Expert meeting for the evaluation of the 146 selected substances

Annex 12 : Scientific evidence used in the Expert meeting for the evaluation of the 146 selected substances

Note 1: W = Wildlife; M = Mammalian

Note 2: (1) = Evidence of endocrine disruption in a living organism
(2) = Evidence of potential to cause endocrine disruption
(3) = No evident scientific basis for inclusion in list

Contents

1. CHLORDANE

W: Has potential to be an ED, because evidence of specific binding to estrogen receptors in alligator - but only in vitro and from only one study (arn97) (2).

M (includes also cis- and trans-Chlordane): in vitro studies on estrogenic activity are both negative (binding to human estrogen receptor, yeast assay) and positive (stimulated proliferation of MCF-7). In vivo studies have been performed in rodents and indicate: testicular toxicity at low dose levels (rats, mice, guinea pigs; dat75, bal87), antiestrogenic effects (rats, 1971 study, wel71) and increase of follicular cell neoplasms (rats, 2-year study, nci77a). Although the possible mechanism needs further clarification, the available evidence overall indicates that Chlordane can affect endocrine homeostasis in vivo (1).

2. CHLORDANE (CIS AND TRANS)

W: No specific data; but should be treated with chlordane (2).

M: See Chlordane (1)

3. KEPONE

W: Some evidence of estrogenic binding in teleosts (tho93) and reproductive impairment. But some confusing evidence for binding with progesterone (+ve) and estrogen receptors (-ve) in alligators (von96). So considered to have potential to be an ED, but needs further study (2).

M: clear evidence for estrogenic effects in vitro and in vivo (vitro: sot92, sot95, sot94, wal96, kel95a, ham79, wil89, ero80, wal96) (vivo: das97, das98, gel78a, gra82, ham79)(1).

4. MIREX

W: One paper indicates inhibition of estradiol-induced plasma vitellogenin but at high dose (che86), so considered to have potential to be an ED, but needs further study (2).

M: Negative in the only in vitro assay performed (MCF-7)(sot92). In vivo studies indicate: clear evidence of reproductive toxicity at low dose levels (rats, mice), impaired testis descent (likely marker of antiandrogenic activity) (che76) and inhibited production of LH in two studies on prenatally exposed rats and immature rats, respectively (ful75, gel78a). Also, histological changes have been observed in the thyroid in rats (iris94, sin82a). Although the possible mechanism needs further clarification, the available evidence overall indicates that Mirex can affect endocrine homeostasis in vivo (1).

5. TOXAPHENE

W: Mixed evidence from same research team: one paper demonstrates estrogen receptor binding for alligator (arn97) but the other study fails to demonstrate binding in same spp. (von96) So has to be problematic: potential to be an ED (2).

M: Positive for estrogenic effects in vitro (MCF-7, Yeast) (vitro: bon97, sot95, sot94, arn96b) Slight, non-significant increase of uterus weight reported in rat study performed in the '70s (wel71), increase of thyroid tumours (vivo: top95). Although the possible mechanism needs further clarification, the available evidence indicates that Toxaphene can affect endocrine homeostasis in vivo. (1).

6. DDT (TECHNICAL)

W: The group intended to handle all three compounds (DDT (technical)(81), p,p-DDT (83) and tetrachloro-DDT (84) together), despite awareness of different mode and strength of actions. *Justification*: Direct and indirect effects in birds (influence on Ca-metabolism, eggshell thickness) (1).[1]

M: positive estrogenic activity in vitro (MCF-7) (sot94). In vivo effects include prolongation of oestrus cycle in mice (orb72) and reduced ovulation in rabbits (lin94). Although the possible mechanism needs further clarification, the available evidence indicates that DDT can affect endocrine homeostasis in different species (1).[2]

7. P,P'-DDT

W: As for 81 (1).

M: abundant evidence of positive effects in vitro, either estrogenic (MCF-7, competition with estradiol at estrogen receptor in rabbit uterus, dan97) and antiandrogenic (receptor competition with DHT in rat epidermis and prostate, dan97). Two in vivo studies indicate that p, p' DDT increases the glycogen content of rat uterus (bit78, bit70). Considering also the many positive in vitro studies and the close relationship with DDT, it is prudent to consider that there is evidence of endocrine disruption for p'p'DDT (1).

8. TETRACHLORO DDT

W: As for 81 (1)

M: increased uterine glycogen content reported in a 1978 rat study (bit78). Similarities to other DDT also considered as potential to cause endocrine disruption (2).

9. VINCLOZOLIN

W There were no data at all to conduct an expert judgement (3).[3]

M: clear evidence for antiandrogenic effects on rodents in vivo (gra94, kel94, ash97a, kel97, pie98, Helwig, et al, 1990 and 1987; Mellert, et al, 1994)(1).

10. MANEB

W There were no data in the BKH database. The available data from birds and fish (ELS) were not conclusive, since the measured endpoints are not clear endocrine related (3).

M: Thyroid effects (the metabolite ethylenthiourea inhibits thyroid hormone synthesis). Vast amount of data. For references see CEFIC information on maneb (O'Neil & Marshall, 1984; Atterwill & Aylard, 1995; Eugler & Burger, 1984, Arnold, et al, 1983) (BKH: top95, fis96, lai85)(1).

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[1] also skewed sex ratio in birds (fox92) and no feminized males in birds (fry81).

[2] Technical DDT is a mixture of the isomers p,p´-DDT and o,p´-DDT and their metabolites p,p´-DDD, o,p´-DDD, p,p´-DDE and o,p´-DDE. The estrogenic activity of DDT isomers and metabolites has been studied intensively in vivo (for review and references see Gülden et al., 1998). Consistently, o,p´-DDT had a higher estrogenic activity than p,p´-DDT. o,p´-DDD and o,p´-DDE were also estrogenic in vivo. p,p´-DDD and p,p´DDE were inactive. p,p´-DDE, however, has been shown later to act in vivo as an antiandrogen (Kelce et al., 1995)

[3] The authors of the publication (Crain et al. (1997) found no effects on male or female alligators for vinclozolin. Therefore no justification for a re-grouping.

11. METAM NATRIUM

W: There were no data at all to conduct an expert judgement (3).

M: Neuroendocrine-pituitary effects (depression of LH surge). See CEFIC information on metam natrium for key reference (Goldman et al., 1994) (1).

12. THIRAM

W: The available data were not conclusive or could not be verified, due to incomplete literature citations in the BKH database (are corrected) (sno98, fis76) (3).

M: Neuroendocrine-pituitary effects (depression of LH surge). Key reference: Stoker et al., 1993 (Sto93). Thyroid effects (decrease of T4, increase of TSH): see CEFIC information on thiram for key reference (D.F. Kehoe, Hazelton Laboratories America, Inc., 1991) (1).

13. ZINEB

W: There were no data in the BKH database. The remaining data for fish were not conclusive regarding an endocrine disrupting potential. These data are more indicative for a slight teratogenic potential (3).

M: Thyroid effects (the metabolite ethylenthiourea inhibits thyroid hormone synthesis). For references see CEFIC (Edwards et al., 1991) and BKH: (gen88, top95, neb95,lai85) (1).

14. GAMMA-HCH =LINDANE

W: The information in the BKH database is based mainly on the review article of KIME, which could however not be verified, since the original literature was not available. In addition there were some personal communications on observed effects with no valid source of information. The compound was preliminary categorised as having potential to cause endocrine disruption, due to effects on steroid hormones in fish (sin94a, sin97, sin91, sin92a)(2).[1]

M: It interferes with either estrogens and androgens. Sufficient evidence from in vivo studies for inclusion in Category 1 (1).[2]

15. LINURON = LOROX

W: There were only data from one in vitro study (ER and vitellogenin mRNA induction in fish at a quite high concentration of 100 microM) in the BKH database (flo95). However, the source of this in vitro study was the Dutch health council report and the cited scientific publication could not be verified (3).

M: Antiandrogenic effects in rats (androgene receptor antagonist). Key reference: Cook et al., 1993 (wal96, Coo93) (1).[3]

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[1] also induction of vitellogenin (flo95) and inhibited LH induced in vitro ovulation (hir75).

[2] Increased LH in workers (tom81). In vitro binding test of dihydrotestosterone (dan97). Delay in vaginal opening (cha88, coo89).

[3] also increased LH (coo93)

16. ATRAZINE

W: In vivo there is sex reversals (male to female) in alligator (cra97); and in vitro evidence of inhibition of both ER and PR binding but at high doses (mg/l) (von96). Signals some potential for ED (2).[1]

M: Neuroendocrine-pituitary effects (depression of LH surge) (Cooper, et al, 1996; Morseth, 1996a; Morseth, 1996b; Simpkins JW, et al, 1998; Cooper, et al, 1999) and effects on testosterone metabolism in rat prostate and pituitary (Babib-Gojmerac, et al, 1989; Simic, et al, 1990; Kniewald, et al, 1995; Simpkins, 1999) and effects on 5α-dihydrotestosterone binding to its receptor (Babib-Gojmerac, et al, 1989; Simic, et al, 1990; Kniewald, et al, 1995; Simpkins, 1999, dan97). For references see CEFIC information on atrazine and simazine (page 8, 9) (1).

17. ACETOCHLOR

W: No data (3)

M: Thyroid effects (decrease of thyroid hormone levels, increase in TSH) (hur98). See CEFIC information for key reference (Ashby, et al, 1996; EU, 1997) (1).

18. ALACHLOR

W: Only one paper: indicating inhibition of ER binding and PR binding in alligator systems (von96). Signals some potential for ED (2).

M: Thyroid effects (decrease of thyroid hormone levels, increase in TSH). See CEFIC and BKH material (Wil96) (1).

19. STYRENE

W: No data (3)

M: Pituitary effects (elevation of prolactin level and enhanced TRH stimulated prolactin secretion in female styrene-exposed workers). For key references see CEFIC information on styrene, Annex 1 (Mutti et al., 1984, Arfini et al., 1987, Bergamaschi et al., 1996) (1).

20. HEXACHLOROBENZENE

W: One paper reports reproductive impairment in Daphnia (cal83), so this is only questionably on the ED list (3).

M: Liver enzyme induction (eli79). T3/T4/Testosterone levels reduced in rat(smi87a,bes93). Testicular pathology rat (ton78). Ovarian pathology rat (iat76)(1).

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[1] Sex reversal in alligators (Crain et al 1997). The authors of this publication described only an increase of the gonadal-adrenal mesonephros (GAM) aromatase activity at 14 ppm, but not at 1.4 and 0.14 ppm. The phenomenon of sex reversal from male to female was not observed.
Furthermore, the same group (Tox. Ind. Health 15, 180-185, 1999; also part of the CEFIC documentation) investigated the effects of atrazine on reptiles in more detail. Since they found no histological abnormalities on testes, ovaries, medullary sex cords, müllerian duct etc. and no induction of GAM aromatase at the same concentrations as previously used, they concluded that the earlier observed elevation of GAM aromatase (Crain 1997) does not affect the gonadal differentiation in reptiles.

21. BUTYLBENZYLPHTHALATE (BBP)

W: No data (3).

M: Fish hepatocyte vitellogenin (job95) +re. Testosterone reduced in rats. See Norway review of phthalates (1).[1]

22. DI-(2-ETHYLHEXYL)PHTHALATE (DEHP)

W: There was presently no clear indication that the reported adverse effects in birds (abnormality of ovaries) found at very high concentrations (5000 mg/kg diet) are related to specific endocrine disrupting endpoints (ish82) (3).

M: Gray 1999 (CEFIC) rat effects (1).[2]

23. DI-N-BUTLYPHTHALATE (DBP)

W: The observed effects in fish, birds or crustaceans were seen as toxic effects in general and not specifically related to endocrine disrupting endpoints. Furthermore there were some inconsistencies of the data (3).

M: Gray 1999 (CEFIC) rat effects (1)[3]

[1] in vitro MCF7, ZR75 cells (job95, sot95)(CEFIC: Zacharewski, 1998). Yeast (Harris 1997, Sohoni and Sumpter, 1998)

[2] decreased serum testosterone levels (Ois80a), decreased T4 levels (ats93), thyroid tumours (NTP82) also CEFIC reduced testosterone levels (Oishi et al 1979, Oishi, et al, 1980)

[3] This reference could only be found in relation to a negative study: no activation with DBP; In CEFIC data are data on decreased serum testosterone levels in rats (NTP1995a). Also estrogen receptor binding study (Nakai, et al, 1999 and Zacharewski, 1998). In BKH data on MCF7 and ZR75 cells (job95).

24. 2,2-BIS(4-HYDROXYPHENYL)PROPAN=BISPHENOL A

W: Evidence of endocrine disruption was mainly based on two studies conducted with fish and amphibians. In a life-cycle study with medaka (Yokota, 1999) the sex ratio of the Fo generation was skewed towards females at 2 mg/l. Although the growth of fish was significantly reduced at this concentration and these effects were not evident at 0.4 mg/l, the effects are seen as a high indication of an endocrine disrupting potential of BPA. In the second study, larval African clawed toads (Xenopus) were exposed for 12 weeks with BPA. At a concentration of 0.023 mg/l, Kloas et al. (1999) found that the sex ratio of tadpoles was skewed towards females. In addition there are some in vitro studies, which demonstrate the ability of BPA to induce the content vitellogenin in male fish (han98, har95)(1).[1]

M: In vivo evidence of estrogenic activity.**Category 1.** (1).[2] [3] [4]

25. PCB:

M: studying the mixture of PCBs, it has been found estrogenic, antiandrogenic and thyroid effects**.** In addition it has also been described adverse outcomes in reproductive systems (Safe, 1994; Ahlborg, 1992) (1)

26. 2,2',4,4',5,5'-HEXACHLOROBIPHENYL (PCB 153):

M: One study *in vitro* shows anti-androgenic effect (Waller, 1996). *In vivo* studies shown increased in uterus weight (Soontornchart, 1994), thyroid (Ness, 1993) and female reproductive system effects – endometriosis- (Gerhard, 1992). (1)

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[1] *Acartia tonsa* : stimulation of the maturation of ovaries, measured as an increase in egg production (20 µg/l, nominal, admimistered via food) (Andersen *et al.*, 1999, Ecotox. Environ. Safe. 44 : 56-61)

[2] MCF7 cells (hon98, nag97, han98, vil95, kri93a, kri93, bro95), estrogen receptor binding (Ole96), Yeast (rou96); CEFIC: estrogen binding (Gaido, et al, 1997, Kuiper et al, 1997, Gould et al, 1998), increased prostate and preputial gland weight (Nagel et al, 1997, vom Saal et al, 1998)

[3] Sufficient evidence of endocrine disruption (estrogenic activity) in living organism (i.e. category 1):

- induction of persistent vaginal cornification in rats (Dodds & Lawson, 1936; Campbell, 1940; Reid & Wilson, 1944),
- increase in rat uterus glycogen (Bitman & Cecil, 1970),
- premature vaginal opening and positive uterotrophic response in AP rats (Ashby & Tinwell, 1998),
- stimulation of cell proliferation in uterus and vagina in F344 rats (Steinmetz et al., in press; see Ben-Jonathan & Steinmetz, 1998),
- stimulation of pituitary prolactin release in F344 rats (Steinmetz et al., 1997).

[4] *In vivo* estrogenic effect of Bisphenol A have been produced:

1) Takao T., et al. (1999): Exposure with the environmental estrogen bisphenol A disrupts the male reproductive tract in young mice. *Life Sci.* 65 (22):2351-7.
2) Welshons WV., et al. (1999): Low-dose bioactivity of xenoestrogens in animals: fetal exposure to low doses of methoxychlor and other xenoestrogens increases adult prostate size in mice. *Toxicol. Ind. Health* 15 (1-2):12-25.
3) Fisher JS, et al. (1999): Effect of neonatal exposure to estrogenic compounds on development of the excurrent ducts of the rat testis through puberty to adulthood. *Environ. Health Perspect.* 107 (5):397-405.
4) Stoker TE, et al. (1999): Prepubertal exposure to compounds that increase prolactin secretion in the male rat. *Biol.Reprod.* 61 (6): 1636-43.

27. 3,3',4,4',5,5'-HEXACHLOROBIPHENYL (PCB 169):

M: *in vitro* data shown a possible antiestrogenic effect (Krishnan, 1993), in vivo data is positive (Patnode, 1994) (1)

28. 2,2',4,4'-TETRACHLOROBIPHENYL (PCB 47):

M: one positive *in vivo* study shows an increase in uterus weight (Soontornchart, 1994).(1)

29. 3,3,4,4',-TETRACHLOROBIPHENYL (PCB 77):

M: *in vitro* and *in vivo* data shown a possible antiestrogenic and thyroid effects (Krishnan, 1993; Jansen, 1993; Seo, 1995). (1)

30. PCB AROCLOR 1242:

M: positive estrogenic effects (Jansen, 1993, Li, 1994) (1)[1]

31. PCB AROCLOR 1248:

M: positive estrogenic and neurobehavioural effects (Ecobichon, 1974: Ahlborg, 1992) (1)

32. PCB AROCLOR 1254:

M: positive estrogenic and thyroid effects (Sager, 1994, Gray, 1993). (1)

W: Lot of evidence both of mechanism and reproduction impairment. Strong evidence of ED. In vitro evidence for disruptor mechanism (1).

33. CLOPHEN A60 = PCB AROCLOR 1260:

M: positive estrogenic effects *in vivo* (Orberg, 1973)[2]. (1)

W: There were no data for wild life available (3).

34. PBBS = BROMINATED BIPHENYLS

M: 209 congeners: epidemiological studies suggest an estrogenic and thyroid activity of these group of compounds (Bahn, 1980; Henderson, 1995). In vivo studies demonstrating their interference with both thyroid and sex hormones (IPCS: EHC N.152, Polybrominated Biphenyls, WHO ,1994; Crisp T. et al. (1998) Environmental Health Perpectives Suppl., 106: 11-56) with some supportive epidemiological evidence on primary hypothyroidism among PBB workers (1)

References VandenBergh
Stross-JK et al, 1981; Butcher and Page, 1981; Byrne et al, 1987; Gupta et al, 1983; Castracane et al, 1982; Rowlands et al, 1981; Anonymous, 1995.

[1] Due to the fact the PCBs have always been employed (and eventually still are) as mixtures of congeners, and are consequently present as mixtures in the environment, the evaluation of their effects should mainly be referred to the commercial mixtures (e.g.Aroclor 1242, 1254, 1260). Consequently, it should be clear that the lack of effects observed for some congeners is not conflicting with the evaluation of mixtures as such.
[2] Increased length of estrous cycle (örb73)

35. 1,2,3,7,8- PENTACHLORODIBENZODIOXIN:

M: different receptor mediated *in vivo* responses have been found: hepatic AHH induction and thymic atrophy (Mason, 1987). It is considered that there is evidence of endocrine disruption for 1,2,3,7,8-Pentachlorodibenzodioxin (1).

36. 2,3,7,8- TETRACHLORODIBENZO-P-DIOXIN (TCDD):

M: different *in vitro* tests (MCF-7 cells, binding to the Ah receptor and decreased in cell proliferation) (Bonefeld, 1997; Mason, 1987: Krishnan, 1993) show a clear antiestrogenic effect. *In vivo* studies have been performed in rodents and indicate: decreased uterus weight, receptor mediated in vivo responses (hepatic AHH induction, EROD activity and thymic atrophy), decreased sperm numbers and thyroid effects. In human epidemiological studies a decreased rate of estrogen-depedent neoplasms - breast- has been found (Bertazzi, 1993) Also reviews: IARC, 1997; IPCS EHC140, 1993; Crisp, et al, 1998; EPA, 1997; Buccini 1999[1]. Since polychlorodibenzodioxins are produced as mixtures of congeners, and due to structural analogy, all the 2,3,7,8-substituted congeners should be classified in as category 1 (1).

37. 2,3,4,7,8- PENTACHLORODIBENZOFURAN = 2,3,4,7,8- PECDF.

M: In vitro data of Krishnan, 1993 (see 1,3,6,8-Tetrachlorodibenzofuran) and in vivo data of Ast90. As there is in vivo and in vitro data (just as for PCB169 and PCB77) it should be categorised as (1). Since polychlorodibenzofurans are produced as mixtures of congeners, and due to structural analogy, all the 2,3,7,8-substituted congeners should be classified in Category 1.

38. TRIBUTYLTIN COMPOUNDS

As for 41

39. TRIBUTYLTIN

As for 41

40. TRIBUTYLTIN OXIDE

As for 41

41. 2-PROPENOIC ACID, 2-METHYL-,METHYL ESTER (=TBT)

W: See Attachment 1 for general criteria for wildlife data on metals and organostannic compounds. The list contains a total number of 18 tributyltin compounds (Nos. 52,60,62-70, 72-78). For reasons explained in the following we decided to refer to all these compounds as "tributyltin compounds" in general in spite of the specific number of references for the single compound. Furthermore, we encourage the Commission to follow these procedures because all tributyltin compounds exhibit a common mode of action and very similar effects both in vivo and in vitro. As reviewed in the literature (e.g. World Health Organization 1990; Fent 1996) the toxicological relevant part of the molecule is the tributyltin moiety (TBT kation). The anionic rest has no significant influence on these effects.

Imposex and intersex as virilization phenomena in molluscs are particularly well documented TBT effects on wildlife populations and have been judged on several occasions (e.g. Matthiessen & Gibbs

[1] Minor comment: the reference "*Buccini 1999"* which is quoted at page 10, has only been produced with regard to the persistence of the molecule, it is not on the endocrine effects.

1998) as one of the most convincing examples of endocrine disruption in invertebrates. Even the mechanism involved has been analysed in detail (increase of testosterone titres in exposed females) although two conflicting biochemical models are discussed currently: aromatase inhibition by TBT (Bettin et al. 1996) or reduced testosterone elimination (Ronis & Mason 1996). Therefore, there is evidence of endocrine activity in vivo for all TBT compounds.(1)

M In contrast to the huge amount of convincing evidence of TBT-mediated endocrine disruption in wildlife and especially invertebrates (e.g. imposex and intersex as virilization phenomena in molluscs) less human relevant data are available. Most of the reported in vivo effects indicate a general reproductive and/or teratogenic endpoint repertoire which may or may not be mediated by endocrine mechanisms. Direct in vivo alterations of hormone titres (as indicated e.g. by Krajinc et al. 1984 for witstar rats) have not been linked to effects and were assessed at high doses which are already in the range for general toxic relevance. We were aware of new but not yet published results of Klingmüller et al. (University Bonn, Germany) which indicate that TBT depresses the aromatase activity in human cell lines and might thus exhibit a comparable androgenic effect as reported for invertebrates. Therefore, all TBT compounds can be considered to have potential to cause endocrine disruption, with evidence for endocrine activity in vivo.(2)

42. METHOXYETYLACRYLATE TINBUTYLTIN, COPOLYMER

As for 41

43. PHENOL, 2- [(TRIBUTYLSTANNYL)OXY]CARBONY

As for 41

44. STANNANE, (BENZOYLOXY)TRIBUTYL-

As for 41

45. STANNANE, [1,2-PHENYLENEBIS(CARBONYLOXY)

As for 41

46. STANNANE, TRIBUTYL

As for 41

47. STANNANE, TRIBUTYL-MONO(NAPHTHENOYLOXY

As for 41

48. STANNANE, TRIBUTYL[(1-OXO-9,12-OCTADECAD

As for 41

49. STANNANE, TRIBUTYL[(1-OXO-9,OCTADECENYL

As for 41

50. STANNANE, TRIBUTYL[[[1,2,3,4,4A,4B,5,6,1

As for 41

51. STANNANE, TRIBUTYLFLUORO

As for 41

52. TRIBUTYL[(20METHYL-1-OXO-2-PROPENYL)OXY]STANNANE

As for 41

53. TRIBUTYLTINCARBOXYLATE

As for 41

54. TRIBUTYLTINNAPHTHALATE

As for 41

55. TRIBUTYLTINPOLYETHOXYLATE

As for 41

56. TRI-N-PROPYLTIN (TPRT)

W: At least in a single in vivo test system (*Nucella lapillus* = dogwhelk), Bryan et al. (1988) have demonstrated that TPrT induces imposex. Therefore, there is evidence of endocrine disruption for TPrT.(1)

M: As no data were available both from the database and our own knowledge, there is no scientific evidence to include TPrT in the list.(3)

57. TRIPHENYLTIN (=TPHT, FENTIN ACETATE)

W: As for 58.

M: Hayes & Laws (1991) report a reduced ovary size, a decrease of mature follicles and corpora lutea numbers in female rats exposed to triphenyltin compounds. These are typical reproductive effects which may or may not be mediated by endocrine mechanisms. Therefore, there is no scientific evidence to include TPhT compounds in the list.(3)

58. FENTIN ACETATE (=TPHT)

W: Although no references were provided in the data base for triphenyltin compounds new findings by Horiguchi et al. (1995, 1997, 1998) and Liu et al. (1997) have indicated clearly that TPhT is capable to induce imposex in the East Asian gastropod *Thais clavigera* although this seems not to be true for the closely related European species *Nucella lapillus.* To the knowledge of our group no further species have been tested so far: Nevertheless, there is evidence of endocrine disruption for TPhT compounds as they exhibit clear ED effects at least in one in vivo test system.(1)

M: As for 57 (3).

59. 3,4-DICHLOROANILINE

W: There is evidence of endocrine disruption, due to findings in fish. Allner (1995) described inhibitory effects at 0.2 mg/l on the synthesis and metabolism of androgens in breeding males of sticklebacks. Although the reported effects are close to the concentration range where subacute and chronic effects might occur, they have been considered as important.

The results of a multigeneration study in the guppy (Schäfers & Nagel, 1991) as well as additional data from the zebrafish demonstrate adverse effects in the FII generation. Whether these adverse effects are based on clear endocrine disrupting endpoints or only of secondary nature could not be decided. However, the results of Allner may be indicative that indeed endocrine disrupting effects are involved (1).

M: Positive in in-vitro assays.(2)[1]

60. RESORCINOL

W: No data (3).

M: Clear evidence of interference with T3 and T4 metabolism in rat and epidemiological studies suggesting a goitrogenic activity in humans.(1)[2]

61. CARBENDAZIM

W: Is considered to be questionably on the list because though there is evidence that this is a reprotoxin there is no available evidence of any specific endocrine disruption (3).

M: thyroid is among main target organs in long-term studies on dogs and rats; it is not clear whether the effect is a primary one or it is secondary to other toxic insults (til72; reu76) (2).

62. ALDRIN

W: Is evidence of endocrine disruption: decreased pituitary hormone production in fish (teleosts). Also impaired reproductive performance. Is metabolised to Dieldrin. So considered strong evidence of ED. In vitro evidence for disruption mechanism: We 032 (sin81), 033 (sin82), Oe O10 (kim95) (2)

M: no data in vitro. No increase of uterine weight but delay of sexual development observed reported in a 1978 study on rats (gel78a) (2).

63. DIELDRIN

W: There is evidence of specific endocrine disruption at realistic doses/concentrations: decreased pituitary hormone production in teleosts (kim95); binding to estrogen receptors in alligators (arn97). There was some negative evidence from in vitro studies. But the positive evidence in vitro was associated with reproductive impairment. So consider strong evidence for ED. In vitro evidence for disruption mechanism: Oe 011 (kim95) (2)

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[1] Inhibition binding androgen receptor (Coo93)

[2] Decreased PBI, ulceration of goitre (BKH: Lin89, Lin86, que51, don53, don50, arn52), thyroid effects (CEFIC: Crisp, et al, 1998, Cooksey et al, 1985, Seffner, et al, 1995)

M: positive for estrogenic effects in vitro (MCF-7, Yeast)(arn96b, sot94, sot95). Slight, non-significant increase of uterus weight and possible antiestrogenic effects, respectively, reported in two rat studies performed in the '70s (wel71, gel78a) (2).

64. ENDOSULFAN

W: Range of evidence for ED: inhibitors of LH induced oocyte maturation in teleosts (hai88, kul84, ras90); damage to pituitary and hypothalamus in teleosts (shu86); stimulated vitellogenin synthesis (cha92)(antiestrogen). Also associated with reproductive impairment. So consider strong evidence for ED. (In vitro evidence for disruptive mechanism: We 034; 035; 037; 038 (hai88, ras90, shu86, kul84) (2).

M: (includes alpha and beta Endosulfan): positive for estrogenic effects in vitro (MCF-7, Yeast)(sot94, sot95, arn96b). Negative in an updated 1996 uterotrophic assay in mice (ash97, she96); induction of accelerated puberty in juvenile rats (sin90)(2).

65. ENDOSULFAN (ALPHA)

W: Should be treated as Endosulfan (2)

M: See Endosulfan (2)

66. ENDOSULFAN (BETA)

W: Should be treated as Endosulfan (2)

M: See Endosulfan (2)

67. ENDRIN

W: Considerable amount of evidence for impairment of reproduction with some pointers to ED mechanism: decreased pituitary and serum gonadotroph hormone in teleosts (sin80a, sin80b). So has potential to be an ED (2).

M: an evident reproductive and developmental toxicant. No in vitro/in vivo hinting to underlying mechanism(s); thus, it is not possible to evaluate whether effects are actually hormone-mediated (2).

68. OXYCHLORDANE

W: No data (3)

M : Reported goitrogenic effects in rats (cap94) (Chlordane may affect thyroid, too). Study not available for evaluation. Considering the evidence for Chlordane, it is prudent to consider that Oxychlordane has potential to cause endocrine disruption (2).

69. PHOTOMIREX

W: No data (3)

M: Reported thyreostatic effects in rats (chu80, sin82a) (Mirex may affect thyroid, too). Study not available for evaluation. Considering the evidence for Mirex, it is prudent to consider that Photomirex has potential to cause endocrine disruption (2).

70. 2,4-D=2,4 DICHLOROPHENOXY ACETIC ACID

W: Most of the data are on non-specific, reproductive impairment. Specific evidence for ER and PR binding in alligator systems is negative (von96). However, there is evidence of sex reversal in alligator eggs at realistic concentrations; this was male to female and categorised as negative evidence (cra97)! And also there is evidence of a skewed sex ratio in meadow voles in favour of males - but this was attributed to reduced survival of females (spe80). So the evidence is weak; but a potential ED cannot be excluded (2).

M: effects mainly on the thyroid but also on other hormonally active tissues (ovaries, adrenals) in subchronic and chronic studies on rodents and dogs (Charles, et al, 1996a, Charles, et al, 1996b, Munro, et al, 1992, Schulze, 1990, Schulze, 1991a, Schulze, 1991b, Serota, 1983a, Serota, 1983b). It is not clear whether the effect is a primary one or it is secondary to other toxic insults (2).[1]

71. PROCHLORAZ

W: No data (3)

M: no studies available for evaluation. Prochloraz belongs to conazole fungicides that are well-recognized "biochemical" endocrine disrupters acting through inhibition of steroid synthesis. In the absence of more detailed data, it is prudent to consider that Prochloraz has potential to cause endocrine disruption (2).[2]

[1] *In vivo evidence*: Thyroid effects (thyroid follicular cell hypertrophy, decreased T3 and T4, and/or increased thyroid weight) were observed in subchronic studies with rodents at dose levels which exceeded the ability of the kidney to clear 2,4-D and which were also toxic to the kidney (see Munro et al., 1992, and CEFIC information on 2,4-D for review and key references). Even if these thyroid effects are secondary to an accumulation of compound beyond the normal capacity of renal clearance they can be primary effects of 2,4-D.
In vitro data: 2,4-D binds competitive with thyroxin to transthyretin in blood and thus may decrease thyroxin in vivo (Van den Berg et al., 1991).
Structural analogy: The structural analogue 2,4-Dichlorphenoxy butyric acid significantly reduces thyroxin in serum of rats (Van den Berg et al., 1991).

[2] The mentioned class of "conazole" fungicides comprises a huge class of chemically very diversified compounds with N-substituted imidazole or triazole groups, and which are used in human medicine and agriculture. Although these classes of fungicides are well known inhibitors of the cytochrome P-450 dependent 14alpa-demethylation of lanosterol in fungi, they express a very different inhibition profile towards cytochrome P-450 systems in fungi, plants or mammals (vanden Bosche, Pest. Science 21, 289-306, 1987, 10 "conazoles" were investigated). Furthermore, investigations of the effects of 14 different "conazoles" or structurally related pesticides on central nervous catecholamines revealed a very different profile of activity (Crofton, K.M., Tox. Letters 84, 155-159, 1996).
Having this in mind, it seems not justified to argue that "conazoles" are "well-recognised biochemical endocrine disrupters" (with the same mode of action and hazard potential), especially in the absence of product-specific data.

72. DICOFOL

W: There were only questionable in vitro data available. The in vivo data on birds could not be verified, due to wrong citations of literature. However, due to publication(s) the group had in mind (MacLellan, K.N.M. et al. (1996): Reproductive and morphological effects of o,p'-dicofol on two generations of captive american kestrels. Arch. Environm. Contam. Toxicol. 30, 364-372), it is obvious that an endocrine potential indeed exists, at least for birds (2).[1]

M: no relevant studies available for evaluation. The documentation provided by CEFIC reports that inhibition of corticosteroid production and ovarian stromal hyperplasia (possibly related to enhanced steroidogenesis) has been observed in experimental studies in vivo at high dose levels. Therefore, it is prudent to consider that Dicofol has the potential to cause endocrine disruption (3).[2]

73. IPRODIONE

W: There were no data in the BKH database. The effects observed in fish and birds were rated as of no values, since they occurred at concentrations where other toxic effects (food consumption, bw change) occurred (3).

M: No studies were available for evaluation. According to the document provided by CEFIC, no significant effects were observed in a two-generation study. However, inhibition of testosterone synthesis was observed in vitro (Benahmed, 1995 en Benahmed, 1996). Potentially endocrine-related effects were observed at high doses levels in long-term studies on rats and dogs (hypertrophy of adrenals, Leydig cell tumours)(Chambers, 1992). It is not clear whether the effects are a primary one or it is secondary to other toxic insults (2).

74. ZIRAM

W: There were no data in the BKH database. However, the available data lead to the assumption that this compound inhibits the DOPA-beta-hydroxylase in vivo and in vitro (CEFIC: Serio, et al, 1984)(2).

M: BKH cites two papers (Mar97, Mai97) reporting effects related to thyroid functions. Ziram inhibited the iodide peroxidase in vitro (Mar97). The second paper reporting effects on the thyroid has not been available during the meeting. However, due to the structural similarities between ziram and thiram, and the fact that in the environment ziram can be metabolised to thiram, ziram should be considered at least as potentially endocrine active (2).

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[1] also in vitro ER and PR binding in alligators (von96).

[2] CEFIC information on Dicofol (see also for key references): " ..dicofol is a reversible inhibitor of adrenal corticosteroid synthesis, leading to inhibition of cortisol release into serum in response to ACTH administration and histopathologic changes in the adrenal at higher doses. First published in the literature nearly forty years ago, this is the primary toxicological finding in dogs, and it is present at higher dose levels in other species."

75. DIURON

W: No data (3).

M: No data from BKH. CEFIC reports that, in contrast to linuron, diuron does not produce Leydig cell tumors (reference not given; ask CEFIC; Coo93?). Nevertheless, diuron is considered to be potentially antiandrogenic because a) of the great similarity in structure of diuron and the antiandrogen linuron and b) the common metabolite, 3,4-dichloroaniline, of diuron and linuron, which was shown to bind to the androgen receptor (Cook et al., 1993) (2).

76. DIAZINON

W: This OP was categorised as having potential to cause endocrine disruption, due to reported effects on the olfactory organ in fish (moo96; Moore & Waring 1996). However, the relevance of this finding could not be verified in the shortness of time (2).

M: BKH and CEFIC: no evidence (3)

77. DIMETHOATE

W: From the available study results (fish, invertebrates and molluscs) there is presently no evidence of an endocrine disrupting potential (3).

M: CEFIC: no evidence. BKH cites one paper (Mai97a, Mai97b) reporting thyroid effects. The paper has not been available. Final categorisation of dimethoate has to be made after consultation of this paper (2).[1]

78. MALATHION

W: Endocrine related effects (as decreased testosterone, estradiol and vitellogenin (!) levels, histological changes of the gonads) indicate a real endocrine disrupting potential. The effects, however, occurred at very high concentrations (2 to 9 mg/l), which are very close to the LC50 values in fish (0.62 to 12.9 mg/l). As the source of literature was again the review article of KIME (1995), the real literature could not be verified (sin89). Therefore the compound was categorised as having potential to cause endocrine disruption (2).

M: CEFIC: no evidence. BKH cites one paper (Akh96) reporting thyroid effects. The paper has not been available. Final categorisation of malathion has to be made after consultation of this paper (2).

79. METHYLPARATHION

W: Endocrine related effects (reduced GSI index, changes in oocyte morphology) indicate a real endocrine disrupting potential (ras 90; cho93). The effects, however, occurred again at concentrations, which are very close to the LC50 values in fish. Furthermore there seems to be several inconsistencies in reported effects for the same species. As the source of literature was again the review article of KIME (1995), the real literature could not be verified. Therefore the compound was categorised as having potential to cause endocrine disruption (2).

M: BKH and CEFIC: no evidence (3)

[1] cited references : mai97a : mice : - no effects on hypophyseal thyroid axis- changes in extrathyroidal conversion of T4 to T3 ; mai97b : cockerel : extrathyroidal conversion of T4 to T3. I suggest for both W and M to be considered as **cat. 2**

80. PARATHION

W: No reliable data to decide on. The only report on fish (degeneration of germinal cells of testis) could not be verified (bil70, was in file), since the data are from a secondary source (review article of KIME, 1995) (3)

M: No data (BKH) resp. no evidence (CEFIC) but Rattner and Ottinger (1986) report reduction in plasma LH in quail after a single oral dose of 5 mg/kg bw not associated with a significant decrease in brain acetylcholine esterase activity nor with signs of intoxication. 10 mg/kg bw, however, produced severe inhibition of acetylcholine esterase activity and signs of intoxication (2).[1]

81. AMITROL

W: Non-specific effects that are not even reproductive impairment. This substance is questionably on the list of Eds (3).

M: Thyroid effects (inhibition of thyroid hormone synthesis). Vast amount of data. For references see: WHO (1994) Environmental Health Criteria 158: Amitrol. WHO, Genf. (wis79, inn69, fei78b, web78, ste79b, may68, gai73, don74, kel59, bec83, joh81, cox78, bag56, str71, ale59a, bab77, fre68, web78, ste79a, ton74, tsu73, hia82, top95)(1).

82. SIMAZINE

W: No data (3)

M: No information about endocrine effects in vivo are provided by BKH or CEFIC. Simazine is, however, structurally very similar to atrazine and the CEFIC information explicitly states "Although the majority of studies were conducted with atrazine, the results are considered to be applicable to simazine as well. This is indicated by essentially comparable toxicological properties in chronic and reproductive toxicity studies as well as a number of in vitro studies." Therefore simazine is considered to be a potential endocrine active compound (2).

83. TRIADIMEFON

W: No data (3)

M: No evidence is reported by CEFIC. BKH lists one paper (Hur98) reporting induction of thyroid tumours. The paper has not been available. Final categorisation of triadimefon has to be made after consultation of this paper (hur98)(2).

84. HEPTACHLOR

W: No data (3)[2]

M: No data from CEFIC. No estrogenic activity in vitro (MCF-7 cells, inactive, Sot92). The papers (Ami95, Akh96, NCI177) possibly providing evidence for endocrine activity listed by BKH have not been available. Final categorisation has to be made after consultation of these papers (2).

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[1] A quail is a bird and should be wildlife data

[2] expression of CYP45 in American lobster after exposure to heptachlor (Snyder, 1998, Arch. Biochem. Biophys. 358(2) : 271-276) ; may be considered as **cat. 2**

85. METHYLBROMIDE

W: No data (3)

M: BKH cites several papers reporting adverse effects on testes but only one (hur88) reporting endocrine effects. Hurt and Working (1988; Hur88) observed a decrease in plasma testosterone and testicular glutathion level during and for a short period after the exposure of rats to 200 ppm methyl bromide for five days (2).

86. NITROFEN

W: No data (3)

M: No data from CEFIC. BKH cites one paper (Gra83a) reporting decrease in T4. The paper has not been available. However, according to the "Handbook of Pesticide Toxicology" (Stevens and Summer, 1991) nitrofen is teratogenic presumably via interference with the thyroid hormone status. Nitrofen has structural similarities to the thyroid hormones and it has been postulated that nitrofen or a metabolite of it may have thyroid hormone activities. Exposure to nitrofen reduced TSH in rats (1).

87. PROPANIL

W: No data (3)

M: BKH cites one paper (Hur98) reporting thyroid effects. The paper has not been available. CEFIC information on propanil does not even mention the thyroid but reports that propanil produced Leydig cell tumors, and, at systemic toxic doses, antiandrogen like effects in male rat reproductive organs and slight increases in serum estradiol and testosterone. This study has not been available. Final categorisation of propanil has to be made after consultation of Hur90 and the CEFIC study (2).

88. 2,4 DICHLOROPHENOL

W: No data(3).

M: ER binding only (job95) (2).

89. 4-CHLORO-2-METHYLPHENOL

W: No data (3)

M: MCF7 +re (Korner, et al, 1996). Fish hepatocyte vitellogenin +re (2)

90. 4-CHLORO-3-METHYLPHENOL

W: No data (3)

M: Positive MCF-7 in CEFIC material (Körner, 1996)(2)

91. 4-TERT-BUTYLPHENOL

W: Two studies on teleosts: on proliferation of trout FHVSA cells and increased vitellogenin synthesis give positive results and signal potential for some ED effects (Sot92; Job93) (2).

M: Fish hepatocyte vitellogenin (job93). Mammalian cell transactivation (ER) (sot95, sot92)(2).

92. 4-TERT-OCTYLPHENOL

W: Two studies on teleosts; on proliferation of trout FHVSA cells (job93, whi94). Signal potential for some ED effects (1).

M: Fish hepatocyte vitellogenin +re. rat uterotrophic assay +re (gra98a, bic95, williams et al, 1996)(1).

93. PHENOL, NONYL-

W: One study indicates increased vitellogenin in fish, but at high dose mg/kg (nim97) - signal some potential for ED effects (assay (Risk Assessment Report Nonylphenol under EC regulation EEC93/93)(1).[1]

M: Rat uterotrophic assay (Risk Assessment Report Nonylphenol under EC regulation EEC93/93; Odum, et al, 1997; Ashby, et al, 1997)(1).

94. DIISODECYL PHTHALATE

W: No data (3).

M: see France + Norway review phthalate. Positive effects thought to be reported (2)

95. DI-"ISONONYL"PHTHALATE

W: No data (3).

M: see France + Norway review phthalate. Positive effects thought to be reported (2)[2]

[1] rainbow trout : vitellogenin synthesis (LOEC : 20.3 µg/l) ; reduced testicular growth (LOEC : 54.3 µg/l) (Jobling *et al* ., 1996, Environ. Toxicol. Chem. 15 : 194-202) ; *Corophium* : effects on male secondary sex characteristics (enlarged 2nd antennae) (50 and 100 µg/l) (Brown *et al.*, 1999, Sci. Total Environ. 233(1-3) : 77-88)

[2] ZR-75 and MCF7 Cell proliferation (Harris, et al, 1997, Env H.Pers 105-802-811)

96. 2,2'-BIS(4-(2,3-EPOXYPROPOXY)PHENYL)PROPANE

W: No data (3).

M: No studies available for evaluation. According to data provided by CEFIC, weak positive response in E-screen assay. Conflicting data (Perez et al., Environmental Health Perspectives 106, 167-173, 1998; Hutson D. H., Environmental Health Perpectives 106, A473, 1998) about the extent of thermal, chemical, and enzymatic degradation of BADGE into Bisphenol A. Assuming a precautionary approach[1], **Category 2** is recommended. (2)

97. O-PHENYLPHENOL

W:There were no data in the BKH database. Categorisation as having potential to cause endocrine disruption is based only on one in vitro study (induction of vitellogenin) (Petit et al, 1997). However, based on the data presented by CEFIC, o-phenylphenol was only by a factor of 100 (!!!) less sensitive that E2. This high affinity has to be verified, since the scientific paper was not available (2).

M: No relevant studies available. According to the information provided by CEFIC, it is positive in E-Screen assay.(2)[2]

98. 2,2',3,3',6,6'-HEXACHLOROBIPHENYL (PCB 136):

M: one positive *in vitro* study that shows proliferation effect in MCF-7 cells (Soto, 1995) (2)

99. 2,3,3',4,4',5, -HEXACHLOROBIPHENYL (PCB 156):

M: *in vitro* data shown a possible antiestrogenic effect (Krishnan, 1993), *in vivo* data is inconclusive (Chu, 1994, 1996) (2)

100. 2,2',4,5'-TETRACHLOROBIPHENYL (PCB 48):

M: one positive *in vitro* study that shows proliferation effect in MCF-7 cells (Soto, 1995) (2)

101. 2,3,4,5,-TETRACHLOROBIPHENYL (PCB 61):

M: one positive *in vitro* study that shows proliferation effect in MCF-7 cells (Soto, 1995) (2)

102. 2,4,4',6-TETRACHLOROBIPHENYL (PCB 75):

M: one positive *in vitro* study that shows proliferation effect in MCF-7 cells (Soto, 1995) (2)

103. 2,2',4,4'-TETRABROMINATED DIPHENYL ETHER = 2,2',4,4'-TETRABDE

M: *In vivo* dose-dependent decreased T4 levels (Darneroud, 1996). (2)

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[1] Minimal effect in MCF7 (CEFIC: Olea 1996, Perez, 1988) stated that BADGE could be conversed to Bisphenol A which could account for the minimal effect. This is contradicted by metabolism and transformation data (2).

[2] estrogenic potency : p-phenylphenol < m-phenylphenol < o-phenylphenol all 3 isomers : **cat. 2**, possibly **cat. 1** for both M and W (review : Sonnenschein & Soto, 1998, J. SteroidBiochem. Molec. Biol. 65(1-6) : 143-150)

104. DECABDE

M: *In vivo* conflicting results in thyroid effects and reproductive toxicant (EHC 162 –1990, BKH). (2)

105. OCTABDE

M: *In vivo* slight to moderate hyperplasia of thyroid and reversible increased in absolute weight; reproductive and developmental toxicant (Great Lakes Chemical Corporation; EHC 162 –1990, BKH) (2)

106. PENTABDE

M: *In vivo* conflicting results on thyroid effects (Great Lakes Chemical Corporation; Fowles, 1994). According, to the environmental risk assessment reports prepared by the UK, it stated that it has been observed that the liver is the principal target organ in rodents, in repeated dose oral studies. In addition, in acute toxicity studies, in rodents, it has been observed an hepatic cytochrome P450 activity at one dose tested and a decreased in levels T4 at all doses studied, however no dose-response relationship was apparent. The effect on T4 levels and on thyroid gland, has been proposed, to be a consequence of induction of hepatic enzymes, which enhance T4 metabolism and excretion, leading to a compensatory increase in TSH output from the pituitary, thus stimulating thyroid growth and metabolism. The clear significance of these effects in humans is not well understood. (2)

107. 1,2,3,7,8- PENTACHLORODIBENZOFURAN:

M: *in vitro* data shown a possible antiestrogenic effect (Krishnan, 1993). (2)

108. 1,2,3,7,9- PENTACHLORODIBENZOFURAN:

M: *in vitro* data shown a possible antiestrogenic effect (Krishnan, 1993; Harris, 1990). (2)

109. 1,2,7,8- TETRACHLORODIBENZOFURAN:

M:*in vitro* data shown a possible antiestrogenic effect (Liu, 1992; Harper, 1994). (2)

110. 1,3,6,8- TETRACHLORODIBENZOFURAN:

M: *in vitro* data shown a possible antiestrogenic effect (Krishnan, 1993; Harris, 1990). (2)

111. 2,3,7,8- TETRACHLORODIBENZOFURAN:

M: In vitro data shown an antiestrogenic activity (MCF-7 cells) (Krishnan, 1993) Also reviews: IARC, 1997; IPCS EHC140, 1993; Crisp, et al, 1998; EPA, 1997; Buccini 1999. (2)

112. 2,3,7,8- TEBDF (TETRABROMODIBENZOFURAN):

M: teratogenic effects has been observed (Birnbaum, 1991). In vitro data shown an estrogenic activity (MCF-7 cells and Yeast) (Nagel, 1997; Routledge, 1996). In vivo data shown inconclusive results. (2)

113. TEBDF (TETRABROMODIBENZOFURAN):

M: One study shown thymic atrophy in rats and decreased in thymus-weight. (The original reference is not on the file). In view of scarce data available it should be prudent to consider and study these compound as a group with the other furans and allocate as (2).

114. CARBON DISULPHIDE

W: No data (3).

M: Studies on rat spermatogenesis show effects that could be related to endocrine disruption. This might be supported also by data on fertility of exposed women. It is prudent to assume **Category 2**. (2)[1]

115. PERCHLOROETHYLENE

W: No data (3).

M: Epidemiological studies demonstrate that there is an increase of reproductive disorders that might be related to Endocrine Disruption. It is suggested that perchoroethylene affects the pituitary funcion in the brain. In the absence of evidence of hormone related mechanisms underlying the reproductive disorders in humans **Category 2** is deemed appropriate. (2)[2]

116. 4-NITROTOLUENE

W: Not sufficient data to decide. It was our view that the data from Jobling (in vitro binding to fish E2 receptor) were not sufficient to suggest a potential to cause endocrine disruption, due to the following reasons. The binding affinity was approx. 10000 less than E2 and the authors could not clarify whether this effect was caused by agonistic, antagonistic or indirect actions (3).

M: No studies available. According to the information provided by CEFIC, it is positive in uterotrophic assay: Positive uterotrophic assay (Smith, ER & Quinn, 1992) (1)[3] [4]

[1] T4 levels decreased (Cav75), male sperm morphology in human (CEFIC reference unknown), reduction testosterone (Tepe & Zenick, 1984), reduction of spermatocyte count and mating behaviour (Zenick, et al, 1984).

[2] Effects on human fertility (Zielhuis et al, 1989a,b; Sallmen, et al, 1995; Rachootin & Olsen, 1983; Taskinen et al, 1989; Eskenazi, et al, 1991 a, b), increased risk of miscarriage believed through endocrine mechanism (agg94; Zielhuis et al, 1989; Ferroni et al, 1992). Effects not always clearly related to PER or study results unreliable.

[3] also atrophy of testes (Ciss 1978, 1980), decrease in reproductive organ weights (Morrissey, et al, 1988), increased proportion of rats in diestrus (NTP92, Dunnick, 1994).

[4] A positive uterotrophic assay at doses (30 and 100 mg/kg bw) lower than those which produced signs of general toxicity (reduced body weight gain) and reproductive toxicity (atrophy/degeneration of testes, reduced number of sperm, disturbed estrus cycling) in subchronic studies with rats is sufficient evidence for category 1.

117. TETRABUTYLTIN (=TTBT)

W: Because in both vertebrates and invertebrates TTBT is debutylated to TBT by the MFO system (e.g. Lee 1985, 1991; Stegeman & Kloepper-Sams 1987; Livingstone et al. 1990; Fent & Stegeman 1991), it is clear that both compounds exhibit the same effects in vivo. Consequently, there is evidence of endocrine disruption for TTBT.(1)

M: Because in both vertebrates and invertebrates TTBT is debutylated to TBT by the MFO system (e.g. Lee 1985, 1991; Stegeman & Kloepper-Sams 1987; Livingstone et al. 1990; Fent & Stegeman 1991), it is clear that both compounds exhibit the same effects in vivo. Consequently, it is considered that TTBT has potential to cause endocrine disruption.(2)

118. OCTACHLOROSTYRENE

W: No data (3)

M: No relevant data (3)

119. PHENOL, ISOOCTYL

W: No data (3)

M: No data (3)

120. BENZOPHENONE

W: No data (3).

M: No data. **Category 3**. (3)

121. DIMETHYLFORMAMIDE

W: The presented data were not conclusive to categorise DMFA as having potential to cause endocrine disruption (3).

M: No data (3)

122. DIBROMOETHANE

W: No data (3)

M: No data from CEFIC. BKH lists several papers reporting effects on testes. Only one paper (Sho79) reports effects on testosterone level and oestrus cycle. These effects, however, were observed at severe toxic (mortality or morbidity) doses (3).

123. EPICHLOROHYDRIN

W: No data (3).

M: The available studies on adverse effects on male fertility do not support underlying endocrine related mechanisms. **Category 3.(**3)

124. PCB 52

M:`2,2',5,5'-Tetrachlorobiphenyl (PCB 52): one positive in vivo study that shows an increased in uterus weight at only one dose tested (Jansen, 1993) and one study with negative results (Nesaretnam, 1997). *In vitro* studies have been shown negative results at different levels: binding to the estrogen response element, activation of other genes and proliferative effect (Nesaretnam, 1997). (3)

125. CHLORDENE

W: No data (3)

M: only one in vitro study available (MCF-7) with negative results (3).

126. TRANS-NONACHLOR

W: No data (3)

M: no relevant studies available for evaluation (3).[1]

127. HEPTACHLOR-EPOXIDE

W: No data (3)

M: No data from CEFIC. Three papers providing no evidence for endocrine activity are cited by BKH (3).

128. PARAQUAT

W: No data (3)

M: CEFIC and BKH provide no evidence for endocrine activity (3).

129. BIS(2-ETHYLEXYL)ADIPATE

W: No data indicating evidence for endocrine activity (3)

M: No data (3)

130. DICYCLOHEXYL PHTHALATE (DCHP)

W: No data (3).

M: No data (3).

131. DIETHYL PHTHALATE (DEP)

W: No data (3).

M: –re NTP multigeneration study to be assessed (Lamb, et al, 1987) (3)

132. DIPHENYL

W: No relevant data.

M: No studies available. According to the information provided by CEFIC, there are not indications to suspect a potential endocrine activity. **Category 3.** (3)

133. PCB 128

M: 2,2',3,3',4,4'-Hexachlorobiphenyl (PCB 128): only one positive in vivo study that shows a decreased in hepatic vitamin A level (Chu, 1996). (3)

134. 2-NAPHTHOL

W*:* There are no relevant data (3).

M*:* Negative results in the only available in vitro study on MCF-7.

135. VINYL ACETATE

W: No data (3).

M: Three chronic toxicity studies on rodents are available: there is no overall evidence for an endocrine disrupting potential.(3)[2]

136. PHENOL

W: There were no conclusive data to categorise phenol as having potential to cause endocrine disruption. The reported effects in fish (increased HSI, decreased GSI at 12 mg/l) (kum88) had its origin from the review article of KIME, 1995 and was not verified.(3)

M: Phenol can induce thyroid gland carcinomas in rodents(CEFIC: NCI 1980; BUA, 1997). However, the underlying mechanism was a topic for lengthy discussion within the Expert Group. It was concluded that there was no evidence for an endocrine-related effect. Therefore, Category 3 was the most appropriate, based on the available evidence. Data produced do not support any prioritization.(3)

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[1] In vitro data indicating a potential to cause endocrine disruption (estrogenic activity) for trans-Nonachlor (as well as cis-Nonachlor) are available: binding to human and alligator estrogen receptors and weak estrogenic activity in transactivation assays with yeast and MCF-7 cells (Klotz et al., 1996; Vonier et al., 1996).

[2] Thyroid cancer (Lij83)

137. FENTHION

W: The data in fish (ovarian atresia at 7 mg/l) were not considered (kli81, Kling 1981 CEFIC). *Justification*: No mortality or other adverse or secondary toxic effects etc. were reported. This seems very critical, since the results of LC50 measurements indicate a range in fish between 1-4 mg/l (3).

M: No data (BKH) resp. no evidence (CEFIC) (3)

138. 1,2 BENZENEDICARBOXYLIC ACID (DIDP)

W: No relevant data (3)

M: No data indicating evidence for endocrine activity (3)

139. ETHYLENE GLYCOL

W: The presented data were not conclusive to categorise ethylene glycol as having potential to cause endocrine disruption (3).

M: No studies available. From the information provided by CEFIC no endocrine effects are evidentiated.(3)

140. ALUMINIUM

W: See Attachment 1 for general criteria for wildlife data on metals and organostannic compounds. As for 142 (3).

M The list contains seven metals and their compounds (Aluminium (140), cadmium (141), copper oxychlor (142), copper sulfate (143), lead (144), mercury (145), methylmercury (146). These metals and their compounds exert serious developmental and reproductive effects which have been known since a long time and are well documented in the scientific literature. However, on the basis of the data provided there is only little evidence that beside of these effects the mentioned metals can also alter or disrupt the endocrine system. It seems more likely that their toxicological profile is dominated by their direct reproductive effects and that an interference with the endocrine system is of secondary nature. Therefore we considered that there is no or not sufficient evidence for endocrine activity for these metals and their compounds (3).

141. CADMIUM

W (Cadmium (141), copper oxychlor (142), copper sulfate (143), lead (144), mercury (145): These metals and their compounds exert serious developmental and reproductive effects which have been known since a long time and are well documented in the scientific literature. However, on the basis of the data provided there is only little evidence that beside of these effects the mentioned metals can also alter or disrupt the endocrine system. It seems more likely that their toxicological profile is dominated by their direct reproductive effects and that an interference with the endocrine system (even if reported like in the case of aluminium (140) and methylmercury (146)) is of secondary nature. Therefore we considered that there is no or not sufficient evidence for endocrine activity for these metals and their compounds (3).[1]

M: As for 140

142. COPPER OXYCHLOR

W: As for 141

M: As for 140

143. COPPER SULFATE

W: As for 141

M: As for 140

144. LEAD

W: As for 141

M: As for 140

145. MERCURY

W: As for 141

M: As for 140

146. METHYLMERCURY

W: As for 141

M: As for 140

[1] *in vitro* effects of $ZnCl_2$, $CdCl_2$ and $HgCl_2$ on cortisol secretion by interrenal steroidogenic cells of rainbow trout (Leblond & hontela, 1999, Toxicol. Appl. Pharm. 157(1) : 16-22) may be **cat. 2** but further research is needed

NOTE ON WILDLIFE EVIDENCE FOR METALS AND ORGANOSTANNIC COMPOUNDS

General criteria for wildlife data

1) Compounds were judged both for their endocrine activity in non-human species and for alterations on animal populations as indicators of endocrine mediated effects on similarly-exposed human populations.
2) Data collected on invertebrate and vertebrate species were considered equally important if the endpoint was considered reliable and indicative of a general endocrine mediated effect.
3) Some endocrine mediated effects on wildlife may have not been considered in the database provided by the Commission, possibly due to uncertainties about the involved chemical(s). Pronounced effects (abnormal sexual behaviour in birds, altered sex ratio in vertebrate offspring, etc.) remain an important issue. Therefore we recommend to enlist any chemical causally linked to these (or any unexpected) wildlife effect for being kept under review.

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