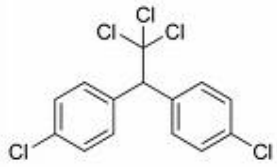
Bijlage 3 van het advies 29-2009 : fiche DDT en zijn metaboliten

DDT AND METABOLITES

CAS no. 50-29-3

Dichloro-diphenyl-tricholoethane (DDT) is an organochlorinated pesticide

Chemical form



Contamination source, origin, use

DDT was commercially introduced as an insecticide in the 1940s. Technical DDT contains 65–80 % *p,p'*-DDT. Other important constituents in the technical grade products are *o,p'*-DDT, *p,p'*-DDE and *p,p*'-DDD. The latter two compounds (along with their ortho, para analogues formed from *o,p'*-DDT) are also the major breakdown products in biological systems (EFSA, 2006). DDT and "related compounds" or sum of DDT refer to *p,p'*-DDT, *o,p'*-DDT, *p,p'*-DDE, *o,p'*-DDE, *p,p*'-DDD and *o,p'*-DDD. The main insecticidal activity can be attributed to *p,p'*-DDT (EFSA, 2006).

DDT is used as an intermediate in the production of the pesticide dicofol and may occur as a major impurity in the final product. The use of DDT as a pesticide has been very restrictive since 1981 and banned since 1986 in the EU. Although being banned in most countries worldwide, DDT is still used for vector control especially in areas with endemic malaria, and extended use was recently recommended by WHO for indoor residual spraying to control malaria (EFSA, 2006).

Because of the lipophilic properties and persistence in the environment, DDT and related compounds are bioaccumulated and biomagnified along the food chain. DDT is included in the Stockholm convention[1] on persistent organic pollutants (POPs) and the United Nations Economic Commission for Europe (UNECE) Convention on long-range transboundary air pollution protocol on POPs (CLRTAP-POP) (EFSA, 2006).

Mode of action (toxicological data: Major biologic effect, active dose)

[1] The objective of this Convention is to protect human health and the environment from persistent organic pollutants. http://www.pops.int/documents/convtext/convtext_en.pdf

Carcinogenicity

DDT is classified by IARC (1991) as possibly carcinogenic to humans (group 2B).

- **Epidemiological studies**

Epidemiological studies in Colombia or in Mexico city have found a moderately high risk of breast cancer in women with higher levels of DDE (cited in Ibarluzea *et al*., 2004).

Endocrine disrupting activity

- **Epidemiological studies**

In a study from Mexico 116 men aged 27 living in a malaria endemic area where DDT was sprayed until year 2000 in a cross-sectional study showed negative effects both on sperm motility parameters and sperm morphology which were positively correlated to plasma levels of *p,p*'-DDE (De Jager *et al.*, 2006).

- ***in vivo studies***

DDT increase uterine weight in rats and mice (Cited in Li and Li, 1998).

o,p' isomer of DDT is oestrogenic at a dose of 1 mg/kg (LOEL in rat), DDE major metabolite of DDT, has androgenic potency of about one thousandth that of dihydrotestosterone (Miyamoto and Klein, 1998).

3-Methylsulfonyl-DDE, which is a persistent but minor DDT metabolite in rats, mice and humans, is a potent adrenal toxicant in mice. This compound can be transported to the fœtus through the placenta and to the offspring via mothers milk. Treatment of mice with a single dose of 3 mg/kg of 3-methylsulfonyl-DDE resulted in covalent binding of the compound to proteins followed by mitochondrial destruction in the adrenal zona fasciculata (Lund *et al*., 1988). The binding and damage probably results from CYP11B activation in adrenal mitochondria (Jonsson *et al.,* 1991; 1995) (cited in EFSA, 2006).

- ***in vitro* studies**

The results of competitive binding assays showed that *o,p'*-DDT, *o,p'*-DDD, *o,p'*-DDE, and *p,p'*-DDT all bind to the human estrogen receptor and *o,p'*-DDT with the strongest affinity. Binding affinities of these compounds were approximately 1000-fold weaker than that of estradiol (EFSA, 2006).
Scippo *et al.* (2004) reported even lower relative binding affinities (compared to 17β-estradiol) for the human estrogen receptor alpha, respectively of 0.003% (o,p'-DDT), 0.002% (o,p'-DDE and p,p'-DDD), 0.001% (p,p'-DDE), 0.0003% (p,p'-DDT) and 0.0006% (o,p'-DDD).
Higher binding affinities were reported for the human progesterone receptor, ranging from 2.5% (p,p'-DDT) to 0.1% (p,p'-DDD) (Scippo *et al*., 2004).

1. MCF-7 proliferation assays
o,p'-DTT, o,p'-DDD, and o,p'-DDE were 8, 15 and 24 million times less potent than 17β-estradiol, in MCF-7 cells, while o'p'-DDT displayed one millionth the activity of 17β-estradiol (Cited in Dodge, 1998).
They stimulate MCF-7 cell growth at 1µM and 10 µM (Cited in Li and Li, 1998).

2. Transcriptional activation assays
In transcriptional activation assays (also called reporter gene assays), o,p'-DDD, p,p'-DDD and o,p'-DDT have been shown to be medium agonists of the estrogen receptor, while o,p'-DDE and p,p'-DDE were slight agonist and p,p'-DDT displayed no agonistic activity (Willemsen *et al.*, 2004).
All DDT metabolites were potent progesterone receptor antagonists, with IC50 concentrations (concentrations needed to inhibit half of the maximum response induced with progesterone) ranging between 1 to 10 µM (Willemsen *et al*., 2004).
The *p,p'*-DDE, hydroxy-DDE and partly *o,p'*-DDT act as anti-androgens and inhibit 5-

dihydrotestosterone-induced transcriptional activation (FAO/WHO, 2001; Hartig *et al.,* 2002; Schrader and Cook, 2000) (cited in EFSA, 2006).
o,p'-DDT binds and activates estrogen receptors stimulating expression of other receptors for progesterone and specific enzymes and the synthesis of uterine DNA (Cited in Preziosi, 1998).

Exposure source

DDT and related compounds are transferred to milk and egg and accumulate in domestic animals and fish (EFSA, 2006).

Level of exposure

Mean, median and 95th percentile intakes for *p,p'*-DDT and *p,p'*-DDE were found to be 2.8, 1.5 and 6.0 and 5.3, 3.8 and 14.7 ng/kg bw per day, respectively in a German study (cited in EFSA, 2006).
Based on occurrence levels in food between 1999 and 2003 and data of the Czech national consumption data base for individuals, a median dietary intake (age 4 - 90 years, both genders) of 29,1 ng/kg bw per day was calculated for total DDT (sum of *p,p*'-DDT, *o,p'*-DDT, *p,p'*-DDE, *o,p'*-DDE, *p,p'*-DDD and *o,p'*-DDD) in the Czech Republic (cited in EFSA, 2006).

Food of animal origin is the major source of human exposure and recent studies performed in some EU Member States indicate a mean dietary intake for adults and children of 5 - 30 ng/kg bw per day. This exposure level is more than two orders of magnitude below the PTDI of 0.01 mg/kg bw (EFSA, 2006).

Worst case exposure in Belgium (through consumption of home produced eggs, CONTEGG study): 648 ng/kg bw/day (Windal *et al.,* 2009).

Theoretical Maximum Daily Ingestion (TMDI) in Belgium: 1290 ng/kg bw (EMRISK & Ribonnet *et al.* (2007)).

TDI

DDT is classified by IARC (1991) as possibly carcinogenic to humans (group 2B). The Joint FAO/WHO Meeting on Pesticide Residues (JMPR) derived a provisional tolerable daily intake (PTDI) for DDT of 0.01 mg/kg bw.

Estrogenic potency

- Relative binding affinity

Relative binding activity of DDT and related compounds is ca 10^3 weaker than œstradiol.

- Uterotrophic activity

o,p-DDT did not affect uterus (wet and blotted) weights at doses of 100 and 500 mg/kg/day in uterotrophic assay using Sprague-Dawley immature female rats (Kim *et al.,* 2005).

% TDI

The level of exposure in Europe range between 0.005 – 0.03 µg/kg bw/day (EFSA, 206), Theoretical Maximum Daily Ingestion (TMDI) in Belgium: 1.290 µg/kg bw.

%TDI ranges between 0.05 – 12.9%.

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