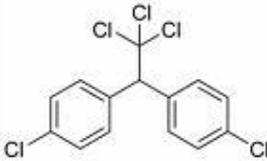


DDT AND METABOLITES
Dichlorodiphenyltrichloroethane (DDT) (CAS no. 50-29-3) is an organochlorinated pesticide
Chemical structure

Contamination source
<p>DDT was commercially introduced as an insecticide in the 1940s. Technical DDT contains 65–80% <i>p,p'</i>-DDT. Other important constituents in the technical grade products are <i>o,p'</i>-DDT, <i>p,p'</i>-DDE and <i>p,p'</i>-DDD. The latter two compounds (along with their ortho, para analogues formed from <i>o,p'</i>-DDT) are also the major breakdown products in biological systems (EFSA, 2006). DDT and “related compounds” or sum of DDT refer to <i>p,p'</i>-DDT, <i>o,p'</i>-DDT, <i>p,p'</i>-DDE, <i>o,p'</i>-DDE, <i>p,p'</i>-DDD and <i>o,p'</i>-DDD. The main insecticidal activity can be attributed to <i>p,p'</i>-DDT (EFSA, 2006).</p> <p>DDT is a broad spectrum insecticide that was popular due to its effectiveness, long time action, relatively low acute mammalian toxicity, and low cost. DDT was used during the Second World War to protect troops and civilians from the spread of malaria, typhus and other vector borne diseases. DDT has been broadly applied in agriculture to control insects on various kinds of crops and for the control of disease vectors. DDT was used in the United States on cotton, peanuts and soybeans. Since the mid-1940s DDT was applied worldwide in large quantities due to its excellent properties to control insect pests on crop and forest lands, around homes and gardens, and for industrial and commercial purposes. DDT helped to almost completely eradicate malaria in Europe. The peak of DDT use was reached around 1960 where approximately 80,000 tons were sprayed annually. DDT is still used as an intermediate in the production of the pesticide dicofol and may occur as a major impurity in the final product. In the EU, the DDT content in dicofol is limited to 0.1%. 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).</p> <p>DDT and especially its break down product DDE are ubiquitous in the environment. 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 convention¹ 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).</p>
Analytical method
Multi-residues methods with high-resolution gas chromatography with electron capture detection (HRGC/ECD) and high resolution gas chromatography/mass spectrometry (HRGC/MS) are used for the analysis of DDT and metabolites.
Toxicity
General toxicological effects The main target organs are the nervous system and the liver. DDT also affects hormonal tissues, reproduction, fetal development and the immune system.
Metabolism The first step in the metabolism of DDT is the formation of DDD and DDE. These metabolites are usually converted to several hydroxylated compounds, and eliminated in a conjugated form in bile and urine. DDT, DDE and to a lesser extend DDD are lipophilic compounds which accumulate in adipose tissue. The half-life for DDT varies from 1 month in rats and dogs to 6 – 14 months in fish

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

and four years in humans. DDE is generally more persistent in organisms than DDT.

Acute toxicity

The main acute effect of DDT is perturbations of ion transport in neuronal membranes leading to potentiation of transmitter release and central nervous system excitation. DDT has relatively low acute toxicity in humans with non-fatal doses up to 285 mg/kg. The oral acute toxicity is comparable in experimental animals, in rats (LD₅₀ 113 - 800 mg/kg/day), in mouse (LD₅₀ 237 - 300 mg/kg/day), guinea pig (LD₅₀ 400 mg/kg/day) and rabbit (LD₅₀ 300 mg/kg/day) (ATSDR, 2002).

Signs of acute toxicity are from the nervous system. Both central and peripheral, are affected to some degree. In animals, DDT can produce hyperexcitability, tremor, ataxia, and finally epileptiform convulsions. Humans have experienced prickling in the tongue and periorally, paraesthesia, nausea, dizziness, confusion, headache, malaise, and restlessness as well as rashes (FAO/WHO, 2001; ATSDR, 2002; Beard, 2006).

Repeated toxicity

At lower doses the liver is the major target organ. The hepatic effects of DDT in rats include increased liver weights, hypertrophy, hyperplasia, induction of microsomal enzymes, including cytochrome P450, cell necrosis, increased activity of serum liver enzymes, and mitogenic effects, which might be related to a regenerative liver response to DDT. The potencies of DDT, DDE, and DDD for induction of CYP2B are of the same order of magnitude. The effects on CYP2B and associated enzymes indicated that males have a lower threshold than females, which induced these enzymes to a greater extent (JMPR, 2001).

No changes in liver function were observed in workers exposed to 0.05 - 0.25 mg/kg bw/day (FAO/WHO, 2001).

Carcinogenicity & genotoxicity

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).

Variable results have been obtained with regard to lung cancer among *p,p'*-DDT production workers (IARC, 1991). In other studies increased risk of lymphatic and haematopoietic, pancreas (particularly with heavy occupational exposure) and liver cancer have been reported, but inconsistencies among studies, confounding by exposure to other pesticides and limitations in study size, exposure assessment and also study design preclude definitive conclusions (IARC, 1991; ATSDR, 2002; Cocco et al., 2005). In a cancer mortality study 4552 male workers exposed to DDT during antimalarial operations in Sardinia, Italy, conducted in 1946 to 1950 were followed from 1955 to 1999 (Cocco et al., 2005). The authors found little evidence for a link between occupational exposure to *p,p'*-DDT and mortality from any of the cancers previously suggested to be associated with DDT exposure. The numbers for some cancers, i.a. pancreatic cancer, were, however, relatively small, which limited the ability to identify smaller risks.

Several investigators have compared serum or tissue levels of DDT and/or DDE among individuals with and without cancer, with inconsistent results (IARC, 1991; ATSDR, 2002). Particularly studies on levels of *p,p'*-DDE and other DDT metabolites in serum or tissues and breast cancer have shown conflicting results. López-Cervantes *et al.* (2004) performed a meta-analysis of 22 studies and found strong evidence to discard the putative relationship between *p,p'*-DDE and breast cancer risk. The lack of a positive association between *p,p'*-DDE body burden levels and breast cancer risk could be explained by the low estrogenicity of *p,p'*-DDE, compared with the metabolites of DDT *p,p'*-DDT and *o,p'*-DDT.

DDT including *p,p'*-DDE and DDD cause tumours mainly in the liver of experimental animals (mice, rats, monkeys) and are mostly negative in genotoxicity studies. In some studies, increased incidences of lung carcinomas and malignant lymphomas were observed. In hamsters, some increase in the incidence of adrenocortical adenomas was observed.

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

In the European Union, DDT was classified as Carc. Cat.3; R40 according to Dir 67/548/EEC and as Carc.2 H351 according to CLP Regulation (EC) No. 1272/2008.

Reproductive toxicity

Neurodevelopmental studies were conducted in the 1-year-old infants from the population of a rural

village of 5000 inhabitants in the vicinity (1 km) of an organochlorine compound factory (Flix, Catalonia, Spain) (Ribas-Fitó et al., 2003). DDT was manufactured during some periods until 1971. Prenatal exposure to *p,p'*-DDE was associated with a delay in mental and psychomotor development at 13 months of age (Ribas-Fitó et al., 2003). Recently this cohort together with a cohort from Menorca, where DDT exposure was higher, was followed up to the age of 4 years. Children, whose DDT concentrations in cord serum were > 0.20 ng/ml, had decreases in the verbal scale and in the memory scale when compared, with children whose concentrations were < 0.05 ng/ml. Stronger associations were seen among girls. No significant associations were seen for DDE (Ribas-Fitó et al., 2006a).

In a prospective cohort of 1712 children born between 1959 and 1996 decreased height in children up to seven years of age was associated to prenatal exposure to *p,p'*-DDE, among those showing the highest prenatal concentrations ($\geq 60 \mu\text{g/l}$) (Ribas-Fitó et al., 2006b).

Few data are available on reproductive effects in humans, and these show no correlation between exposure to DDT and stillbirth, miscarriage, or premature rupture of foetal membranes and neurodevelopmental effects (FAO/WHO, 2001).

The effects of the DDT complex on reproduction and development in humans and experimental systems have been reviewed (Coulston, 1985; Agency of Toxic Substances and Disease Registry, 1994; Environmental Protection Agency, 1998). The effects on reproduction in animals include decreased fertility and abortions, and stillbirths. In multigeneration studies in rodents, DDT decreased fertility and gonadal weights, increased the length of the estrous cycle, decreased the number of implantations, increased the rate of embryo mortality, decreased litter size, and increased the length of gestation. In a three-generation study in rats, the mortality rate of offspring increased at all doses, the lowest of which corresponded to about 0.2 mg/kg bw/day (Laug et al., 1950). Three other studies in rats and mice showed no effects on reproduction at higher doses (1–6.5 mg/kg bw/day (Agency of Toxic Substances and Disease Registry, 1994).

The effects on development observed pre- or postnatally after DDT treatment that may be related to estrogenicity include embryoletality, decreased fetal growth, and prematurity in rabbits and dogs fed diets providing a dose of 5 mg/kg bw per day, and decreased ovarian weights, cystic ovaries, loss of corpora lutea, infertility, premature puberty, altered onset of vaginal opening, tail anomalies, and increased pup mortality rates in rodents. The lowest relevant NOAEL for developmental effects was reported to be 1 mg/kg bw/day in rats (Agency of Toxic Substances and Disease Registry, 1994; Environmental Protection Agency, 1998).

Endocrine disrupting activity

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).

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 foetus 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).

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 17 β -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).

Establishment of Health Based Reference Values

The Joint FAO/WHO Meeting on Pesticide Residues (FAO/WHO, 2001) derived a provisional tolerable daily intake (PTDI) for DDT of 0.01 mg/kg bw on the basis of the NOAEL of 1 mg/kg bw/day for developmental toxicity in rats and a safety factor of 100.

Occurrence in food

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

Mean concentration of DDT measured for commercially Atlantic salmon fillets on the Norwegian market in 2007 is 19 ng/g wet weight (ww) (range (13–28 ng/g ww, n =12) (Berntssen *et al.*, 2011). Mean concentration of DDT (sum) measured in ponds in Lorraine Region (France) in 2008 is 0.71 (0.15–2.20) ng/g ww in carp (n=25) and 0.61 (0.11–0.85) ng/g ww in Perch (Thomas *et al.*, 2012).

The sum of DDT metabolites measured in smoked fish products available in Szczecin, Poland ranged from 1.48 (smoked mackerel) to 35.53 ng/g wet weight (smoked sprat) (Witczak & Tomza-Marciniak, 2010). The range of p,p'-DDE concentrations determined by Macgregor *et al.* (2010) for eels from Scottish rivers (<1- 227 μ g/kg,) was greater than that observed in a Flemish study (Covaci *et al.*, 2005) which examined eels from three ponds and one canal and reported concentrations from 6 to 24 μ g/kg. Concentration of DDT (sum) measured by Szlinder-Richert *et al.* (2010) in eels in Poland ranged between 9.8 and 273.9 ng/g ww. The residue levels of DDT and its metabolites occurred in the following order DDE > DDD > DDT in all the samples examined.

DDT or its metabolites were detected in 95% of free range eggs collected in Belgium in the spring 2007. The median concentration of DDT in eggs was 63.4 ng/g fat, and the mean was 457.2 ng/g fat, close to the norm of 500 ng/g fat (17% of the samples are above the norm of 500 ng/g fat). The level found in one sample is extremely high, with a concentration of 12,170 ng/g fat (Windal *et al.*, 2010). DDT is usually not detected anymore or only at trace level in commercial eggs, as observed in Spain (Fontcuberta *et al.*, 2008), in Belgium (17.30 ng/g fat) (Van Overmeire *et al.*, 2006) or in Sweden (6.6 ng/g fat) (Darnerud *et al.*, 2006).

DDT and its metabolites in concentration of less than 20 ng/g fat were measured in 93.5% of the samples of exported meat (chicken and pork) in 1999 by Schepens *et al.* (2001). In some samples, concentrations of DDTs exceeded the maximum limit set by the European Union Council Directive EEC 93/57 of 1,000 ng/g fat and were as high as 8,535 ng DDTs/g fat.

Martinez *et al.* (1997) in Spain detected pp-DDT in pasteurized milk at the levels of 0.0007 mg/kg milk fat. Heat treatment such as pasteurization showed the efficient role on the degradation of OC pesticide residues. Generally, the consumption of pasteurized milk may be safer than raw milk.

Content of sum DDT in food samples taken by Fromberg *et al.* (2011) from 1998 to 2003 in Denmark are presented in table 1

Table 1: Content of sum DDT in food samples taken by Fromberg *et al.* (2011) from 1998 to 2003 in Denmark

Foodstuff	Mean sum DDT (μ g/kg fish and egg and μ g/kg fat for other foods).
Chicken fat	1.7
Turkey fat	2.1
Duck fat	1.8
Other poultry fat	15.3
Beef fat	3.2
Pork fat	2.8
Lamb sheep fat	5.8

Milk, Danish	3.4
Milk, foreign	2.9
Cheese, Danish	3.4
Cheese, foreign	3.6
Butter, Danish	1.5
Butter, foreign	10.9
Butter fat, mixed	0.9
Eggs	2.0
Cod, raw	0.6
Eel, farmed, raw	61
Garfish, raw	5.0
Greenland halibut, raw	14.7
Herring, raw	7.9
Herring, pickled	11.4
Herring, smoked	6.9
Lumpsucker, raw	14.5
Mackerel, raw	3.6
Mackerel, smoked	5.0
Mackerel, tinned in tomato	1.7
Plaice, raw	0.0
Rainbow trout, farmed, raw	5.1
Salmon, raw	15.3
Swordfish, raw	9.3
Trout, marine farmed, raw	12.5
Fish oil	43
Cod liver oil	196

p,p'-DDE was detected in all samples of Belgian human milk collected in 2006 during the fourth World Health Organization Human biomonitoring campaigns (Colles et al., 2008). Mean concentration was 121,6 +/-93.3 ng/g fat. *p,p'*-DDT was detected just above the detection limit. Mean concentration was 1.5 +/-7.7 ng/g fat.

Dietary exposure assessment

Data from total diet studies, as well as from human milk monitoring programmes performed in various EU Member States, show a considerable decline of up to 90% in human exposure to DDT and related compounds over the past three decades (EFSA, 2006).

Fromberg et al. (2011) have estimated the dietary intake of DDT (sum) for Danish adults to 3.7 ng/kg bw/day (mean), 6.5 ng/kg bw/day (P90) and 8.4 ng/kg bw/day (P95). Calculated estimation for children was 6.7 ng/kg bw/day (mean), 12.5 ng/kg bw/day (P90) and 15.7 ng/kg bw/day (P95).

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/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/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/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) was estimated to 648 ng/kg bw/day (Windal et al., 2009).

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

Risk characterization

The Joint FAO/WHO Meeting on Pesticide Residues (JMPR) derived a provisional tolerable daily

intake (PTDI) for DDT of 0.01 mg/kg bw (FAO/WHO, 2001).

The level of exposure in Europe range between 0.005 – 0.03 µg/kg bw/day (EFSA, 2006). The theoretical Maximum Daily Ingestion (TMDI) in Belgium is about 1.290 µg/kg bw. The percentage of the PTDI ranges between 0.037 and 12.9% (table 2).

Table 2: DDT dietary exposure for adult and children and percentage of the PTDI

Population	Dietary exposure (ng/kg bw/day)	%PTDI (= 1000 ng/kg bw/day) (WHO, 2000)
Danish adults – mean (Fromberg et al., 2011)	3.7	0.037
Danish adults - P90 (Fromberg et al., 2011)	6.5	0.065
Danish adults - P95 (Fromberg et al., 2011)	8.4	0.084
Danish children – mean (Fromberg et al., 2011)	6.7	0.067
Danish children - P90 (Fromberg et al., 2011)	12.5	0.125
Danish children - P95 (Fromberg et al., 2011)	15.7	0.157
Population Czech Republic (EFSA, 2006)	29.1	0.291
Adults - Children EU membres states (EFSA, 2006)	5 - 30	0.05 - 0.3
Belgian, eggs consumer(worst case)	648	6.48
theoretical Maximum Daily Ingestion (EMRISK PROJECT & Ribonnet et al. (2007)).	1290	12.90

Nougadère et al. (2011) have calculated an estimated daily intake (EDI) (mean % of TDI) between 0,4 and 2.1% for the French children and between 0.2 and 1.3% for the French adult.

Legislation

Regulation (EC) No 396/2005 of the European Parliament and of the Council of 23 February 2005 on maximum residue levels of pesticides in or on food and feed of plant and animal origin and amending Council Directive 91/414/EEC which will repeal the four Council Directives

Recommendations

The CONTAM Panel of EFSA made the following recommendations for DDT in feed (EFSA, 2006):

- Besides the parent compound, *p,p'*-DDT, the analyses of feed samples should also include determination of *o,p'*-DDT, *p,p'*-DDE, *o,p'*-DDE and *p,p'*-DDD because these compounds represent impurities in the technical mixtures, are major metabolites and are biological active.
- In the clean-up of samples, treatment with acids must be avoided in order to prevent the formation of DDE from dicofol, an authorised pesticide that is widely used and thus may be present in feed commodities.
- Proficiency tests performed on biological samples revealed large discrepancies in the performance of laboratories, indicating scope for improvement of the analytical methods.
- Toxicity data on some target animal species are lacking, however, given the relatively low levels identified in feed there does not seem to be an urgent need for additional toxicity studies.
- The Members States are requested by the Commission to report the results of their

monitoring programmes on undesirable substances in animal feed as compliant or non-compliant only. The availability of detailed occurrence data concerning compounds and corresponding concentrations rather than condensed summary reports would be one prerequisite for an exposure assessment and identification of areas with an unusual high level of contamination. A European reporting system that facilitates these tasks should be set up.

- Given the large variation in the levels of DDT and related compounds in butter samples, it seems appropriate to collect more data from the regions where comparatively high levels have been reported.
- Special attention should be paid to the control of feed materials coming from areas of the world where DDT is still in use or has been used recently.

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