Due to uncontrolled use for several decades, dichlorodiphenyltrichloroethane (DDT), probably the best known and most useful insecticide in the world, has damaged wildlife and might have negative effects on human health. This review gives a brief history of the use of DDT in various countries and presents the results of epidemiologic and experimental studies of carcinogenesis. Even though its use has been prohibited in most countries for ecologic considerations, mainly because of its negative impact on wildlife, it is still used in some developing countries for essential public health purposes, and it is still produced for export in at least three countries. Due to its stability and its capacity to accumulate in adipose tissue, it is found in human tissues, and there is now not a single living organism on the planet that does not contain DDT. The possible contribution of DDT to increasing the risks for cancers at various sites and its possible role as an endocrine disruptor deserve further investigation. Although there is convincing experimental evidence for the carcinogenicity of DDT and of its main metabolites DDE and DDD, epidemiologic studies have provided contrasting or inconclusive, although prevalently negative, results. The presence and persistence of DDT and its metabolites worldwide are still problems of great relevance to public health. Efficient pesticides that do not have the negative properties of DDT, together with the development of alternative methods to fight malaria, should be sought with the goal of completely banning DDT. Key words: carcinogenesis, DDT, estrogenic effects, wildlife.

**Environmental Pollution**

Like most organochlorine insecticides, DDT is not very acutely toxic, an advantage that has favored its widespread use. It is slowly biodegraded, persists for a long time in the environment, and accumulates in the food chain and in the tissues of living organisms. DDT is stored in all tissues, with the highest concentration occurring in fat. It has been calculated that it would take between 10 and 20 years for DDT to disappear from an individual if exposure would totally cease, but that DDE would possibly persist throughout the life span (4). The half-life of plasma DDE has been estimated to be approximately 10 years (5).

We give here a brief history of the use of DDT, examples of its persistence in the environment, its effects on wildlife, the results of epidemiologic studies, its estrogenic effects, and the results of studies that demonstrate its ability to induce tumors in laboratory rodents. Our emphasis is on the possible carcinogenicity of DDT in humans.

**Production and Use**

DDT was first synthesized in 1874, but its insecticidal properties were not discovered until 1939 (4), and large-scale industrial production started in 1943. The low price of DDT, which fell from $1 U.S. per pound in 1945 to about $0.25 per pound in the mid-1950s (6), contributed to its worldwide use. It is of interest that the control of malaria and typhus during and immediately after World War II was achieved with relatively small quantities of DDT, while much more DDT was used after 1945 for the control of agricultural and forest pests. In the early 1960s, about 400,000 tons of DDT were used annually worldwide (70–80% of which was used for agriculture) (4,7).

All soils have a strong absorptive capacity for DDT that is related to their organic matter content. DDT is toxic to freshwater and marine microorganisms, fishes, amphibians, and birds. On the basis of ecologic considerations, Sweden was the first country to ban the use of DDT beginning in January 1970 (8,9). In the former Union of Soviet Socialist Republics (U.S.S.R.) in 1970, DDT and DDT-based products were prohibited for use as pesticides by the U.S.S.R. Ministry of Health because of their persistence, bioaccumulation, and carcinogenicity (10). In the U.S.S.R., in 1981, the production and use of DDT in agriculture were banned (1/), but its use for public health purposes (destruction of insects such as mosquitoes, malarial plasmodia, fleas, lice, ticks) was still permitted. In March 1989, DDT was also banned for medical-disinfecting purposes. Its use, in limited volumes, was permitted for medical purposes after epidemiologic alerts and only with the permission of the state administration for sanitary matters.

In other countries, most uses of DDT were banned in 1972 or shortly thereafter because of its negative impact on wildlife (12), not because of the evidence for carcinogenicity in long-term tests in rodents. Epidemiologic studies that showed no significant long-term adverse effects were held to be more relevant than the experimental evidence of dose-related induction of liver tumors in rodents, although studies were carried out on a limited number of exposed people and had a relatively short follow-up (7,8,13).

After the prohibition of many of the uses of DDT as an insecticide in the United States in 1973, its production and use decreased rapidly in most industrialized countries. In 1985, however, about 300 tons of DDT were exported from the United States (8), although no data are available on current production. In 1990 DDT was produced by one company each in Italy, India, and Indonesia with a total worldwide production estimated at about 30 million pounds (8,14).
occurrence of DDT, mainly as its metabolite DDE, in the eggs of fish-eating birds, such as falcons, causing a considerable thinning of the eggshell. The consequent difficulties in hatching resulted in a severe population decline. In parallel, high levels of DDT in lakes were a cause of reproduction failure in certain fishes (4,9,12). In spite of banning its use in many countries, DDT and its metabolites are still found all over the world.

In the United States, storage of total DDT in body fat increased from 5 ppm in 1950 to 15.6 ppm in 1956, and decreased thereafter to 3 ppm in 1980. In Italy the concentration of DDT in body fat was 4.5 ppm in 1965 and 16.7 ppm in 1970, and decreased to 8.9 ppm in 1984. In 1984 in Central America, the total DDT in body fat was 59.3 ppm (8). Although the concentrations of DDT in humans show a decreasing trend, those of DDE, which is ingested with food, in particular fish, remain constant or are decreasing only slightly. Although it was reported recently that DDE may be dechlorinated microbially to DDMU [1-chloro-2,2-bis(4-chlorophenyl)ethane] (15), its persistence in marine sediments remains a reason for concern.

In developing countries there is still a particularly high exposure to residues of insecticides, mainly DDT and hexachlorocyclohexane, which are present in food. The current intake of organochlorine insecticides in developing countries in Asia are up to 100 times greater than those in more developed countries, and the estimated intake of DDT by children is reported to be 100 times greater than the admissible daily intake (ADI) established by the Food and Agriculture Organization (FAO)/WHO in 1985 at 0.02 mg/kg (16,17). The body burden of several organochlorine insecticides, most notably p,p’-DDE [1,1-dichloro-2,2-bis(p-chlorophenyl)ethylene], is also particularly high among Inuits living in Greenland, who consume large quantities of fat from sea mammals (18). In this same population, prenatal exposure to DDT and other organochlorine insecticides has been found to affect the immune status of the children and increase their susceptibility to infections (19).

In two large cities in the Ukraine, Kiev and Poltava, 100% of the pregnant women investigated who had no somatic disease nor occupational contact with organochlorine insecticide had DDT and its metabolites in their blood at concentrations of 0.28–76 µg/L (Kiev: 0.86–76 µg/L; Poltava: 0.28–45 µg/L) (20). The high values found in Kiev may be at least partly attributable to the presence of a factory producing DDT. Likewise, 100% of women who breast-fed their babies had organochlorine insecticides in their milk. The main milk contaminants were DDT and its metabolites, but hexachlorocyclohexane was also found, and hexachlorobenzene was present in 45% of cases. In more than 90% of cases, the concentration of DDT and its derivatives was 5.8 µg/L. An important index of exposure is the content of lipophilic agents in breast milk. DDT was found at concentrations of 190–1,400 ng/g of milk fat, with p,p’-DDE representing 38–95% of the total content of DDT and its derivatives. As the daily consumption of breast milk is about 130 ml/kg of baby weight, the daily consumption of DDT (and its derivatives) from exclusive breast-feeding is 0.75–5.6 µg/kg of body weight with a maximum of 52 µg/kg of body weight. These concentrations greatly exceed the acceptable daily doses established for the U.S.S.R. (0.0025 µg/kg of body weight per day), which is still valid in the Ukraine (21). In another study, samples of breast milk from 197 women in two Ukrainian cities (Kiev and Dneprodzerzhinsk) were analyzed for organochlorine compounds. The median DDE concentration was 2,500 ng/g of milk fat, which is higher than that in most, but not all, other reports from Europe (22).

The levels of DDT in women’s milk have decreased in most countries around the world in the last decades, with considerable differences between rural and urban districts within the same country. They were between 5,000 and 10,000 µg/kg in milk fat in 1951, and around 1,000 µg/kg in the late 1990s (23). A survey carried out in the United States in 1986 showed that all samples of human milk analyzed contained DDE with levels as high as 25.4 ppm and median value of 2.4 ppm (24). In a small proportion of breast-fed babies in Mexico City, the daily intakes of DDT still exceeded the level recommended by the World Health Organization, and the estimated daily intakes of DDT by infants in a region of Thailand was up to 20 times higher than the recommended ADI (25,26).

Epidemiologic Evidence of Carcinogenicity

Reports on the long-term adverse effects of occupational exposure to DDT raised the suspicion of possible carcinogenic effects in humans. Many epidemiologic studies were published up to 1991 in which the authors reported either positive or negative associations between exposure to DDT and the development of tumors in humans. However, a working group convened by the International Agency for Research on Cancer qualified these studies as providing inadequate evidence for carcinogenicity in humans (8). Since then, the results of new epidemiologic investigations have become available. An increased risk for pancreatic cancer after self-reported exposure to DDT (27,28) and significant excess incidences of liver cancer and multiple myeloma were reported after occupational exposure to DDT (29,30). The association with an increased risk for pancreatic cancer was not confirmed in a subsequent study, but the conditions of exposure were not comparable (31).

Subsequent investigations on the long-term adverse effects of DDE confirmed the association between the concentrations of this metabolite in adipose tissue and an increased risk for mortality from liver cancer but did not confirm an increased mortality rate from cancer of the pancreas or multiple myeloma (32), nor from non-Hodgkin lymphomas (33).

DDT as an Endocrine Disruptor

A number of reports have indicated that organochlorine insecticides, including DDT and its metabolites, may act as endocrine disruptors (13,34). There is evidence that DDE is an androgen receptor antagonist, and the hypothesis has been advanced that DDE may interact in an additive or multiplicative way with other endocrine-disruptive environmental pollutants (35–39). Indirect evidence of the hormonal activity of DDE comes from the observed association between levels of DDE in maternal fat and earlier weaning (40,41). Because a considerable proportion of all cancers in women are hormonally mediated, the possibility that xenoestrogenic substances, such as organochlorine insecticides, contribute to an increased cancer risk is particularly alarming (42). Early reports showed higher concentrations of DDT and DDE in fat tissue of individuals with mammary cancer (43), and an association between DDE blood levels and mammary cancer was reported in some epidemiologic studies (44–46). Subsequent studies provided conflicting results, with most of them not confirming the association (34,47–59). The analysis of five large studies carried out in the United States, which had the limitation of not considering occupational exposures nor exposures in utero or during adolescence, did not provide evidence to support a role of DDE or polychlorinated biphenyls in increasing the risk for breast cancer (60). The hypothesis that minute doses of organochlorine insecticides act synergistically to activate human estrogen receptors could not be confirmed experimentally (39). However, the available data do not allow determination of whether the estrogenic effects of DDT and metabolites are dose related nor determination of the actual shape of the dose–response relationship.

A number of experimental studies indicate that DDT has estrogenic effects in rats it facilitated implantation and maintained pregnancy...
(61), exerted a uterotropc effect (62), inhibited the binding in vitro of [3H]-estradiol to the cytosolic estrogen receptor in utero (63), and accelerated mammary gland carcinogenesis induced by 2-acetylamidophenanthrene (64). In mice, the uterotrophic effect of DDT increased the weight of the uterus and the development of pseudoestrus (65). A permanent, functional male-to-female sex reversal following a single exposure of eggs to o,p'-DDT was observed in medaka fish (66).

**Experimental Evidence of Carcinogenicity**

The carcinogenicity of DDT and its metabolites has been studied in a number of laboratories in animals including nonhuman primates. Lifetime treatment of mice with DDT induced liver tumors in a dose-related manner, and the tumors included overtly malignant metastasizing hepatoblastomas (67). The first liver tumor in male mice was seen at 50 weeks after exposure to 250 ppm of DDT in the diet, and at 65 weeks after exposure to 50, 10, or 2 ppm. In female mice the first liver tumors were seen at 60 weeks of age at the dose of 250 ppm of DDT in the diet, and after 100 weeks of age at the 50-ppm dose (68).

DDT also induced tumors in mice after treatment for a limited period of time. When treatment was continued for 15 or 30 weeks and mice were killed at various intervals, similar proportions of mice bearing liver tumors were observed 65, 95, and 130 weeks after the beginning of the experiment. More mice had large liver tumors at 95 and 120 weeks than at 65 weeks. These results indicate that although no new tumors were induced after cessation of exposure to DDT, the persistence of DDT-induced hepatomas did not depend on the continuous administration of DDT because the tumors that have already appeared continue to grow (68,69). After treatment of mice with DDT for six generations at four doses, no increase in the incidence of liver tumors was observed from generation to generation, as might have been expected in the presence of a genotoxic carcinogen (67).

DDT also increased incidences of lung tumors and lymphomas in mice, incidences of liver tumors in rats, and incidences of adrenal adenomas in hamsters (8). Long-term oral administration of DDT to nonhuman primates was reported to result in hepatic toxicity, and a few malignant and benign tumors at various sites were also found at an incidence that was of borderline statistical significance (70). In the absence of tumors in the controls, the few tumors observed may be considered to be biologically significant, thus confirming the carcinogenic effect observed in rodents (71).

The main metabolites of DDT, o,p'-DDE and p,p'-DDD [1,1-dichloro-2,2-bis(p,p'-chlorophenylethane), are both carcinogenic. Exposure to DDE resulted in a high incidence of liver tumors in both male and female mice (about 100% of treated mice versus 1% in controls) with the first tumors seen at 50 weeks of age. Exposure to DDD moderately increased the incidence of liver tumors in males only, with the first tumors seen at 80 weeks of age, and markedly increased the incidence of lung tumors in animals of each sex. The combined exposure to DDE and DDD resulted in a marked increase and early appearance of liver tumors in both sexes with the first tumors seen at 70 weeks of age (68,72).

DDT and other organochlorine pesticides are cytochrome P450 inducers, and reactive products are formed during their metabolism including free radicals, epoxides, and acid chloride, which can bind covalently to cell macromolecules. Tests for genotoxicity gave controversial results. DDT did not induce DNA damage in bacteria or cultured rodent and human cells. It induced chromosomal aberrations in mouse but not in rat bone-marrow cells in vivo. DDT, tetra-chlordiphenylethane (p,p'-TDE) and p,p'-DDE inhibited gap-junctional intercellular communication (4,8).

By inducing cytochrome P450, DDT can detoxify some chemical agents and alter the susceptibility of the organism to their toxic effects. Thus, DDT prevented the lethal and adrenolytic effects of 7,12-dimethylbenz[a]anthracene in rats (73).

**Conclusion**

The available epidemiologic and experimental data indicate that the presence and persistence of DDT and its metabolites worldwide are still problems of great relevance to public health. The possible contribution of DDT and its metabolites to the risks for cancers at various sites and their possible role as endocrine disruptors, by themselves and in combination with other organochlorine insecticides and xenoestrogenic substances, deserve further investigation.

It has been recently debated at the United Nations Environment Program whether DDT should have been totally banned together with 11 other persistent organic pollutants. The total ban of DDT was sharply criticized; in South Africa, a temporary total ban on the use of DDT for indoor spraying resulted in a sudden increase in malaria (74). Eleven countries in Africa, 7 in Asia, and 5 in Latin America still use DDT for vector disease control. There is a general consensus that limited and strictly controlled use of DDT should be allowed for public health purposes, in particular where other effective, safe, and affordable alternatives are not available, and the benefits are clearly far superior to possible risks (75). The DDT question has stimulated heated debates from several scientists, with emphasis on the tragic consequences that a total ban of DDT would have in several developing countries (76). It would be unjustified to minimize the actual and potential risks for health and the environment caused by DDT or to downgrade confirmed evidence of adverse effects in humans (77), but it is clear that a total ban of DDT could only be achieved at a cost that poor countries, which still badly need this insecticide for public health purposes, cannot afford without substantial and long-term financial help from the richer countries.

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