**The “Dirty Dozen” of Pesticides. Chemical and Toxicological Issues**

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**The “Dirty Dozen” of Pesticides. Chemical and Toxicological Issues.**

The Stockholm Convention on Persistent Organic Pollutants (POPS) signed in 2001 banned or greatly restricted twelve chlorinated organic compounds or classes due to their toxicity and ability to accumulate in the environment and to magnify through the global trophic network. Among them are eleven pesticides namely Aldrin, Chlordane, DDT, Dieldrin, Endrin, Heptachlor, Hexachloro-benzene, Chlordecone, Hexachlorocyclohexane, Mirex, Toxaphene. These pesticides played a historical role in mitigating the health impact of parasite-borne human pathogens such as malaria parasites and in protecting food crops to allow better feeding of an increasingly raising population especially in sub-tropical and tropical areas. These compounds were named, in journalistic jargon, as **“The Dirty Dozen”** and were listed in Annex A, B and C (Annex A- Intentionally produced chemicals that need to be eliminated**;** Annex B-Intentionally produced chemicals with restrictions**,** Annex C - Unintentionally produced chemicals).

Parties to the Stockholm convention agreed to periodically reviewing the list to add more compounds or classes, if they meet certain criteria for persistence and trans-boundary threat. The second set of nine new chemicals to be added to the Convention was agreed at a conference in Geneva on 8 May 2009. Of these, four are pesticides, three isomers of Hexachlorocyclohexane (among which is Lindane) and Chlordecone (Kepone). Others are brominated flame retardants and perfluorinated organic acids, both without any connection with pesticides. In May 2011 technical Endosulfan and its related isomers were added in the list.

Concern for human and environmental health is mainly due to long-term effects of some substances, in particular through endocrine disruption, interference with reproduction, carcinogenicity, although the actual size of effects of real-life exposure is still an active and debated research topic. Risk assessment and risk-benefit analysis of some key pesticides such as DDT still need a thorough understanding of the toxicity mechanisms and of its relevance to humans in the different life-stages.

As a consequence of the Stockholm ban, large stockpiles of unusable pesticides accumulate in some countries and thus present considerable threat to the environment and to human health, also due to unavoidable degradation of the active formulated substances into poorly tractable materials.

**ALDRIN** (Annex A) has been used in industry, agriculture and in public health control. Aldrin was widely used to treat seed and soil until it was banned in most countries in the 1970s. It was applied to soils to kill termites, grasshoppers, corn rootworm and other insect pests. About 270 000 tons of Aldrin and related pesticides were produced between 1946 and 1976.

CAS: 309-00-2

Aldrin is toxic to humans; the lethal dose of Aldrin for an adult man has been estimated to be about 5 g, equivalent to 83 mg/kg b.wt. Signs and symptoms of Aldrin intoxication may include headache, dizziness, nausea, general malaise, and vomiting, followed by muscle twitching, myoclonic jerks, and convulsions. Although this may be somewhat relevant in accidental or voluntary acute intoxication, it has little, if any, relevance with regard to environmental exposure.

**CHLORDANE** (Annex A- Intentionally produced chemicals that need to be eliminated). Production by registered parties and used as a local ectoparasiticide, insecticide, termiticide (including in buildings, dams and roads) and as an additive in plywood adhesives. Chlordane is a more highly chlorinated analogue of Heptachlor, also prepared from Hexachlorocyclopentadiene and Cyclopentadiene, followed by chlorination by insertion of three chlorine atoms, and the yield is a technical mixture of two isomers, α and β, the β isomer being more bioactive. The technical mixture contains Chlordane, Heptachlor, Nonachlor and related compounds. Chlordane was first synthesized in 1944 and entered the United States market from 1948 to 1988 both as a dust and an emulsified solution.

 CAS: 57-74-9

Multiple toxicological studies published in the last five years that measured metabolites of Chlordane in the human blood reported that higher concentrations of Oxychlordane increase the risk of cognitive decline,liver damage (liver enzymes),peripheral arterial disease,prostate cancer,type 2 diabetes,and obesity (waist circumference). In other large epidemiological surveys, higher levels of Oxychlordane in both blood and adipose (fatty tissues, or related to fat) increased the risk of non-Hodgkin lymphoma, and likewise higher concentrations in brain tissues increase the risk of Parkinson diseases.

**DDT** (Annex B - Intentionally produced chemicals with restrictions)

**D**ichloro**d**iphenyl**t**richloroethane (DDT) was first synthesized in 1874. Its insecticidal properties were discovered in 1939 in **Paul Müller’s** laboratory at Ciba in Basel, Switzerland. Müller was awarded the Nobel Prize in Physiology and Medicine in 1948 "*for his discovery of the high efficiency of DDT as a contact poison against several arthropods*." DDT was used with great success in the World War II to control malaria and typhus among civilians and troops. At the time of its discovery, the advantages of DDT that made it the best known and most useful insecticide were its stability, greater persistence, low cost, low mammalian toxicity and broad spectrum of insecticidal activity. Following more than 15 years of liberal use in agricultural and household (in the 1960s about 400000 tons where applied annually worldwide, which resulted in the almost complete eradication of malaria in several previously endemic areas).

 CAS: 50-29-3

DDT is an endocrine disruptor. It is considered likely to be a human carcinogen, although the majority of studies suggest it is not directly genotoxic. DDT acts as a weak androgen receptor. DDT's main component, has little or no androgenic or estrogenic activity. The minor component of DDT has weak estrogenic activity.

Acute toxicity. DDT is classified as "moderately hazardous" by WHO (World Health Organization). DDT has on rare occasions been administered orally as a treatment for barbiturate poisoning.

Chronic toxicity. Epidemiological evidence indicates that endocrine disrupting activity effects may be occurring in humans as a result of DDT exposure. EPA (Environmental Protection Agency) states that DDT exposure damages the reproductive system and reduces reproductive success. These effects may cause developmental and reproductive toxicity, human data also indicate possible disruption in semen quality, menstruation, gestational length, and duration of lactation. Documented are decreases in semen quality among men with high exposures to DDT, DDT is associated with early pregnancy loss. A Japanese study of congenital hypothyroidism concluded that DDT exposure may affect thyroid hormone levels and "play an important role in the incidence and/or causation of cretinism. Other studies found that DDT interfere with proper thyroid function in pregnancy and childhood.

**DIELDRIN** (Annex A). Dieldrin is the active epoxide of Aldrin and is industrially prepared by chemical epoxidation of Aldrin. It was used to control termites and textile pests, and insect-borne diseases and insects living in agricultural soils. Dieldrin is toxic to humans and its lethal dose has been estimated to be 10 mg/kg b.wt, so it is more toxic than its metabolic precursor, Aldrin. For a first time in 1969 the pharmacodynamics of Dieldrin was studied in human volunteer studies. An observation on the workers of a chemical plant for production of pesticides (Aldrin, Dieldrin, Endrin as well as the known animal carcinogen, Dibromochloropropane) showed an increase of liver and biliary tract cancers.

 CAS: 60-57-1

For a first time in 1969 the pharmacodynamics of Dieldrin was studied in human volunteer studies. It has been linked to health problems such as Parkinson's, breast cancer, and immune, reproductive, and nervous system damage. It is also an endocrine disruptor, acting as an estrogen and antiandrogen, and can adversely affect testicular descent in the fetus if a pregnant woman is exposed to it.ltural

**ENDRIN** (Annex A). About 80% of Endrin was consumed for controlling insect pests of cotton. It was also used on rice, sugar cane, grain crops, sugar beets, tobacco and cole crops, as well as in orchards as a control of rodents and as a treatment for cotton and beans seeds. Endrin has been shown to be carcinogenic at several body sites in the rat, and possibly in the mouse and in the dog. Several cases of acute and fatal intoxication were reported from consumption of Endrin-contaminated food in different countries along with poisoning of animals and pets. One puzzling cluster of cases of seizure occurred in 1988 in the USA was reported as ‘*The tale of the toxic taquitos*’. Traces of Endrin were found in tortilla shells (2.4 to 4.6 ppm, corresponding to less than 0.1 mg per piece) purchased at an individual store by several families in Orange County (California, USA) and after the intake from affected individuals, toxic effects were observed at doses of 50 mg/kg b.wt). In comparison with Dieldrin, Endrin is less persistent in the environment.

 CAS: 72-20-8

**Exposure.** Exposure to Endrin can occur by inhalation, ingestion of substances containing the compound, or by skin contact. In addition to inhalation and skin contact, infants can be exposed by ingesting the breast milk  of an exposed woman and *in utero* (unborn, before birth) fetuses are exposed by way of the placenta.

**Neurological effects**. Symptoms of Endrin poisoning include headache, dizziness, nervousness, confusion, nausea, vomiting, and convulsion. Acute Endrin poisoning in humans affects primarily the central nervous system, acting as a neurotoxin, which blocks the activity of inhibitory neurotransmitters, resulting in seizures and death. Endrin can be stored in body fat tissues, symptoms of acute poisoning can occur even months after the initial exposure is terminated. An abnormal EEG is possible to be recorded, even with no clinical symptoms, due to injury to the brain stem.

**HEPTACHLOR** (Annex A). It has both insecticidal and fumigant activity. As per Stockholm Convention, the sale of Heptachlor products has been limited to the specific application of fire

ant control in underground transformers. Heptachlor epoxide remains in the soil for decades without significant further degradation. Heptachlor and its epoxide can be absorbed to soil particles and evaporate. The half-life of Heptachlor in the environmental compartments is ~1.3-4.2 days in air, ~0.03-0.11 years in water and ~0.11-0.34 years in soil. Like other POPs, Heptachlor is lipophilic and poorly soluble in water and thus it tends to accumulate in the body fat of humans and animals. ltural

 CAS: 76-44-8

**Exposure**. Humans are exposed to Heptachlor through drinking water and foods, including breast milk. Heptachlor epoxide is derived from the pesticide that was banned by the Stockholm convention in the 1980s. It is still found in soil and water supplies and can turn up in food and be passed along in breast milk. High levels of it seemed to increase Diabetes type 2 risk to about 7 %.

The International Agency for Research on Cancer (IARC - Paris) and the EPA (Environmental Protection Agency - USA) have classified the compound as a possible human carcinogen. Animals exposed to Heptachlor epoxide during gestation and infancy are found to have changes in nervous system and immune function. Higher doses of Heptachlor when exposed to newborn animals caused decrease in body weight and death.

The U.S. EPA MCL (Maximum contaminant level) for drinking water is 0.0004 mg/L for Heptachlor and 0.0002 mg/L for Heptachlor epoxide. An ATSDR (Agency for Toxic Substances and Disease Registry) report in 1993 found no studies with respect to death in humans after oral exposure to Heptachlor or Heptachlor epoxide.

**HEXACHLOROBENZENE** (Annex A & C). It was used as a fungicide for seed treatment on wheat to control the fungal disease bunt. Its half-life in humans is estimated to be in the range of 6 years. The most sensitive target organs are the liver, the ovary and the central nervous system. HCB is well known to induce porphyria through a free-radical generation mechanism due to its rather unique chemical characteristics of lipophilicity. Eating wheat treated with HCB has been associated with human dermal toxicity which can result in blistering of the skin. e

 CAS: 118-74-1

**Exposure to** Hexachlorobenzene. The material has relatively low acute toxicity but is toxic because of its persistent and cumulative nature in body tissues in rich lipid content.e key factors

**Unique Exposure Incident**. In 1955 and 1959 consumption of bread produced with HCB-treated seeds caused epidemic of chemical *porphyria* in Anatolia, Turkey where 500 people were fatally poisoned and > 4,000 people fell ill. The victims were affected with a liver condition called *porphyria cutanea tarda*, which disturbs the metabolism of hemoglobin and results in skin lesions. Most breastfeeding children < 2 years of age, died from a condition called "*pembe yara*" or "*pink sore*," suspected to be due to high doses of HCB in the breast milk. In the same follow-up study of 252 patients, 20–30 years after the exposure, many subjects had dermatologic, neurologic, orthopedic symptoms and signs, scarring of the face and hands (83.7%), hyperpigmentation (65%), hypertrichosis (44.8%), pinched faces (40.1%), painless arthritis (70.2%), small hands (66.6%), sensory shading (60.6%), myotonia (37.9%), cogwheeling (41.9%), enlarged thyroid (34.9%), and enlarged liver (4.8%).

**CHLORDECONE (KEPONE)** (Annex A) In the USA it was produced by Allied Signal Company in Hopewell, Virginia, and dumping of the substance into the James River in the 1960s and 1970s caused toxic effects on wildlife to the point that in 1975 the Governor of the State raised a ban to fishing. Production in the USA was stopped in 1976. In the French island of Martinique it was used without restrictions in banana plantations arguing that no alternative pesticide was available and despite a 1990 ban of the substance by France. Since 2003, the local authorities restricted cultivation of crops because the soil has been seriously contaminated by Kepone.

 CAS: 143-50-0

**Exposure.** Similarly, the nearby island of Guadeloupe was also contaminated and has one of the highest prostate cancer rates in the world. In 1978 it was observed a number of workers in Kepone production plant with clinical illness characterized by nervousness, tremor, weight loss, pleuritic and joint pain, and oligospermia. The illness incidence rates for production workers (64%) were significantly higher than for non-production personnel (16%). The mean blood **Kepone** level was significantly higher among workers with illness than those without disease (mean: 2.53 and 0.60 ppm, respectively; p < 0.001).

**HEXACHLORO-CYCLOHEXANE** (Annex A) Has been used as a human health pharmaceutical for control of head lice and scabies as second line treatment. This product is also incorrectly referred to as Benzene hexachloride, but must not be confused with Hexachloro-benzene, also a pesticide listed in Annex A of the Stockholm Convention. Hexachloro-cyclohexane exists in at least nine stereoisomers, of which three are of insecticidal importance and are: the α-, β- and γ- isomers, the latter, which is the most active one, being also known as Lindane. The crude mixture of products obtained by photochemical chlorination of Benzene consists of 10-18% of the γ-isomer, 55-70% of the racemic α-isomer, 5-14% of the β-isomer, 6-8% of the δ-isomer, 3-4% of the ε-isomer, and a trace of the η-isomer, along with traces of hepta- and octa-chlorocyclohexane which contribute to the unpleasant odour of technical Lindane.

 CAS: 319-84-6, 319-85-7, 58-89-9

**Exposure**. The EPA and WHO both classify **Lindane** as "moderately" acutely toxic. Most of the adverse human health effects reported for **Lindane** have been related to agricultural uses and chronic, occupational exposure of seed-treatment workers. Exposure to large amounts of **Lindane** can harm the nervous system, producing a range of symptoms from headache and dizziness to seizures, convulsions and, more rarely, death. **Lindane** has not been shown to affect the immune system in humans and it is not considered to be genotoxic. Prenatal exposure to **Lindane** and production byproduct, has been associated with altered thyroid hormone levels and could affect brain development.

**Cancer risk.**  Most evaluations of **Lindane** have concluded that it may possibly cause cancer. In 2015, the International Agency for Research on Cancer (IARC) classified **Lindane** as a known human carcinogen,which was confirmed in 2001 by EPA.   **Lindane** and its isomers have also been on several lists of known carcinogens since 1989.

**MIREX** (Annex A). It was popularized to control red imported fire ants (*Solenopsis saevissima richteri* and *Solenopsis invicta*) but by virtue of its chemical robustness and lipophilicity it was recognized as a bioaccumulative pollutant in aquatic and terrestrial food chains to harmful levels. Mirex is highly resistant to microbiological degradation. It only slowly dechlorinates to a monohydro derivative by anaerobic microbial action in sewage sludge and by enteric bacteria. Ironically, the use of Mirex encouraged the spread of the red imported fire ants since it also kills native ants that are highly competitive with the fire ants. The US EPA prohibited its use in 1976 after *approx.* 250000 kg of Mirex was applied to field between 1962 and 1975.

 CAS: 2385-85-3

**Exposure**. It can enter the body via inhalation, ingestion, and via the skin. The most sensitive effects of repeated exposure in animals tests are principally associated with the liver. At higher dose levels, it is fetotoxic (25 mg/kg in diet) and teratogenic (6.0 mg/kg per day). There is sufficient evidence of its carcinogenicity in mice and rats.Delayed onset of toxic effects and mortality is typical of **Mirex** poisoning.**Mirex** is toxic for a range of aquatic organisms. IARC (1979) evaluated **Mirex** carcinogenic hazard and concluded that "there is sufficient evidence for its carcinogenicity to mice and rats. In the absence of adequate data in humans, it could be stated that it has carcinogenic risk to humans”.

In a 1995 report of ATSDR (Agency for Toxic Substances and Disease Registry) is stated that  **Mirex** caused fatty changes in the livers, hyperexcitability and convulsion, and inhibition of reproduction in animals. It is a potent endocrine disruptor, interfering with estrogen-mediated functions such as ovulation, pregnancy, and endometrial growth. It also induced liver cancer by interaction with estrogen in female rodents.

**TOXAPHENE** (Annex A). Toxaphene is a complex mixture, in which at least 670 chemicals, including chlorobornanes, chlorocamphenes, and other bicyclic chloroorganic compounds, have been identified. At least some of them are volatile enough to be transported for long distances through the atmosphere. Toxaphene was used as an insecticide. Between 1970 and 1995, cumulative global usage of Toxaphene was estimated to be 670 000 tons. In USA during the early to mid-1970s, Toxaphene became the most heavily used pesticide. Production peaked in 1975 at 30000 tons. It was chiefly used in the cotton and soybean growing areas in the southeastern region.

In 1982, it was banned for most uses, and in 1990 it was banned for all uses in the USA. However, in 2010, Toxaphene was still available from eleven suppliers worldwide, including seven in the USA.

 CAS: 8001-35-2

**Exposure.** The three main paths of exposure to **Toxaphene** are ingestion, inhalation, and absorption. For humans, the main source of **Toxaphene** exposure is through ingested seafood. When **Toxaphene** enters the body, it usually accumulates in fatty tissues. It is broken down through dechlorination and oxidation in the liver. People that live near an area that has high **Toxaphene** contamination are at high risk to **Toxaphene** exposure through inhalation of contaminated air or direct skin contact with contaminated soil or water.

**Health effects in humans**. When inhaled or ingested, **Toxaphene** can damage the lungs, nervous system, and kidneys, and may cause death. The major health effects of **Toxaphene** involve central nervous system stimulation leading to respiratory failure and convulsive seizures. The dose necessary to induce nonfatal convulsions in humans is about 10 mg/kg.bw.day. Chronic inhalation exposure in humans results in reversible respiratory toxicity. Evidence from studies indicates higher proportions of bronchial carcinoma in exposed to **Toxaphene**. Tests on laboratory animals show that **Toxaphene** causes liver and kidney cancer, so **Toxaphene** is classified as a ‘probable human carcinogen’. **Toxaphene** can be detected in blood, urine, breast milk, and body tissues at high levels exposure. It is classified as an IARC Group 2B carcinogen.

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