

Pesticides II

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HERBICIDES

Herbicides are chemicals that are capable of either killing or severely injuring plants.

Nonselective herbicides will kill all vegetation, whereas selective compounds are those used to kill weeds without harming the crops.

A number of herbicides can cause dermal irritation and contact dermatitis, particularly in individuals prone to allergic reactions. Other compounds have generated much debate for their suspected carcinogenicity or neurotoxicity.

Chlorophenoxy Compounds

- Chlorophenoxy herbicides are chemical analogs of auxin, a plant growth hormone, that produce uncontrolled and lethal growth in target plants.
- Because the auxin hormone is critical to the growth of many broad-leaved plants, but is not used by grasses, chlorophenoxy compounds can suppress the growth of weeds (e.g., dandelions) without affecting the grass.
- The most commonly used compound of this class is 2,4-dichlorophenoxyacetic acid (2,4-D).

Toxic effects of 2,4-D (2,4-dichlorophenoxyacetic acid)

- Ingestion of 2,4-D has caused acute poisoning in humans, resulting in vomiting, burning of the mouth, abdominal pain, hypotension, myotonia, and CNS involvement including coma.
- Dermal exposure is the major route of unintentional exposure to 2,4-D in humans.
- There are several case reports suggesting an association between exposure to 2,4-D and neurologic effects like peripheral neuropathy, demyelination and ganglion degeneration in the CNS and behavioral alterations.
- 2,4-D does not appear to have genotoxic or carcinogenic properties in rats, mice, and dogs.
- The chlorophenoxy herbicides have attracted much attention because of an association between exposure and non-Hodgkin's lymphoma and tissue sarcoma, found in a few epidemiological studies. Nevertheless, 2,4-D is classified as a group D agent (not classifiable as to human carcinogenicity).

Agent Orange

Mixture of 2,4-D (2,4-dichlorophenoxyacetic acid) and 2,4,5-T (2,4,5-trichlorophenoxyacetic acid)

Agent Orange was a powerful herbicide used by U.S. military forces during the Vietnam War to eliminate forest cover and crops for North Vietnamese and Viet Cong troops. The U.S. program, codenamed Operation Ranch Hand, sprayed more than 20 million gallons of various herbicides over Vietnam, Cambodia and Laos from 1961 to 1971. Agent Orange, which contained the deadly chemical dioxin, was the most commonly used herbicide. It was later proven to cause serious health issues—including cancer, birth defects, rashes and severe psychological and neurological problems—among the Vietnamese people as well as among returning U.S. servicemen and their families.

- TCDD is 2,3,7,8-Tetrachlorodibenzodioxin, a chemical in a group of compounds named dioxins.
- TCDD wasn't purposely part of Agent Orange, it's a by-product of the process by which creates organochloride herbicides.
- Agent orange was intended to be a mixture of 2,4,5-Trichlorophenoxyacetic acid (2,4,5, T) and 2,4-Dichlorophenoxyacetic acid, (2,4-D) which were commonly used herbicides.
- There was already some controversy related to the health effects of these herbicides (particularly 2,4,5-T,) but it was the contamination of Agent Orange somewhere during the manufacturing process with TCDD that really made it so deadly.



Post-Vietnam Dioxin Exposure in Agent Orange-Contaminated C-123 Aircraft.

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2 TCDD: Physicochemical Properties and Health Guidelines

Of the components and contaminants of the several herbicides used by the US military in Vietnam, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) stands out as having the greatest toxic potency. It was an unintended contaminant of 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), one of the phenoxy herbicides comprising Agent Orange (AO) and also Agents Pink, Green, and Purple ([IOM, 2014](#)). TCDD, or dioxin, is the most toxic of the polychlorinated dibenzo-*p*-dioxin (PCDD), dibenzofuran (PCDF), and biphenyl (PCB) congeners. Several of the PCDD, PCDF, and PCB congeners share TCDD's major mechanism of action in producing several adverse health conditions by binding to the aryl hydrocarbon receptor (AHR), but at a fraction of its potency. Toxic Equivalency Factors (TEFs), where the TEF of TCDD has a value of one, have been assigned to these congeners providing the basis for a summary metric that expresses the total “dioxin-like activity” in a mixture of chemicals, referred to as its Toxicity Equivalency Quotient (TEQ). The exceptionally high proportion of TEQs accounted for by TCDD itself in AO formulations (compared to other TCDD-containing mixtures) can serve as a chemical “signature” of these herbicides used by the military in Vietnam. After the Vietnam War, analyses of residual herbicide stocks found that contamination by the TCDD congener specifically ranged from less than 0.05 parts per million (ppm) up to almost 50 ppm, averaging 2–3 ppm ([NRC, 1974](#); [Young et al., 1978](#)). Consequently, the TCDD contaminant of AO has been regarded as the primary reason for health concerns associated with exposure to the herbicides used in Vietnam, and so it is the committee's focus.

The Seveso disaster was an industrial accident that occurred around 12:37 pm on July 10, 1976 in a small chemical manufacturing plant approximately 20 kilometres (12 mi) north of Milan in the Lombardy region of Italy. It resulted in the highest known exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in residential populations,[1] which gave rise to numerous scientific studies and standardized industrial safety regulations. The EU industrial safety regulations are known as the **Seveso II Directive**.



Major accident hazards



The Seveso Directive - Technological Disaster Risk Reduction

Protecting the environment, health and our economy

Major accidents involving dangerous chemicals pose a significant threat to humans and the environment. Furthermore such accidents cause huge economic losses and disrupt sustainable growth. However, the use of large amounts of dangerous chemicals is unavoidable in some industry sectors which are vital for a modern industrialised society. To minimise the associated risks, measures are necessary to prevent major accidents and to ensure appropriate preparedness and response should such accidents nevertheless happen.

From disasters to success

In Europe, the catastrophic accident in the Italian town of Seveso in 1976 prompted the adoption of legislation on the prevention and control of such accidents. The so-called Seveso-Directive ([Directive 82/501/EEC](#)) was later amended in view of the lessons learned from later accidents such as Bhopal, Toulouse or



The Seveso Directive has two main objectives. The first is to prevent major accidents caused by hazardous substances, and the second is to minimize the consequences for people and the environment if they occur. Serious monitoring is required to ensure a high level of protection across the Community. The specifications of the Directive are as follows;

- Classification, packaging and labeling of chemicals,
- Investigation of major industrial accidents that have occurred before,
- reporting and auditing of wrong practices,
- Determination of a competent authority for the performance and supervision of the duties specified in the Directive,
- Planning of land use,
- Informing the public,
- Preparing and testing emergency plans to be implemented during any major industrial accident and updating them when necessary

Times Beach is a ghost town in St. Louis County, Missouri, United States. There was two thousand people living before dioxin contamination. The town was completely evacuated early in 1983 due to TCDD—also known as dioxin—contamination. It was the largest civilian exposure to this compound in the history of the US.

Bipyridil Compounds

- Paraquat is a fast-acting, nonselective contact herbicide, used to control broad-leaved weeds and grasses in plantations and fruit orchards, and or general weed control.
- Paraquat has one of the highest acute toxicities among herbicides.
- On absorption, independent of the route of exposure, paraquat accumulates in the lung and the kidney.
- Paraquat is very poorly metabolized, and is excreted almost unchanged in the urine.
- It has minimal to no genotoxic activity, is not carcinogenic in rodents, has no effect on fertility, is not teratogenic, and only produces fetotoxicity at maternally toxic doses.
- The major toxicologic concerns for paraquat are related to its acute systemic effects, particularly **in the lung**, and secondarily, **the kidney**.

Phosphonomethyl Amino Acids

- The two compounds of this class are **glyphosate** (N-phosphonomethyl glycine) and glufosinate (N-phosphonomethyl homoalanine).
- Both are broad-spectrum nonselective systemic herbicides used for postemergent control of annual and perennial plants. Though both compounds contain a P=O moiety, they are organophosphonates and do not inhibit AChE.
- Glyphosate—Glyphosate exerts its herbicidal action by inhibiting the enzyme phenolpyruvylshikimate-3-phosphate synthase, responsible for the synthesis of an intermediate in the biosynthesis of various amino acids.
- Although important in plant growth, this metabolic pathway is not present in mammals. It has no teratogenic, developmental, or reproductive effects.

- **Glyphosate is one of the most widely used herbicides**, and the development of transgenic crops that can tolerate glyphosate treatment has expanded its utilization.
- Given its widespread use, including the home and garden market, accidental or intentional exposure to glyphosate is inevitable.
- The most widely used glyphosate product is Roundup[®] which is formulated as a concentrate containing water, 41% glyphosate (as isopropylamine salt), and 15% polyoxethyleneamine (POEA).

Glyphosate Fact Sheet: Cancer and Other Health Concerns

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Posted on [April 12, 2020](#) by [Stacy Malkan](#)

Glyphosate, a synthetic herbicide patented in 1974 by the Monsanto Company and now manufactured and sold by many companies in hundreds of products, has been associated with cancer and other health concerns. Glyphosate is best known as the active ingredient in Roundup-branded herbicides, and the herbicide used with “Roundup Ready” genetically modified organisms (GMOs).

Herbicide tolerance is the most prevalent GMO trait engineered into food crops, with some 90% of corn and 94% of soybeans in the U.S. engineered to tolerate herbicides, [according to USDA data](#). A [2017 study](#) found that Americans’ exposure to glyphosate increased approximately [500 percent](#) since Roundup Ready GMO crops were introduced in the U.S in 1996. Here are some key facts about glyphosate:

IARC found "strong evidence" that glyphosate can damage DNA in cells. This kind of damage, inducing mutations, is the first step in causing cancer.

IARC says there's "limited evidence" that people exposed to glyphosate had higher rates of a particular kind of cancer — non-Hodgkin lymphoma.

- In March 2015, IARC classified glyphosate as “**probably carcinogenic to humans**” (Group 2A).
- Mild intoxication results mainly in transient gastrointestinal symptoms. Moderate or severe poisoning presents with gastrointestinal bleeding, hypotension, pulmonary dysfunction, and renal damage

FUNGICIDES

- Fungal diseases are virtually impossible to control without chemical application. Fungicidal chemicals are derived from a variety of structures, ranging from simple inorganic compounds, such as copper sulphate, to complex organic compounds.
- Most fungicides are surface or plant protectants and are applied prior to potential infection by fungal spores, either to plants or to postharvest crops. Other fungicides can be used therapeutically, to cure plants when an infection has already begun. Still others are used as systemic fungicides that are absorbed and distributed throughout the plant. With a few exceptions, fungicides have low acute toxicity in mammals. Some fungicides have been associated with severe epidemics of poisoning.

Dithiocarbamates

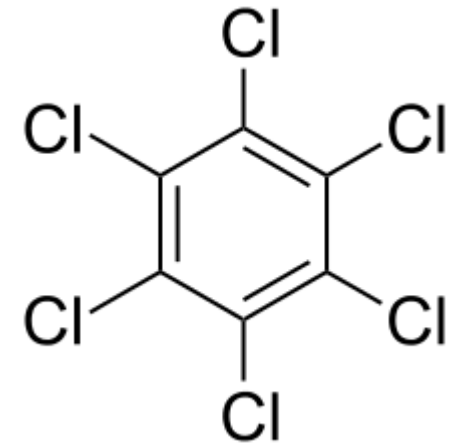
The nomenclature of many of these compounds arises from the metal cations with which they are associated; thus, there are, e.g., **Maneb (Mn)**, **Ziram and Zineb (Zn)**, and **Mancozeb (Mn and Zn)**

The dithiocarbamates have low acute toxicity by the oral, dermal, and respiratory routes. However, chronic exposure is associated with adverse effects that may be due to the dithiocarbamate acid or the metal moiety.

These compounds are metabolized to a common metabolite, **ethylenethiourea (ETU)**, that is responsible for the effects of dithiocarbamates on the thyroid, which include hypertrophy and hyperplasia of thyroid follicular cells that progress to adenomas and carcinomas. (Cancer and hypothyroidism)

Hexachlorobenzene

Hexachlorobenzene was used as a fungicide and was also used as a chemical intermediate in the manufacture of dyes, synthesis of organic chemicals, rubber and in wood preservation. Prolonged oral exposure to this substance results in a liver disease with associated skin lesions. Hexachlorobenzene is reasonably anticipated to be a human carcinogen based on association between thyroid, liver and kidney cancer and oral exposure in animals.



Hexachlorobenzene episode in Turkey.

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Author information

Abstract

During the period 1955-1959, approximately 4000 people in southeast Anatolia developed porphyria due to the ingestion of hexachlorobenzene (HCB), a fungicide added to wheat seedlings. These HCB exposures subsequently led to the development of bullae on sun-exposed areas, hyperpigmentation, hypertrichosis, and porphyrinuria. The condition was called kara yara or "black sore." Many of the breast-fed children under the age of 2 years whose mothers had ingested HCB-treated grain died from a disease known as pembe yara or "pink sore." In this follow-up study of 252 patients, 20-30 years postexposure, there were 162 males and 90 females, with an average current age of 35.7 years, an average of onset of 7.6 years, and a duration of 2.2 years. Many patients had dermatologic, neurologic, and orthopedic symptoms and signs. The observed clinical findings include scarring of the face and hands (83.7%), hyperpigmentation (65%), hypertrichosis (44.8%), pinched facies (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%). Urine and stool porphyrin levels were determined in all patients, and 17 have at least one of the porphyrins elevated. A total of 56 specimens of human milk obtained from mothers with porphyria were analyzed for HCB. The average value was 0.51 ppm in HCB-exposed patients compared to 0.07 ppm in unexposed controls. Offspring of mothers with three decades of HCB-induced porphyria appear normal.

Naphthalene

Naphthalene is a white, volatile, solid polycyclic hydrocarbon with a strong mothball odor. Naphthalene is obtained from either coal tar or petroleum distillation and is primarily used to manufacture phthalic anhydride, but is also used in moth repellents. Exposure to naphthalene is associated with hemolytic anemia, damage to the liver and neurological system, cataracts and retinal hemorrhage. Naphthalene is reasonably anticipated to be a human carcinogen and may be associated with an increased risk of developing laryngeal and colorectal cancer.

IARC Classifications of Pesticides 1971-2016

Classification	Number	Details/Comments
Group 1	3	Arsenic and arsenical compounds, including pesticides; Lindane; Pentachlorophenol
Group 2A	9	Captafol; DDT; Diazinon; Dieldrin, Aldrin metabolised to Dieldrin; Dimethylcarbamoyl chloride; Ethylene dibromide; Glyphosate; Malathion; Tetrachloroazobenzene (contaminant)
Group 2B	27	Examples evaluated in 2015-2016: Parathion, Tetrachlorvinphos, 2,4,6- Trichlorophenol
Group 3	48	

International Agency for Research on Cancer

References

Klaassen, C. D., & Watkins, J. B. (2015). *Casarett & Doull's essentials of toxicology*. McGraw Hill Professional.