

By John Hardy University of Bristol School of Chemistry



Molecule of the Month December 2000

## Introduction.

Agent Orange is the name used by the U.S. military for a 1:1 mixture of the herbicides 2,4-D and 2,4,5-T. The name, Agent Orange, was derived from the orange stripe on drums in which the herbicide was stored.

Large quantities were sprayed in Vietnam to defoliate trees that might hide the enemy. Fears that Agent Orange can cause human illness stem from the presence in it of a contaminant called TCDD (short for 2,3,7,8-tetrachlorodibenzo-para-dioxin). TCDD is only one of a family of substances called dioxins, but it is the one that has gained the greatest notoriety. TCDD is commonly referred to as dioxin

Dioxin is produced as an undesired contaminant during the manufacture of 2,4,5-T. Tests show that it is a potent teratogen for some laboratory animals; that is, exposure of pregnant females to exceedingly small amounts of dioxin causes malformed offspring.

## **Background.**

Agent Orange was not the only herbicide sprayed in Vietnam, although due to its intensified usage, it is the herbicide most commonly mentioned and blamed for health problems in connection with the Vietnam War. There were two other herbicides, an insecticide and a chemical irritant used during the Vietnam War. Each had a code name: Agent Blue, Agent Orange, Agent White, CS and Malathion.

Agent Orange (A-O) and Agent White (A-W) contain mixtures of plant hormone mimicking compounds that destroy plants by interfering with their normal metabolism. Agent Blue (A-B) destroys vegetation by preventing plants from retaining moisture.

A-O (61% usage) and A-W were effective against dicotyledonous plants (two leaves emerging from seed) and A-B (11% usage) was used for monocotyledonous plants (single leaf emerging from seed). A-W and A-O were used to destroy the forests of South Viet Nam while A-B was mainly used for the destruction of grain crops, particularly the staple crop of rice. The level of usage for military operations was 20 to 40 times greater than for normal agricultural usages. The chemicals were dispensed by fixed-wing aircraft and ground troops, a C-123 (Provider) could dump 11,000 lbs. of Agent Orange over 300 acres in four minutes.



Loss of foliage, flower and fruit occurred within two to three weeks after spraying. Not all of the trees died but a large percentage of those surviving trees were permanently damaged. Dioxin has an environmental half-life of approximately three years and has shown up in the food chain. The effect of A-O on humans has been an area of intense debate for the past two decades. It has now been established that dioxin is a very potent poison that can cause a wide range of organ and metabolic dysfunctions. In laboratory animals dioxin has shown to be Carcinogenic, Mutagenic and Teratogenic.



1: Unharmed forest.

2: Forest after treatment with Agent Orange.

Agent Orange caused Vietnamese farmers to lose about 70% of their crops. (One of the goals for using herbicides was to deprive the enemy of food.) 6250+ square miles of south Vietnam cannot be farmed due to defoliation. This is still true almost 30 years later.

A televised news report covering more general information, has been published on the internet. If you would like to view it, follow the link below.

MSCBC's Kari Huus explores the legacy of unexploded bombs, and Agent Orange, in central Vietnam.

## Hormone Weed killers.



Indolylacetic acid (<u>IAA</u>) was the first plant growth hormone to be discovered. As it encourages plant growth, it was reasoned that applications of large amounts of it would cause excessive plant growth, resulting in the death of the plant. However, it was found that plants are able to regulate the level of IAA by metabolism and thus it is not herbicidal.

It was discovered early in the 1940s that chlorinated phenoxyacetic acids (such as 2,4-D and MCPA) had herbicidal activity. These are plant growth stimulants like IAA, but differ from IAA, as they are not metabolized.

2,4-D and MCPA have several advantages:

- Effectiveness at low concentrations.
- Low mammalian toxicity.
- Selectivity. (They affect broad leaves weeds, but not cereal or grass crops)
- Synthesis is simple and cheap.

2,4-D is still extensively used in the USA, but in the UK MCPA is more commonly used, especially in the form of a combined fertiliser/weed-killer for controlling dandelions and daisies in lawns.



#### <u>2,4,5-T</u>.

Whereas 2,4-D and MCPA have been used extensively all over the world for the past 50 years without any problems, their chemically similar derivative, 2,4,5-T has been surrounded with controversy. It was combined with 2,4-D, and used as a defoliant by the USA in the Vietnam war in the 1960s. It has even been used in the UK to control brambles encroaching on footpaths or railway lines by the Forestry Commission and British Rail, respectively. It has great advantages in that is has low toxicity to animals and is cheap to manufacture. It is the small amounts of dioxin impurity that have been responsible for the problems with its use.

## Dow synthesis of 2,4-D and MCPA.

2,4-D and MCPA are produced by the Dow Process. In the USA, 2,4-D is preferred to MCPA, but the reverse is true in the UK; in the rest of Europe there no preference. The main reason for this is historical, and was the availability of the starting phenol when the compounds were introduced in the 1940s. o-creosol was readily available in the UK from coal tar, whereas in the USA synthetic phenol was available.

# Synthesis of 2,4-D.



Synthesis of MCPA.



#### Synthesis of 2,4,5-T and Dioxin.

The synthesis of 2,4,5-T is similar to that for 2,4-D and MCPA. However, the temperature during the second step must be controlled carefully, because if it rises above  $160^{\circ}$ C a side reaction occurs, and tetrachlorodioxin is produced.

Synthesis of 2,4,5-T.







Tetrachlorodioxin

## Structures.



2,4-D:

2,4,5-T

Dioxin

MCPA

# The method of action of 2,4,5-T and 2,4-D.

#### Auxins are plant hormones.

The most important Auxin produced by plants is indole-3-acetic acid (IAA). It plays important roles in a number of plant activities, including:

- 1. Phototropism.
- 2. Gravitropism.
- 3. Apical dominance.
- 4. Fruit development.
- 5. Abscission.
- 6. Root initiation.

A couple of synthetic auxins are 2,4-D and 2,4,5-T.

## How does Auxin achieve its many different effects in the plant?

Auxin effects are mediated by two different pathways:

- 1. Direct effects on the cell.
- 2. "Turning on" of new patterns of gene expression.

#### 1. Direct effects of Auxin.

The arrival of Auxin at the surface of the cell initiates such immediate responses as:

- Changes in movement of ions in and out of the cell through the plasma membrane.
- Extension of the cell wall causing elongation of the cell.

Auxin initiates these events after binding to specific receptors at the cell surface, probably transmembrane proteins such as ABP1 ("Auxin-binding protein 1")

#### 2. Effects of Auxin on gene expression.

Many Auxin effects are mediated by changes in the transcription of genes. The steps appear to be:

- Auxin enters the cell by active transport through special Auxin transporter molecules in the plasma membrane.
- Auxin binds to molecules in the cytosol such as ARF1 ("Auxin response factor 1") ARF1 is a transcription factor it enters the nucleus and binds to the DNA sequence.

#### TGTCTC

#### ACAGAG

This sequence is found in the promoters of Auxin-responsive genes; that is, it is an Auxin response element. The action of Auxin on gene transcription is quite similar to the action of steroid hormones in animals.

## Synthetic Auxins as weed killers.

Some of the most common weed killers are synthetic Auxins. Such as: 2,4-D and 2,4,5-T.

2,4-D and its many variants are popular because they are selective herbicides, killing broad-leaved plants but not grasses.

#### Why should a synthetic Auxin kill the plant?

Auxin (IAA) is actively transported into cells by a transmembrane transporter and leaves the cells by facilitated diffusion through a different transporter. It turns out that the importer works fine for 2,4-D but that 2,4-D cannot leave the cell through the exporter. It is the resulting accumulation of 2,4-D within the cell that kills it.

More detail can be found at: http://www.ultranet.com/~jkimball/BiologyPages/A/Auxin.html#herbicides

# The method of action of Dioxin.



For a detailed description of the method visit:

http://dioxins-r-us.ucdavis.edu/TCDDAhR.HTML

Permission to use the picture was given by Professor Denison.

# Health effects of exposure to Dioxin.

Certain televised news reports have been published on the internet, if you would like to view any, proceed to the videos page.

The most common effects of dioxin are summarised below:

## Skin:

The most clearly established health effect of dioxin in humans is a skin eruption called Chloracne. The Seveso incident in 1976 contaminated the vicinity with dioxin and caused many cases of chloracne.



## Visual:

Dioxin can cause burning, blurring and more seriously blindness in those who suffer exposure to it. Below is a photo of 2 victims.



## **Birth Defects:**



Dioxin has caused both the Vietnamese and Veterans to father a greater percentage of children with birth defects.

A study in 1987 of Vietnam ground troops who served in sprayed areas revealed that they averaged 4 parts per trillion (ppt) of dioxin in their blood. The half-life of dioxin in the body is 6-10 years so assuming that these men got all their dioxin exposure in Vietnam, they would have had some 20 ppt (the maximum permissible amount in U.S. civilians) at that time. However, this assumption is almost certainly false, as Dioxins are produced whenever organic matter is burned (backyard barbecues, municipal incinerators, wood-burning stoves). Furthermore, 4 ppt of dioxin was also found in the blood of an otherwise matched group of veterans who did not serve in Vietnam. Civilians with no known exposure to TCDD should not have serum levels of TCDD exceeding 20 ppt. The highest level found in persons living near Seveso was 1,800 ppt.

The health of Vietnam veterans is still being monitored. Those that were directly involved in the spraying itself (called "Operation Ranch Hand") are now developing diabetes at a significantly higher rate than the others.



Above is a veteran who has been confined to a wheelchair.

A summary of the reported health effects of exposure to Dioxin can be found at:

http://www.lyghtforce.com/HomeopathyOnline/issue5/articles/ritchie\_orange.html

## The Seveso incident.

On 10 July 1976, at, there was an accident in Givaudan's chemical plant belonging to the ICMESA firm near Seveso, Northern Italy.

A reactor vessel safety plate ruptured, resulting in the release of a toxic vapour cloud. The reactor was used for the production of 2,4,5-trichlorophenol (TCP) and the cloud contained various components and byproducts of the process, including TCP, ethylene glycol and chlorinated phenols. Most notably, it also contained 2,3,7,8-tetrachloro-dibenzo-paradioxin (TCDD).

The cloud spread over a large area, contaminating humans, animals, crops and land in the vicinity of the plant. The failure of the safety plate occurred while the plant was shut down for the weekend. The plant had closed midway through the production of a batch of TCP, leaving the reactor full of material at an elevated temperature. Among these were ethylene glycol and sodium hydroxide, which eventually underwent an uncontrolled exothermic reaction that released sufficient gas to exceed the pressure limit of the safety plate. The reaction also raised the reactor temperature to 450-500 Celsius, conditions that greatly increased the formation of TCDD. The reactor had no automatic cooling system; since only maintenance and repair personnel were in the plant over the weekend, no one was present to initiate cooling manually and suppress the reaction. Fortunately, the cloud vented for only 20 minutes before a worker noticed and stopped the release. It is estimated that 2kg of the dioxin were in the cloud, and the area was immediately sealed off and the population was evacuated.

Locally grown food was banned for several months, and several inches of topsoil were removed and incinerated, as were the livestock from the local farms. However, despite all these worries, only one person, to date, appears to have died from liver cancer, although there were a number of cases of skin disease (chloracne). No employees of the company suffered damage to their organs, a number of women had abortions due to the potential danger to their unborn children. The incidence of malformed children was comparable to that found elsewhere, so it appears as though the inhabitants of Seveso escaped relatively lightly.

## Videos.



A number of televised news reports have been published on the internet, if you would like to view them follow the links below.

## General:

- MSCBC's Kari Huus explores the legacy of unexploded bombs, and Agent Orange, in central Vietnam.
- Dioxin in the food chain.

#### **Birth Defects:**

- Birth defects 1.
- Birth defects 2.

## **Dioxin and Diabetes:**

- Dioxins are more dangerous than thought: (link to diabetes)
- News link confirming the link between Dioxin exposure and Diabetes.

## Dioxin as a Human Carcinogen:

- Draft Environmental Protection Agency report declares dioxin a human carcinogen.
- Environmental Protection Agency declares dioxin a human carcinogen.

## **Glossary of terms:**

## 2,4**-**D:

2,4-dichlorophenoxyacetic acid.



## 2,4,5-T:

2,4,5-trichlorophenoxyacetic acid.



#### **Agent Blue:**

Code name for cacodylic acid (dimethyl arsenic acid).

## **Agent Orange:**

Code name for mixture of <u>2,4,5-T</u> (2,4,5-trichlorophenoxyacetic acid) and 2,4-D (2,4-dichlorophenoxyacetic acid).

## **Agent White:**

Code name for a mixture of an approximate ratio of 4:1 of <u>2,4-D</u> (2,4-dichlorophenoxyacetic acid) and picloram (4-amino-3,5,6-trichloropicolinic acid).

#### Auxins:

most important Auxin produced by plants is indole-3-acetic acidIAA). Some of the most common weed killers are synthetic auxins, such as:

Plant hormones. The2,4-D and 2,4,5-T.

## Carcinogenic:/i>

Causing cancer.

#### **Chloracne:**

The most clearly established health effect of dioxin in humans is a skin eruption called chloracne.

## CS:

(o-chlorobenzalmalonitrile), an anti-personnel (harassing) agent.

#### **Dioxin:**

Short for 2,3,7,8-tetrachlorodibenzo-para-dioxin, also TCDD.



Dioxin is formed as an unintentional by-product of many industrial processes involving chlorine such as waste incineration, chemical and pesticide manufacturing and pulp and paper bleaching. The major sources of dioxin are in our diet. Since dioxin is fat-soluble, it accumulates in the food chain and it is mainly found in meat and dairy products. In fish alone, the toxins accumulate so that dioxin levels in fish are 100,000 times that of the surrounding environment.

## Indolylacetic acid:

(IAA) Was the first plant growth hormone to be discovered.

## Malathion:

(S-(1,2-dicarbethoxyethyl)-0,0-dimethyldithiophosphate), an insecticide.

## **Mutagenic:**

Causing genetic damage.

## Half Life:

The length of time required for half a quantity of drug, or other substance residing in a living organism to be metabolized, or eliminated by normal biological processes. It is also called the biological half-life. The half-life of dioxin is 8.7 years in humans (as determined in the Ranch Hand (follow-up) studies).

## MCPA:

2-methyl-4-chlorophenoxyacetic acid.



## **Teratogenic:**

Causing birth defects.

## Credits

Thanks to:

Professor Denison of UC Davis; for allowing use of images.

```
http://dioxins-r-us.ucdavis.edu/Dioxin.HTML
```

Gary Moore; for allowing use of images, and providing valuable information.

http://dns.advnet.net/gdmoore/index.html

# **REFERENCES.**

## **Background Information.**

General:

- The Chemical Industry: Ed. A. Heaton. Pub: Blackie, London, 1994.
- <u>http://dns.advnet.net/gdmoore/index.html</u>
- <u>http://www.ultranet.com/~jkimball/BiologyPages/A/AgentOrange.html</u>
- <u>http://www.lyghtforce.com/HomeopathyOnline/issue5/articles/ritchie\_orange.html</u>

#### **Dioxin:**

- <u>http://dioxins-r-us.ucdavis.edu/Dioxin.HTML</u>
- <u>http://www.enviroweb.org/issues/dioxin/index.html</u>
- http://www.essential.org/orgs/cchw/campaign/dioxref.html

#### Seveso incident:

- <u>http://www.miacc.ca/content/about/seveso.htm</u>
- http://www.roche.com/roche/about/esevesa.htm
- <u>http://lorien.ncl.ac.uk/ming/safety/comah.htm</u>

#### Vietnam War.

• <u>http://hubcap.clemson.edu/~eemoise/bibliography.html</u>

## Scientific Information.

#### Health Effects:

- <u>http://www.monitor.net/rachel/r353.html</u>
- <u>http://www.lyghtforce.com/HomeopathyOnline/issue5/articles/ritchie\_orange3.html</u>

#### Method of action of 2,4-D and 2,4,5-T:

• http://www.ultranet.com/~jkimball/BiologyPages/A/Auxin.html#herbicides

#### Method of action of Dioxin:

- <u>http://dioxins-r-us.ucdavis.edu/TCDDAhR.HTML</u>
- <u>http://www.dioxin2000.ucdavis.edu/</u>
- <u>http://www.stanford.edu/group/whitlock/</u>

#### Synthesis:

• The Chemical Industry: Ed. A. Heaton. Pub: Blackie, London, 1994.

#### Images:

Where possible an attempt has been made to contact the owner of the image to ask for permission to copy the pictures. Note that the alternative text for each picture should give credit to the webpage that it was copied from. Please <u>contact</u> <u>me</u> if you would like me to remove the picture from the webpage.

