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THE 'DRIN' PESTICIDES



HISTORY

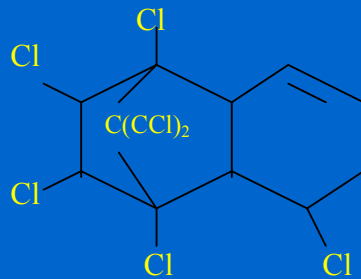
- ‘Drin’ pesticides (aldrin, dieldrin, endrin): organochlorine pesticides
- Drin pesticides belong to cyclodiene group of compounds
- DDT first synthesized by Zeidler in 1874 and rediscovered in 1939 by Paul Muller
- Endrin is a stereo-isomer of dieldrin
- Drin pesticides related to DDT - produced before 1945
- 1940s to 1960s drin pesticides used extensively in agriculture, forestry, building, control of pests

HISTORY

- Aldrin more effective than dieldrin- Aldrin more extensively used as soil insecticide
- Endrin primarily used as cotton insecticide
- Endrin rapidly metabolized in environment
- Rachel Carson in her book “Silent Spring” recognized environmental effects of organochlorine pesticides
- Aldrin/dieldrin banned in North America and Europe in the 1970s apart from Denver, Colorado plant in US and Royal Dutch Plant in The Netherlands (operated until 1990s)
- Aldrin/dieldrin still used in developing countries

PHYSICAL AND CHEMICAL PROPERTIES

The cyclodienes have the following general structure:



PHYSICAL AND AND CHEMICAL PROPERTIES

- Aldrin: empirical formula = $C_{12}H_8Cl_6$ and molecular weight = 364.93
- The pure compound is odorless, white, crystalline solid, melting point of 104-104.5°C and boiling point of 145°C at 2mm Hg
- Dieldrin: empirical formula = $C_{12}H_8Cl_6O$ and molecular weight = 380.93
- Pure dieldrin is white, crystalline, odorless solid that melts at 176-177°C

PHYSICAL AND CHEMICAL PROPERTIES

- Technical dieldrin contains not less than 95% of the 85%/15% mixture
- Technical compound - buff to light brown flakes, mild odor and melting point 95°C
- Endrin ($C_{12}H_8Cl_6O$), molecular weight = 380.93. Technical product (85% endrin)
- Light tan powder with a distinct odor
- Pure compound a white crystalline material easily decomposed by heat above 200°C

COMMON SOURCES AND ROUTES OF EXPOSURE

- Little information on current occupational exposure to aldrin/dieldrin
- Persistence, long period use & bioaccumulation- environmental exposure will continue for a long time
- Dieldrin used in agriculture, public health to control mosquitoes and tsetse flies. Also, as sheep dip, & for treatment of wood and mothproofing of woolen products
- Aldrin/dieldrin used for rootworms, beetle and termites.
- Exposure through inhalation & skin
- Main risk groups: living in close proximity to National priority List (NPL) sites, contaminated foods and water

COMMON ROUTES OF EXPOSURE

- Sensitive populations: persons with chronic illness, extremes of age, pregnancy, breast-feeding infants, malnutrition, immunocompromised, limited available water source and recreational water use
- Residual contamination: waste sites from the disposal of used stocks. Exposure to cleanup workers
- WHO monitoring studies (1960-1980): mean values for dieldrin in human body fat range of 0.1-0.3 mg/kg fat, liver 0.009, 0.047mg dieldrin/kg liver. Intakes dropped since the discontinuation or restriction of the use of aldrin/dieldrin
- Possible new releases from individually owned stockpiles of aldrin for underground control of termites

SOME EPIDEMIOLOGICAL STUDIES

- Concern about long-term exposure cancer. Chronic oral studies in mice: increased incidences of benign and malignant liver tumors
- Mainly two situations of human exposure to aldrin and dieldrin- manufacturing and formulating agents, application of insecticides in the field or in homes
- Two previous production sites subject to epidemiological investigations for possible long-term health effects
- Study of Denver workers by Ditraglia and Rotterdam cohort study by De Jong. Total mortality of exposed groups lower than expected. Total mortality from cancers also lower than expected regardless of very high exposures

Summary of study of Denver Workers (Ditralgia, 1981)

Causes of death	Observed cases	SMR	95% CI
All causes	173	84	74-98
All malignant neoplasms	31	82	56-116
Liver	2	225	39-12
Lymphatic/hematopoietic	6	147	54-319
Circulatory system	69	77	60-97
Nonmalignant respiratory disease	22	212	133-320
Nervous system diseases	9	68	31-128

SMR = Standardized Mortality Ratio

SMR = Observed no.of deaths per year/Expected no. of deaths per year

Summary of Rotterdam study (De Jong, 1997)

Causes of death	Obs	Exp	SMR	95% CI
All causes	118	156.0	75.6	63-91
Neoplasms	46	47.5	96.8	71-129
Other diseases	23	31.6	72.8	46-109
Multiple myeloma	1	0.6	163.9	4-913
Leukemia	2	1.4	140.7	17-508
Lung Cancer	19	19.1	99.8	60-156

TOXICOKINETICS

- Aldrin rapidly metabolized to dieldrin by wide range of organisms, including humans
- Dieldrin considered as the primary toxic substance of aldrin. Conversion from aldrin to dieldrin very fast
- Metabolism of aldrin to dieldrin by mammals not confined to the liver; lung also involved
- Aldrin readily absorbed through the gastrointestinal tract via the hepatic portal vein; toxicity almost as high via the dermal (skin) route indicating extensive dermal absorption
- The conversion to dieldrin carried out by cytochrome P450 to dieldrin and this occurs in the liver and lungs

TOXICOKINETICS

- Dieldrin is metabolized by liver microsomal enzymes to less toxic metabolites, including *cis*-aldrinol, 9-hydroxy dieldrin, and photoconverted to the more toxic 2 - ketodieldrin
- Adipose tissue major storage tissue followed by liver, brain and blood. Water-soluble metabolites of aldrin detoxification excreted in feces and urine
- Dieldrin is also found in mothers milk. Dieldrin absorbed from the gastrointestinal tract via the hepatic portal vein
- Dieldrin is slowly absorbed from the small intestine

TOXICOKINETICS

- Endrin metabolized by liver microsomal enzymes to more water-soluble metabolites including the hydroxylation products *syn*-12-hydroxyendrin and anti-12 hydroxyendrin
- The oxidative metabolite 12-ketoendrin is significantly more toxic than the parent compound and exerts its toxic effects earlier than endrin
- Oxidative metabolism very efficient, therefore, endrin does not accumulate as effectively as other organochlorines pesticides
- Higher concentrations may be found in the liver than adipose tissue. More than 90% of the compound and its metabolites excreted in feces and/or bile

TOXICODYNAMICS

- Organochlorine insecticides have potent estrogenic and enzyme-inducing effects which interfere directly or indirectly with fertility and reproduction
- Cyclodiene pesticides among the most toxic and environmentally persistent pesticides known
- At low doses the compound induce convulsions before less serious signs
- Also headaches, nausea, vertigo and mild clonic jerking, motor hyperexcitability, and hyperflexia, some patients have convulsions without symptoms
- Skin absorption - very serious problem to occupationally exposed persons

TOXICODYNAMICS

- Chronic exposure to low or moderate concentrations affect both sensory and motor components of the CNS
- Aldrin and dieldrin interfere with reproduction, increased loss of vitality and viability
- Poisoning causes persistent tremoring and/or convulsive seizures suggestive of repetitive discharges in neurons.
- Repetitive tremors, seizures, and electrical activity initiated by tactile and auditory stimuli
- Dieldrin inhibits gap junctional intercellular communication (GJIC) in a dose-response manner after 90 minutes treatments
- Action localized in the CNS than sensory division of the peripheral nervous system (PNS)

MECHANISMS OF TOXICITY

- Aldrin/dieldrin exhibit toxicity by inhibiting chloride ion flux
- Also mimic action of the chemical picrotoxin, a nerve excitant and antagonist of the neurotransmitter γ -aminobutyric acid (GABA) found in the CNS
- GABA induces the uptake of chloride ions by neurons.
- The blockage of this activity by picrotoxin, picrotoxinin, or cyclodiene insecticides results in only partial repolarization of the neuron and a state of uncontrolled excitation

MECHANISMS OF TOXICITY

- Organophosphorus pesticides also potent inhibitors of Na^+ , K^+ -ATPASE
- Also inhibits the enzyme Ca^{2+} , Mg^{2+} -ATPASE that is essential for the transport of and uptake and release of calcium across membranes
- The inhibition of Ca^{2+} , Mg^{2+} -ATPASE, located in the terminal ends of neurons in synaptic membranes results in the accumulation of intracellular, free calcium ions, the promotion of calcium-induced release of neurotransmitters from storage vesicles, the subsequent depolarization of adjacent neurons and the propagation of stimuli throughout the CNS

REGULATIONS

- WHO uses two major approaches to determine the exposure of the general population to dieldrin.:
- 1. Concentrations of dieldrin in the blood or adipose tissue - to estimate human exposure
- 2. Dieldrin residues in agricultural commodities or prepared meals
- In biological organisms, aldrin is rapidly oxidized to dieldrin, therefore aldrin cannot be detected in animals or humans unless there is current exposure
- Monitoring studies conducted during 1960-1980, found mean values for dieldrin in human body fat in range of 0.1-0.3 mg/kg fat

REGULATIONS

- In 1974, the US EPA suspended nearly all uses of aldrin and dieldrin because of cancer risks
- All uses of aldrin/dieldrin on food crops banned
- Aldrin used as subterranean termiticide until 1987 when all registrations were suspended
- EPA currently reevaluating recommended tolerances for unavoidable residue levels of aldrin\ieldrin in food products
- Exposure Limits for aldrin/dieldrin in the USA are: OSHA PEL: TWA:0.25mg/m³; ACGIH TLV: TWA: 0.25mg/m³; NIOSH REL:TWA: 0.25mg/m³. For endrin they are: OSHA PEL:TWA:0.1mg/m³, ACGIH TLV:TWA: 0.1mg/m³ and NIOSH REL:TWA:0.1mg/m³

REASSESSMENT OF HUMAN CANCER RISK TO ALDRIN/DIELDRIN

- The US EPA cancer risk assessment of aldrin and dieldrin in 1987 classified aldrin/dieldrin as class B² carcinogens (probable human carcinogens)
- Study based on evidence on mice studies which induced cancer of the liver
- Production of these substances therefore banned in the US and Europe
- Evidence now accumulated questioned value of the mouse liver tumors as reliable predictor of carcinogenic potential in humans especially for non-genotoxic carcinogens

REASSESSMENT OF HUMAN CANCER RISK OF ALDRIN/DIELDRIN

- Epidemiological studies and experimental models explaining the mouse specificity has strengthened the view that workers who are occupationally exposed to aldrin/dieldrin show no increase in cancer mortality
- Stevenson et al (1999) published monograph of present knowledge of aldrin/dieldrin
- In light of overwhelming evidence , they proposed that the most appropriate cancer risk descriptor for aldrin/dieldrin is "not likely a human carcinogen"