

D I A Z I N O N

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DIAZINON

- Organophosphate Insecticide₁
 - Non-systemic
 - Synthetic
- Over 13 Million lbs. Used Annually in the U.S.₂
- Both Agricultural and Non-Agricultural Uses₂
 - Homeowners and lawn care professionals = 70%
 - Agricultural = 30%

1. Organophosphates. Tarek Ladaa, Gretchen Bielmyer, Kim-Lee Murphy. Clemson University, Environmental Organic Chemistry Spring 1998.

2. US EPA Overview of Revised Risk Assessment. December 5, 2000.

DIAZINON - USES

- Agricultural₁
 - more than 64 different food crops, on livestock
 - Nuts, fruits, sugar-cane, tobacco
- Outdoor Residential/Homeowner₂
 - Lawns, turf, gardens, school grounds
- Indoor Residential₂
 - Cracks/crevices, office buildings, warehouses

1. US EPA Memo. Diazinon Revised HED Human Health Risk Assessment for the RED December 5, 2000. 2. EPA Questions & Answers Diazinon Revised Risk Assessment and Risk Mitigation Measures. December 5, 2000

DIAZINON - Target Pests

- Cockroaches
- Aphids
- Scales
- Mites
- Ants
- Fleas
- Ticks
- Flies
- Crickets
- Grubs
- Yellow Jackets
 - Western U.S.

DIAZINON - Agriculture

- Formulation₁
 - granules
 - seed dressings
 - dust
 - impregnated materials
- Application₂
 - Soil treatment
 - ground boom bill
 - hand held spray

1. US EPA Memo. Diazinon Revised HED Human Health Risk Assessment for the RED December 5, 2000.

2. US EPA Overview of Revised Risk Assessment. December 5, 2000.

Poisonings

- One of the leading causes of acute insecticide poisonings for humans and wildlife₁
 - Bird Kills

Exposure

- General population₁
 - inhalation: air, rain, fog
 - dietary: food residues
- Occupational₂
 - Dermal: Workers who mix, load, and apply diazinon and harvesters of treated crops

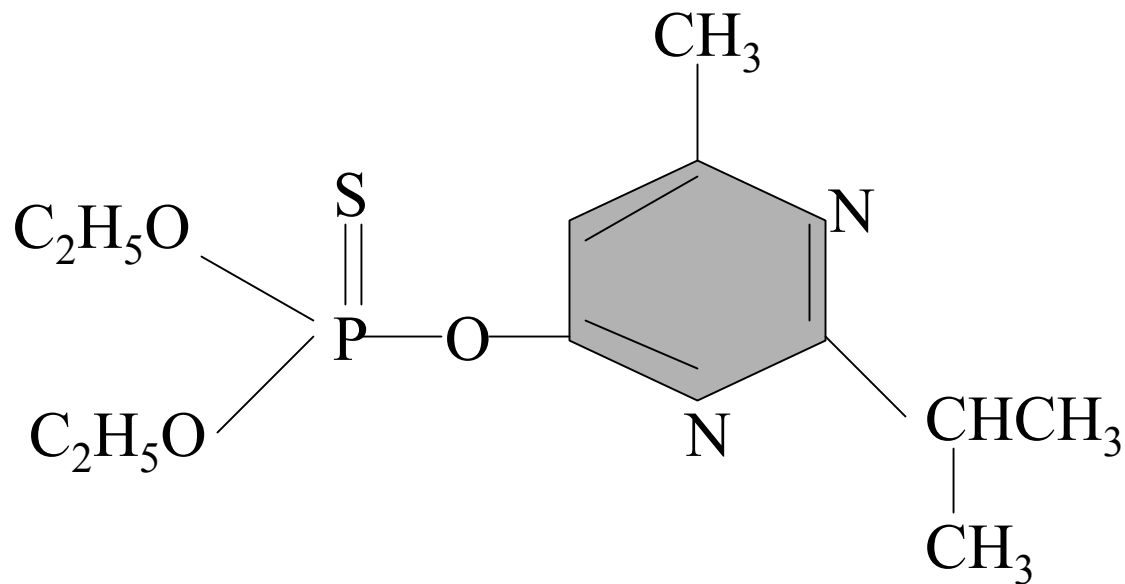
1. EPA Questions & Answers Diazinon Revised Risk Assessment and Risk Mitigation Measures. December 5, 2000

2. International Programme on Chemical Safety INCHEM Environmental Health Criteria 198 Diazinon.

Basics

- Non-Systemic Organophosphate
 - Insecticide, Pesticide
- Molecular Formula
 - C₁₂ H₂₁ N₂ O₃ PS
- Synonyms
 - 0,0-diethyl 0-2-isopropyl-4methyl-6-pyrimidinyl thiophosphate; Spectracide*

Molecular Structure



Toxicological Profile for Diazinon. US Department of Health and Human Services. ATSDR.

Properties

- Phosphorothioate with pyrimidine ring
- Hydrophobic
- Slight sulfur-like odor
- Insoluble in water

Toxicokinetics

ABSORPTION

- Inhalation
- Dermal
- Oral (Ingestion)

Absorption - Inhalation

- Low volatility: aerosols, vapor
- Absorption by lung = 100%₁
- NIOSH and OSHA have recommended a PEL 0.1 mg/m³₁
- Acute Inhalation LD50 (Rat): >3.0mg/L₂

1. Toxicological Profile for Diazinon. US Department of Health and Human Services. ATSDR.

2. Crop Data Management Systems Inc. AgChem Information Services. Material Data Sheet, Diazinon.

Absorption - Dermal

- Dermal Exposure
 - Human experiments found dermal absorption rate of 34%

Absorption - Oral/Ingestion

- Rapid absorption from the GI tract
 - Female Beagles absorbed 85%
 - (Iverson et al. 1975)
- Human $LD_{50} = 350-400$ mg/kg
- Rat $LD_{50} = 76-300$ mg/kg

DIAZINON - Dietary Risk

From Diazinon Residues on Food

- CRD = 0.0002mg/kg/day
 - NOAEL of 0.02
- ARD = 0.0025 mg/kg/day
 - NOAEL of 0.25 mg/kg/day

Case Fatality - Ingestion

- Death from ingestion of 293 mg/kg of a 10% diazinon mixture.
- Diazinon Concentrations in Body
 - blood
 - stomach
 - kidney
 - adipose tissue.

DISTRIBUTION

- Distributed throughout the body via blood
- Target of action is Central Nervous System receptors

Mechanism of Action

- Inhibits the enzyme acetylcholinesterase by binding to acetylcholine which carries electrical signals across the synapse
- Prevents AChE from removing neurotransmitter ACh which leads to build up of ACh.

More Mechanisms of Action

- Plasma pseudocholinesterase
- Neuropathy target esterase (NTE)
- A-esterases
- Carboxyesterases

Metabolism

- Two-step process
 - Oxidation
 - Hydrolysis
- Organs
 - Gut
 - Liver
 - Kidney

Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment Organophosphates. Department of Health Great Britain.

Metabolism

- Phase I reactions
 - Cytochrome P-450
 - bioactivated to diazoxon and hydroxy diazinon
- Site of oxidation - liver.

Metabolism

- Phase II Reactions
- Hydrolysis by liver enzymes yields metabolites
 - 2-isopropyl-4methyl-6hydroxypyrimidine
 - diethyl phosphorothioic acid
 - diethyl phosphoric acid

Extrahepatic Metabolism

- Hydrolysis of Diazoxon in plasma₁
 - Kidney
- Hydrolysis₂
 - Acidic and alkaline conditions
 - Acidic and lack of water
 - tetraethyl dithio - and thiopyrophosphates

1. International Programme on Chemical Safety INCHEM Environmental Health Criteria 198 Diazinon.

2. Organophosphates. Tarek Ladaa, Gretchen Bielmyer, Kim-Lee Murphy. Clemson University, Environmental Organic Chemistry Spring 1998.

Metabolic Pathways

- Cleavage of the ester bond -
- Transformation of the P-S moiety -
- Oxidation of isopropyl substituent -
- Oxidation of the methyl substituent -
- Glutathione-mediated cleavage -

Excretion

- Diazinon is rapidly excreted from the body
- Rats - 50% of dose excreted in 12 h.
 - 69-80% in urine
 - 18 -25% in feces
 - 5% in expired air

Excretion

- Humans
- Primarily urinary
 - 59-95% is excreted within 24 hours
 - 95-98% is excreted within 7 days

Biomarker

- Urinary excretion of metabolites
 - 70% are metabolites
- 24 hour urine collections

Exposure Effects

- Acute
 - Inhalation
 - Skin
 - Ingestion
- Chronic

Acute Health Effects-Inhalation

- Convulsions
- Dizziness
- Labored breathing
- Nausea
- Unconsciousness
- Vomiting
- Pupillary constriction
- Muscle cramp
- Excessive salivation

Acute Health Effects - Skin

- Redness
- Pain
- Pupillary constriction

Acute Health Effects - Ingestion

- Abdominal cramps
- Diarrhea
- Labored breathing
- Nausea
- Unconsciousness
- Vomiting

Chronic Health Effects

- 10 mg/kg/day for swine
- 1000 mg/kg/day for rats
- The above levels showed enzyme inhibition in blood cells, blood plasma, and brain cells

Health Effects - CNS

- Respiratory depression
- Anxiety
- insomnia
- headache
- restlessness, tension
- mental confusion
- loss of concentration

Toxicological Profile for Diazinon. US
Department of Health and Human Services.
ATSDR.

Children's Health Effects

- Lack of Liver enzyme₁
 - PON1
- Seizures₂
- Pancreas₂

1. *Am. J. Hum. Genet.* 35:393-408.

2. Zwiner, R.J. and C.M. Ginsburg. 1988. Organophosphate and Carbamate Poisoning in Infants and Children. *Pediat.* 81:121-126

Controversial Adverse Effects

- Carcinogenicity
 - Brain Cancer ??₁
 - Non-Hodgkin's Lymphoma??₂

1. Davis, J.R. et al. 1993. Family Pesticide Use and Childhood Brain Cancer. *Arch. Environ. Contam. Toxicol.* 24:87-92.

2. Cantor, K.P. et al 1992. Pesticides and other agricultural risk factors for non-Hodgkin's lymphoma among men in Iowa and Minnesota. *Cancer Res.* 52:2447-2455

Controversial Adverse Effects

- Cholinergic Syndrome/Pancreatitis
 - Suicidal or accidental poisoning
 - Impurities such as TEPP

International Programme on Chemical Safety. INCHEM.
Environmental Health Criteria 198.

Controversial Adverse Effects

- Teratogenic
 - Chicken Eggs
 - Spinal and skeletal deformities
 - Hamsters, Rabbits
 - Dogs and Pigs

Controversial Adverse Effects

- Neuropsychiatric sequelae
 - Memory
 - Concentration
 - Mood

Regulatory

- Classified as a “Restricted Use” Pesticide for Agricultural Use
 - Class II or III pesticide₁
 - Avian and Aquatic Organism Toxicity
- No Restrictions on Use for Homeowners₂

1. US EPA Diazinon Revised Risk Assessment and agreements with Registrants. January 2001

2. ChemicalWATCH Diazinon Factsheet

Regulatory

- US EPA and registered users of diazinon reached an agreement on 12/5/2000 to phase out and eliminate certain uses by December 2002.¹
 - Indoor
 - Homeowner
 - Certain crops

1. EPA Questions & Answers Diazinon Revised Risk Assessment and Risk Mitigation Measures. December 5, 2000

Use Precautions

- Use gloves, long pants and shirts
- Water-in when using
- Keep kids and pets away for several hours
- Wash hands and clothes after application