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No. 72

AZINPHOS-ETHYL

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CLASSIFICATION:

Primary use: Insecticide
 Secondary use: Acaricide
 Chemical group: Organophosphorus compound

1.0 GENERAL INFORMATION

1.1 **COMMON NAME:** azinphos-ethyl (ISO, BSI).

1.1.1 **Identity**

IUPAC chemical name: S-(3,4-dihydro-4-oxobenzo[d]-[1,2,3]-triazin-3-ylmethyl) 0,0-diethyl phosphorodithioate

CAS name: O,O-diethyl S-[(4-oxo-1,2,3-benzotriazin-3(4H)-yl)methyl] phosphorodithioate

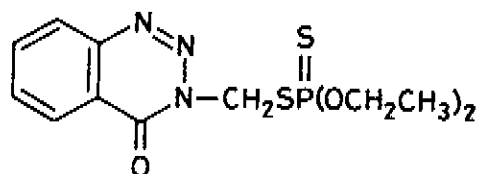
CAS registry number: 2642-71-9

RTECS number: TD8400000

Molecular formula: C₁₂H₁₆N₃O₃PS₂

Relative molecular mass: 345.4

Structural formula:



Synonyms & tradenames: Athyl-Gusathion^R; azinphosethyl; Azinos^R; Azinophos-aethyl^R; Azinphos-ethyl^R; Bay 16255; Bayer 16259; Benzotriazine derivative of ethyl dithiophosphate; Cotnion-ethyl^R; Crysthion^R; ENT 22,014; Ethyl-azinophos^R; Ethyl-Gusathion^R; Ethyl-Guthion; Gusation^R; Gusathion^R; Guthion (ethyl); R1513; triazotion.

1.2 **SYNOPSIS:** Azinphos-ethyl is a broad spectrum, non-cumulative and non-systemic organophosphorus insecticide/acaricide with good ovicidal properties and good contact and stomach action. It has excellent residual activity and is not phytotoxic. It is very toxic to mammals with a WHO hazard classification of a technical product in class IB, Highly hazardous.

1.3 **SELECTED PROPERTIES**

1.3.1 **Physical characteristics:** Azinphos-ethyl forms colourless (clear) crystals melting at 50 °C and boiling at 147 °C. It has a density of 1.284 and a refractive index of 1.5928. The technical material is 92% pure compound.

1.3.2 **Solubility:** The compound is virtually insoluble in water (4-5 mg per litre at 20 °C), it is soluble in most organic solvents except light petroleum and aliphatic hydrocarbons.

1.3.3 **Stability:** Azinphos-ethyl is thermally stable but is readily hydrolysed in alkaline media.

1.3.4 **Vapour pressure:** 0.32 mPa at 20 °C.

1.4 AGRICULTURE, HORTICULTURE AND FORESTRY

1.4.1 **Common formulations:** These include emulsifiable concentrates, 200 - 400 g a.i./L; wettable powders, 250-400 g a.i./kg; and, an ULV product, 500 g a.i./L.

1.4.2 **Pests controlled:** These include susceptible spider mites, aphids, caterpillars, potato bug, beetles, bollweevils, whiteflies, bollworms, thrips and other biting and sucking insects.

1.4.3 **Use pattern:** Azinphos-ethyl is no longer registered for use in many countries, but it is still widely used in some countries, especially on fruit and vegetable crops, cotton, pastures, coffee, cereals, potatoes, hops, grapes, citrus, rice, tobacco and other crops.

1.4.4 **Unintended effects:** Considered to be non-phytotoxic when used as recommended.

1.5 **PUBLIC HEALTH USE** - No recommended use.

1.6 **HOUSEHOLD USE:** No recommended use.

2.0 TOXICOLOGY AND RISKS

2.1 TOXICOLOGY - MAMMALS

2.1.1 **Absorption route:** Azinphos-ethyl is absorbed from the gastrointestinal tract, through the intact skin, and by inhalation of fine spray mist and dusts.

2.1.2 **Mode of action:** Azinphos-ethyl after conversion to the oxygen analogue is an inhibitor of acetylcholinesterase thereby causing impairment of nervous transmission.

2.1.3 **Excretion products:** After oral administration azinphos-ethyl was almost completely absorbed from the gastrointestinal tract of the rat. Following intravenous or oral administration of 0.1 - 6 mg/kg b.w. to rats, 60 - 65% of the compound was eliminated in urine and 20 - 40% was excreted in faeces irrespective of route of administration or dose level. Less than 0.1% of the compound when dosed intravenously or orally at 2 mg/kg, was eliminated with the exhaled air within 24 hours.

2.1.4 **Toxicity, single dose (technical product):**

Oral LD₅₀

Rat	12 mg/kg b.w.
Rat (F)	7.2 mg/kg b.w.
Rat (M)	15.2 mg/kg b.w.
Guinea-pig	17.0 mg/kg b.w.

Dermal LD₅₀

Rat	72-280 mg/kg b.w.
Rat (M)	545 mg/kg b.w. (24 hour exp.)
Rat (F)	402 mg/kg b.w. (24 hour exp.)

Intraperitoneal LD₅₀

Rat (M)	7.5-9.2 mg/kg b.w.
Rat (F)	4.4 mg/kg b.w.
Mouse	3.8-4.0 mg/kg b.w.

Inhalation LC₅₀

Rat	c0.15 mg/L (4 hours exposure)
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2.1.5 Toxicity, repeated dose:

Oral: Male rats given 1.0 mg/kg b.w. orally for 28 consecutive days showed no clinical signs of toxicity and no changes in body weight gain. Cholinesterase activity was depressed in erythrocytes by 50% after 2 days, 82% by three days and 90% by 28 days. Normal cholinesterase activity was re-established by 35 days after administration ceased.

Dermal: Male and female rabbits were treated for three weeks with 15 x 7 hour applications of 0.1 - 0.05 mg/kg b.w. The no-effect-level (NOEL) was 0.05 mg/kg b.w.

Inhalation: Male and female rats were exposed 15 times for 6 hours to 0, 0.3, 1.8 or 12.7 mg/m³ air over a three week period. The NOEL was 0.3 mg/m³ air.

Cumulation of compound: Groups of female rats were administered doses of 0.5, 1, 2, or 3 mg/kg b.w. intraperitoneally for 60 days. Only the two highest dosage levels caused a reduction in weight gain and an increased mortality. Azinphos-ethyl does not accumulate in body tissues, but a cumulation of effect was demonstrated at higher doses.

2.1.6 Dietary studies:

Short term: Groups of 15 male and female rats were fed azinphos-ethyl at 0, 1, 2, 4 and 8 mg/kg/diet for 90 days. There were no clinical signs of toxicity, no changes in blood chemistry and no increases in mortality in any of the treatment groups. After 30 days the erythrocyte cholinesterase activity was depressed in rats fed on a diet containing 4 mg/kg azinphos-ethyl. In a group of rats fed 8 mg/kg plasma cholinesterase activity was depressed and stabilized after one week, while the erythrocyte cholinesterase activity continued to fall for the first 30 days. Females were more sensitive than males. There were no treatment related gross or histological abnormalities found in the organs or tissues of the treated animals. 2 mg/kg of diet was accepted as the no-effect level.

In another experiment, groups of 12 male and female rats were fed diets containing 0, 5, 10 or 50 mg of azinphos-ethyl/kg/diet for 16 weeks. At 50 mg/kg/diet males showed a decrease in body weight but no clinical signs of toxicity. In this group cholinesterase activity was depressed in erythrocytes, serum and brain. At 10 mg/kg/diet only serum and erythrocyte cholinesterase activities were inhibited. Rats on the 5 mg/kg/diet showed only erythrocyte cholinesterase activity depression. No gross or histological abnormalities were observed in any of the treatment group animals.

In a 12 week study, groups of two male and female young dogs were fed 0, 0.25, 0.5, 1, 2, 3 and 10 mg of azinphos-ethyl/kg/diet. At dietary levels of 3 and 10 mg/kg the dogs exhibited clinical signs of poisoning after 6 and 1 weeks respectively. They were removed from these diets and their cholinesterase activity returned to normal after 3-4 weeks on normal diet. Cholinesterase activities were depressed in all other treatment groups, but they returned to normal in treated animals after 2-3 weeks on normal diet. Only in the group receiving 0.25 mg/kg of diet did the erythrocyte activity remain unchanged, and this was accepted as the no-effect-level.

Long term: Male and female Rhesus monkeys were dosed orally with azinphos-ethyl at 0, 0.02, 0.04 and 0.08 mg/kg b.w./day for 32 months. A NOEL of 0.02 mg/kg b.w. was obtained. At higher doses depression of plasma cholinesterase activity was observed.

In a two-year feeding study male and female dogs were fed azinphos-ethyl at 0, 0.1, 0.2, 2, 20, 30, 60 and 90 mg/kg/diet. A NOEL of 0.1 - 0.2 mg/kg/diet was obtained. At doses up to 30 mg/kg/diet only depression of cholinesterase activity in plasma and erythrocytes was observed.

In a two year feeding study in male and female rats, azinphos-ethyl was fed at 0, 2, 8 and 32 mg/kg/diet. No carcinogenic effects were observed up to and including 32 mg/kg/diet.

In a two year feeding study in male and female mice, azinphos-ethyl was fed at 0, 0.5, 1.4, 4.0 and 11.3 mg/kg/diet. No carcinogenic effects were observed up to and including 11.3 mg/kg/diet.

2.1.7 **Supplementary studies of toxicity:**

Carcinogenicity: In long term studies in mice and rats carcinogenicity was not demonstrated at 11.3 and 32 mg/kg/diet respectively.

Teratogenicity: Studies in rats and rabbits did not show any embryotoxic or teratogenic effects.

Mutagenicity: Azinphos-ethyl was not mutagenic in the Salmonella/Microsome Test (Ames-test), micronucleus-test nor in the dominant-lethal test. It has no DNA-damaging properties.

Neurotoxicity: No ataxia was observed in hens five weeks after a single administration of 10 or 25 mg/kg b.w. given orally. There were no clinical or histological signs in hens fed 75, 150, 300 or 600 mg/kg/diet for 30 days during the treatment period or at 4 weeks after cessation of treatment.

2.1.8 **Modification of toxicity:** No potentiation occurred when azinphos-ethyl was used with a variety of pesticides including parathion, methyl parathion, malathion, trithion, phosdrin, carbaryl, diazinon, azinphos-methyl, coumaphos, chlorobenzilate or fenclorphos. A twofold potentiation occurred when used with ethion.

2.2 TOXICOLOGY - MAN

2.2.1 **Absorption route:** Azinphos-ethyl may be absorbed from the gastrointestinal tract, through the intact skin, and by inhalation of fine spray mist and dusts.

2.2.2 **Dangerous doses:** No information available.

2.2.3 **Observations on occupationally exposed workers:** No information available.

2.2.4 **Observations on exposure of the general population:** No information available.

2.2.5 **Observations on volunteers:** Six volunteers received 0.01 or 0.02 mg azinphos-ethyl technical product per day in gelatine capsules for 28 consecutive days. The volunteers tolerated the treatment without any effect.

2.2.6 **Reported mishaps:** None.

2.3 TOXICITY TO NON-MAMMALIAN SPECIES

2.3.1 Fish:

LC₅₀ (96 h)

Goldfish	0.1 mg/L
Guppies	0.01 - 0.1 mg/L

2.3.2 Birds:

<u>Oral LD₅₀</u>	Chicks	34 mg/kg b.w.
<u>Oral LD₅₀</u>	Quail (F)	20 mg/kg b.w.

2.3.3 Other species: Toxic to bees.

3.0 FOR REGULATORY AUTHORITIES - RECOMMENDATIONS OF COMPOUND

3.1 RECOMMENDED RESTRICTIONS ON AVAILABILITY

[For definition of categories see the 'Introduction to Data Sheets'].

Liquid formulation of 6.0% and over, Category 2

Other liquid formulations, Category 3

Solid formulations of 25% and over, Category 2

Other solid formulations, Category 3

Azinphos ethyl has been banned or severely restricted in several countries.

3.2 TRANSPORTATION AND STORAGE

All formulations: Should be transported in clearly labelled impermeable containers and stored under lock and key, secure from access by unauthorized persons and children. No food or drink should be stored in the same compartment.

3.3 HANDLING

All formulations: Full protective clothing (see 4.3 part 4) should be used by those handling the compound. Adequate washing facilities should be available at all times during handling and should be close to the site of handling. Eating, drinking and smoking should be prohibited during handling and before washing after handling.

3.4 DISPOSAL AND/OR DECONTAMINATION OF CONTAINERS

All formulations: Whenever possible containers should be either returned to the supplier, or safely disposed of in an approved manner. Care must be taken to avoid subsequent contamination of water sources. Decontamination of containers in order to use them for other purposes should not be permitted.

3.5 SELECTION, TRAINING AND MEDICAL SUPERVISION OF WORKERS

All formulations: Pre-employment and periodic medical examination of workers is necessary and should include blood cholinesterase activity tests. Special account should be taken of the workers' ability to comprehend and follow instructions. Training of workers in techniques to avoid contact essential.

3.6 ADDITIONAL REGULATIONS RECOMMENDED IF DISTRIBUTED BY AIRCRAFT

All formulations: Pilots and loaders should have special training in application methods and early symptoms of poisoning, and must wear a suitable respirator. Use of flagmen not recommended. Flagmen, if used, should wear protective clothing and be located well away from the dropping zone.

3.7 LABELLING

DANGER - POISON
(Skull and cross bones insignia)

Azinphos-ethyl is an organophosphorus compound which inhibits cholinesterase enzymes. It is of very high toxicity. Contact with the skin, inhalation of dust or spray, or swallowing may be fatal. Wear protective gloves, clean protective clothing, and a respirator of the organic-vapour type when handling this material. Bathe immediately after work. Ensure that containers are stored under lock and key. Empty containers must be disposed of in such a way as to prevent all possibility of accidental contact with them. Keep the material out of reach of children and well away from foodstuffs, animal feed and their containers. In case of contact, immediately remove contaminated clothing and wash the skin thoroughly with soap and water; for eyes, flush with water for 15 minutes. If poisoning occurs, call a physician. Atropine sulphate is a pharmacological antidote. Artificial respiration may be needed.

3.8 RESIDUES IN FOOD

3.8.1 **Maximum residue levels:** The Joint FAO/WHO Meeting on Pesticide Residues has not recommended maximum residue levels neither has it established an Acceptable Daily Intake (ADI).

4.0 PREVENTION OF POISONING IN MAN AND EMERGENCY AID

4.1 PRECAUTIONS IN USE

4.1.1 **General:** Azinphos-ethyl is an organophosphorus pesticide of high toxicity. It is readily absorbed through the intact skin, from the gastrointestinal tract and by inhalation. Repeated exposure may have a cumulative effect on cholinesterase activity. Most formulations should be handled by trained personnel only. Its use is severely restricted in several countries.

4.1.2 **Manufacture and formulation:** Closed systems and forced ventilation may be required to reduce as much as possible the exposure of workers to the chemical.

4.1.3 **Mixers and applicators:** When opening the container and when mixing, protective impermeable boots, clean overalls, neoprene gloves and respirator should be worn. Mixing, if not mechanical, should always be carried out with a paddle of appropriate length. When spraying tall crops or during aerial application, a face mask should be worn, as well as an impermeable hood, clothing, boots, and neoprene gloves. The applicator should avoid working in spray mist and avoid contact with the mouth. Particular care is needed when equipment is being washed after use. All protective clothing should be washed immediately after use, including the insides of gloves. Splashes must be washed immediately from the skin, or eyes with large quantities of water. Before eating, drinking,

or smoking, hands and other exposed skin should be washed.

4.1.4 **Other associated workers:** Persons exposed to the compound and associated with its application should wear protective clothing and observe the precautions described above in 4.1.3. under "Mixers and Applicators".

4.1.5 **Other populations likely to be affected:** Subject to 4.2 below, persons other than applicators are not likely to be exposed to hazardous amounts of azinphos-ethyl.

4.2 ENTRY OF PERSONS INTO TREATED AREAS

Unprotected persons should be kept out of treated crops for four days.

4.3 SAFE DISPOSAL OF CONTAINERS AND SPILLAGE

Residues in containers should be kept to a minimum and emptied in a diluted form into a deep dry pit (depth over 0.5 m), taking care to avoid contamination of ground waters. The empty containers should be disposed of in an approved manner. If not returned to the producer, re-use of containers should not be permitted for any purpose.

Spillage of liquid azinphos-ethyl formulations should be contained with absorbent material. This material or spillage of dry residues should be collected and burned or buried as described above. Residues should be removed by scrubbing with detergent and then rinsing with large quantities of water.

Impermeable gauntlets and protective overalls should be used for all handling procedures.

4.4 EMERGENCY AID

4.4.1 **Early symptoms of poisoning:** Early symptoms of poisoning may include excessive sweating, headache, weakness, giddiness, nausea, vomiting, increased salivation, stomach pains, diarrhoea, blurred vision, slurred speech and muscle twitching. Later there may be shortness of breath, convulsions and coma.

4.4.2 **Treatment before person is seen by physician, if these symptoms appear following exposure:** The person should stop work immediately, remove contaminated clothing and wash contaminated skin with soap and water and flush the area with large quantities of water. If swallowed, and if the person is conscious, vomiting should be induced. Artificial respiration should be given when necessary bearing in mind that if mouth-to-mouth resuscitation is used, vomit may contain toxic amounts of pesticide. Call a physician immediately or organize immediate transport to a physician or hospital.

5.0 FOR MEDICAL AND LABORATORY PERSONNEL

5.1 MEDICAL DIAGNOSIS AND TREATMENT IN CASES OF POISONING

5.1.1 **General information:** Azinphos-ethyl is an organophosphorus pesticide of high mammalian toxicity. It is readily absorbed from the gastrointestinal tract, through the intact skin and by inhalation. It is converted *in vivo* to the oxygen analogue which inhibits cholinesterases. It does not accumulate in body tissues.

5.1.2 **Symptoms and signs:** Poisoning is due to excessive stimulation by acetylcholine of all cholinergic innervation. Thus initial symptoms and signs of poisoning may include excessive sweating and

salivation, headache, weakness, miosis, dyspnoea, nausea, vomiting and diarrhoea, blurred vision and muscle fasciculations. More severe poisoning leads to respiratory failure due to a combination of bronchorrhea, bronchoconstriction (muscarinic effects), paralysis of respiratory muscles (nicotinic effects) and respiratory centre paralysis (central effects). The latter include, in severe cases, coma and convulsions.

5.1.3 **Laboratory:** Diagnosis is confirmed by finding inhibition of erythrocyte or whole blood acetylcholinesterase. However, treatment must start immediately and cannot be delayed until confirmation from the laboratory. This test cannot be used to control the effectiveness of the treatment nor is it of help for prognosis.

5.1.4 **Treatment:** Patients with respiratory failure must be given artificial ventilation, then diazepam (10 mg intravenously) to control convulsions. When vital functions are controlled, atropine sulfate is given (initial dose is usually 2 mg intravenously) followed by pralidoxime (1000 mg) or toxogonin (250 mg) by slow intravenous infusion.

If the pesticide has been ingested, gastric lavage might be needed or vomiting induced. Protection of airways (intubation) is required if inducing vomiting in unconscious patients.

For skin contact, the skin should be washed with soap and large amounts of water. Precautions should be taken by medical personnel during these decontamination procedures to prevent their own overexposure. If the compound has entered the eyes, they should be washed with large quantities of saline or water.

Atropine treatment might be required for several days after poisoning. Only clinical assessment determines atropine dose, i.e. evident signs of atropinization (dry mouth, tachycardia, vasodilation, mydriasis) should be maintained. Total amounts of atropine given to these patients might be extremely high because they are tolerant to the effects of atropine.

Caution should be taken when doses of atropine are reduced because reappearance of symptoms might occur, due to redistribution processes in the body. Cholinesterase reactivators such as pralidoxime and toxogonin are usually only effective during the first few days of poisoning, unless the slow disposal of the chemical within the body suggests that some acetylcholinesterase is newly inhibited. Indications for the continuing use of reactivators might derive from measurements of erythrocyte cholinesterase before and after treatment with such reactivators.

5.1.5 **Prognosis:** Unless brain hypoxia has occurred, full recovery is expected.

5.1.6 **References to previously reported cases:** No information available.

5.2 SURVEILLANCE TESTS

Any fall in erythrocyte cholinesterase activity to 70% of the pre-exposure values, requires an investigation of working methods and hygiene and more frequent cholinesterase tests. Symptoms of poisoning may appear when the erythrocyte cholinesterase activity is less than 35% of normal. If erythrocyte cholinesterase activity is less than 50% of normal, the worker must be suspended from all contact with organophosphorus or carbamate pesticides until the level rises above 70% of pre-exposure value. Pseudocholinesterase activity in the plasma can fall to very low levels without evidence of symptoms. This only indicates undesirable exposure.

5.3 LABORATORY METHODS

5.3.1 Detection and assay of compound:

Analysis of the product is by colorimetric measurement of the complex of the liberated O,O-diethylphosphorodithioate (following alkaline hydrolysis) and copper (II) ions, extracted and measured at 420 nm. Residues are measured by GLC. The following are some basic references:

CIPAC Handbook, 1070, 1, 18.

Curini M et al (1980), *Talanta* 27(1): p. 45.

Ferreira JR, & Fernandes A (1980), *J Assoc Off Anal Chem* 63(3):p. 517.

Meagher WR et al (1960), *J Agric Food Chem* 8: p. 282.

Mestres R et al (1977), *Anal Falsif Expert Chim*, 70(751): p. 177.

Miles JRW (1964), *J Assoc Off Agric Chem*, 47: p. 882.

Stan HJ et al (1977), *Fresentius Z Anal Chem*, 287 (4-5): p. 271.

Stein UB & Pitman KA (1976), *J Assoc Off Anal Chem* 59(5): p. 1094.

5.3.2 Other tests in case of poisoning: Activity of cholinesterase in the blood provide the most useful diagnosis of poisoning.

Ellman GL et al (1961), A new and rapid colorimetric determination of acetylcholinesterase activity, *Biochem pharmacol* 7: 88-95.

Wilhelm K & Reiner E (1973), *Bull Wld Health Org*, 48: 235-238.

Urine metabolites such as dialkylphosphates and dialkylthiophosphates may also be determined in order to give an indication of exposure, particularly when exposure is so low as not to inhibit cholinesterase. For methods see section 5.3.1, Detection and Assay.

REFERENCES

1. The Pesticide Manual, A World Compendium (9th edition 1991), Worthing CR & Hance RJ, eds., British Crop Protection Council, 20 Bridport Road, Thornton Heath, CR4 7QG, United Kingdom.
2. WHO (1974) 1973 Evaluations of some pesticide residues in food. WHO Pesticide Residues Series, No. 3, Geneva, World Health Organization.
3. WHO (1986), Environmental Health Criteria 63; Organophosphorus Insecticides. A General Introduction; Geneva, World Health Organization.
4. WHO (1994) The WHO Recommended Classification of Pesticides by Hazard and Guidelines to Classification 1994-1995, Geneva, World Health Organization mimeographed document (WHO/PCS/94.2).

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