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FOOD AND AGRICULTURE ORGANIZATION
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WHO/FAO DATA SHEET ON PESTICIDES

No. 79

AMITROLE

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CLASSIFICATION:

Primary use: Herbicide

Secondary use: Plant growth regulator

Chemical group: Triazole

1.0 GENERAL INFORMATION

1.1 **COMMON NAME:** Amitrole (E-ISO, F-ISO).

1.1.1 **Identity**

IUPAC chemical name: 1-H-1,2,4-triazol-3-ylamine,
(formerly 1-H-3-amino-1,2,4-triazole)

CAS chemical name: 1-H-1,2,4-triazol-3-amine,
(formerly 3-amono-s-triazole).

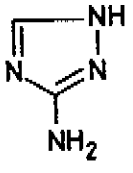
CAS registry number: 61-82-5

RTECS registry number: XZ 3850000

Chemical formula: $C_2H_4N_4$

Relative molecular mass: 84.08

Structural formula:



1.1.2 **Synonyms:** Aminotriazole; Triazolamine; ATA; Amitril; Amitrol; Amizol^R; Cytrol^R; Domatol^R; Elmasil^R; ENT 25455; Vorox^R; Weedar^R; Weedazol^R; 3A-T.

1.2 **SYNOPSIS:** Amitrole is a non-selective foliage-absorbed herbicide that inhibits chlorophyll formation and regrowth from buds. The acute mammalian toxicity is low. Repeated exposure induces goitre and repeated high doses resulted in thyroid tumours in rats. Its use is restricted to non-food and non-feed stuff crops.

1.3 **SELECTED PROPERTIES:**

1.3.1 **Physical characteristics:** Pure amitrole is a colourless crystalline powder with a bitter taste. It is a strong chelating agent with a melting point of 153-159 °C and a specific gravity of 1.138 at 20 °C. Corrosive to iron, aluminium, copper and copper alloys.

1.3.2 **Solubility:** 300 g/L water at 20 °C; 260 g/kg ethanol at 75 °C; moderately soluble in methylene chloride, chloroform; insoluble in acetone, diethyl ether and hydrocarbons.

1.3.3 Stability: Amitrole is thermally stable. It is also stable in neutral or alkaline media, but it forms salts. It breaks down in ultraviolet light. Forms chelates with metals, and is thus corrosive to aluminium, copper and iron.

1.3.4 Vapour pressure: Negligible (55 nPa, at 20 °C).

1.4 AGRICULTURE, HORTICULTURE AND FORESTRY

1.4.1 Common formulations: Available as water soluble powder (50-95%) as well as liquids, water soluble concentrate and aerosol sprays. Often used with an activator, ammonium thiocyanate and with other herbicides like simazine.

1.4.2 Pests controlled: Used against perennial broadleaf weeds, annual grasses such as bermuda grass, Canada thistle, cattails, poison oak, poison ivy, quackgrass. Particularly effective in the control of water hyacinth.

1.4.3 Use pattern: Foliar application to non-feed and non-food crop locations, such as industrial land. Used around established fruit trees after harvest, for spot application to control Tussock grass. Applied while weeds in vigorous growth.

1.4.4 Unintended effects: Amitrole has high potential mobility in soil. Degradation of amitrole in soil is usually fairly rapid but variable with soil type and temperature. Therefore, its retention in moist soils by absorption makes high leaching potential very unlikely to be realised in practice. The few reports of effects on non-target vegetation support this view.

1.5 PUBLIC HEALTH USE: No recommended usage reported.

1.6 HOUSEHOLD USE:

1.6.1 Common formulations: Technical grade solutions (200 g/L) and as water soluble powder (10%), and in combination with simazine and/or other herbicides.

1.6.2 Pests controlled: Amitrole has a wide spectrum of activity against annual and perennial broad leaf and grass type weeds.

1.6.3 Use pattern: Foliar application, but amitrole is also translocated to the roots to kill deep rooted perennials. May take up to three weeks for full effect. Do not plant vegetable crops within eight months of autumn spraying of garden plots.

2.0 TOXICOLOGY AND RISKS

2.1 TOXICOLOGY - MAMMALS

2.1.1 Absorption route: Amitrole is absorbed from the gastro-intestinal tract, by inhalation of spray-mists and to a lesser extent through intact skin.

2.1.2 Mode of action: Amitrole has been shown to be goitrogenic in several animal species. Biochemical mechanisms include reduced thyroid uptake of iodine and inhibition of peroxidase activity of the thyroid. The resulting reduction of thyroid hormones induces a hypothalamus mediated TSH stimulation on the thyroid itself. This prolonged stimulation is thought to be responsible for the induction of thyroid cancers in animals treated with high doses of amitrole.

2.1.3 **Excretion products**: Little metabolic transformation of amitrole occurs in mammals and it is excreted in the urine mainly unchanged within a few hours. Two urinary metabolites have been identified in rats, i.e. 3-amino-5-mercapto-1,2,4-triazole and 3-amino-1,2,4-triazolyl-(5)-mercapturic acid.

2.1.4 **Toxicity, single dose**:

Oral LD_{50}			
	Rat	5 000	mg/kg b.w.
	Rat	25 000	mg/kg b.w.
	Mouse	11 000 - 14 700	mg/kg b.w.
	Rabbit	>2 150	mg/kg b.w.
Intraperitoneal LD_{50}			
	Mouse	>4 000	mg/kg b.w.
Intravenous LD_{50}			
	Mouse	5 000	mg/kg b.w.
	Rat	>2 500	mg/kg b.w.
Dermal LD_{50} (24h)			
	Rabbit	>10 000	mg/kg b.w.
Inhalation LC_{50} (4h)			
	Rat	>439	mg/L

Signs of toxicity include dyspnoea, ataxia and diarrhoea with vomiting. Coma and death appeared to be associated with respiratory insufficiency. Gastrointestinal irritation and haemorrhage were the only macroscopic findings. Single doses of amitrole (10 mg/kg s.c. to rats) were shown to decrease iodine uptake and thyroid hormone levels.

Dermal irritancy: Cutaneous application of 10 000 mg/kg b.w. to rabbits or 2500 mg/kg b.w. to rats produced a temporary mild erythema.

Ocular irritancy: A mild irritation of 28 - 48 hour duration was observed following application of 3 mg to the conjunctival sac of rabbits. No permanent damage was observed.

2.1.5 **Toxicity, repeated doses**:

Oral: Gavage administration of 100, 200 or 400 mg/kg b.w./day, five days/week for four weeks, to rats resulted in a reduced growth rate, reduced iodine content of the thyroid and an increased relative thyroid weight.

Male and female beagle dogs showed no adverse effects in growth, behaviour, haematology, histopathology (including thyroid), or in liver and kidney function tests following exposure to gelatin capsule doses of up to 12.5 mg/kg b.w./day, six days/week for 52 weeks.

Intraperitoneal: Increased thyroid weights (300-400%) were noted in male and female rats receiving 21 intraperitoneal injections of 1000 mg/kg b.w. over a period of 45 days. No effect on growth or food consumption was observed. Liver catalase activity was reduced more than 90% in rats receiving 1000 mg/kg b.w, 14 times over a period of 30 days.

Amitrole (500 or 1000 mg/kg day), five days per week for five weeks to chicks increased relative thyroid weight from day 10 onward. Histopathology indicated hyperplasia and disappearance of the colloid. The reversibility of the lesions was shown in birds treated only for 17 days and allowed to recover for two weeks after the end of treatment.

Inhalation: Exposure of rabbits, guinea pigs, rats or mice to 4 mg/L air, 2 hour/day for 10 weeks caused a reduction in body weight in rabbits and guinea pigs, and a slight reduction in body weight in rats and mice. Slight anaemia, lymphocytopenia and neutropenia were observed in rabbits.

Rats were exposed to amitrole (0, 0.1, 0.32, 0.99 or 4.05 mg/L for five hours/day, 5 times per week for 4 weeks). Blood levels of thyroid hormones were found to be decreased and thyroid hyperplasia was noted at all but the lowest dose level.

2.1.6 **Dietary studies**:

Short term: Numerous investigations have shown that amitrole administered in drinking water or in the diet, may cause decreased body weight gain, increased thyroid weight related with changes of thyroid function in rats.

Amitrole was given to rats at a dose of 1000 mg/kg/diet for 83 days. Thyroid weight and iodine content of thyroid were increased, starting 3 days after the beginning of treatment. Amitrole was given to rats (0, 30, 100 or 300 mg/kg/diet) for 28 days followed by a recovery period of 28 days. At dose levels of 100 mg/kg/diet or more, amitrole rapidly suppressed T_3 and T_4 hormone levels and maintained the depressed levels during treatment. Both T_3 and T_4 levels returned to control values within three weeks following withdrawal of amitrole from the diet. The NOEL was 30 mg/kg/diet.

Groups of rats were administered amitrole in the diet at dose levels of 0, 2, 10 and 50 mg/kg/diet for 13 weeks. The only significant findings were the histopathological changes found in the 10 and 50 mg/kg groups. The number of blood vessels per thyroid section was found to be a good indication of histopathological changes in the thyroid. The NOEL was 2 mg/kg/diet.

In a series of experiments in rats giving amitrole at various dose levels (0 through 200 mg/kg/diet for 6 to 13 weeks) it was found that measurement of iodine uptake is a sensitive method for assessing the effects of amitrole on the thyroid. The NOEL was 2 mg/kg/diet.

Long term: Reversible thyroid hyperplasia has been reported with long term feeding of mice with amitrole at levels of 1000 mg/kg/diet. In another study in mice (0, 1, 10, 100 mg/kg/diet), infective thyroid weights were elevated at the highest dose level.

Amitrole was given to rats (0, 10, 50 or 100 mg/kg/diet for two years) and found to cause thyroid hyperplasia after 68 weeks of treatment. The NOEL was 10 mg/kg/diet. In another study in rats (0, 1, 10 and 100 mg/kg/diet) similar findings were reported including dysplasia of the thyroid and reduced iodine uptake. The NOEL was 10 mg/kg/diet.

Authors who have detailed the time-course of the response of the thyroid to amitrole treatment have shown that after a short lag phase of a few days there is a rapid rise in TSH that is paralleled by thyroid hypertrophy and hyperplasia. These effects peak and plateau after 3-4 months and thereafter remain relatively stable despite further exposure. A number of studies have shown that the goitrogenic action of amitrole is reversible on withdrawal of the herbicide exposure.

2.1.7 **Supplementary studies of toxicity**:

Carcinogenicity: In a mouse long-term study of over 100 chemicals, amitrole was used as a positive control compound at the maximum tolerated dose level (1000 mg/kg b.w. by gavage from one to four weeks of age, then 2192 mg/kg/diet for life). The majority of male and female mice of two strains developed carcinoma of the thyroid, and hepatomas. This dosage regimen reduced longevity. Another study in mice confirmed a high incidence of hepatocellular carcinomas and hepatomas following long term exposure to amitrole at the highest dose.

In a study in rats (0, 10, 50 and 100 mg/kg/diet) showed an increased incidence of thyroid tumours at the higher doses only.

In a study in rats amitrole was given in the drinking water (0.1% corresponding to 1000 mg/kg/diet) for 18-20 months. All animals developed follicular adenomas and some animals developed follicular carcinomas as well. In another similar experiment (same dose level) the latency for developing thyroid tumors was estimated to be one year.

Teratogenicity: No malformations were observed in mice foetuses removed on day 18. There was a marked decrease in body weight gain in dams receiving over 1000 mg/L in drinking water from days 6 to 18. Maternal body weight was reduced at and above 1000 mg/L and the foetuses of these mice were small and underdeveloped.

No teratogenic effects have been detected in rats given up to 1000 mg/kg b.w. day on days 6 to 15 gestation.

Reproduction: No effects on reproduction were observed in a multi-genarian study where rats were fed amitrole at dietary levels of 0, 25 or 100 mg/kg/diet for 61 and 173 days before mating to produce the F1a and F1b generation respectively. Hyperplasia of the thyroid was observed in all animals at the 100 mg dose but not at the 25 mg dose.

Mutagenicity: Amitrole was not mutagenic to the repair deficient strains of *Escherichia coli* nor to several strains of *Salmonella typhimurium*, with or without metabolic activation. Weak mutagenic activity was observed with *Streptomyces coelicolor*. No evidence of chromosomal damage was observed following *in vitro* incubation of human leucocytes with 0.2 - 1% (w/v) amitrole. Concentrations over 0.2% were cytotoxic, inhibiting lymphoblast transformation.

Male and female *Drosophila melanogaster* reared on 10 mg amitrole/kg media showed no evidence of amitrole induced sex-chromosome non-disjunction or sex-linked dominant lethal mutations.

Other: The inhibition of many haem containing enzymes has been demonstrated *in vivo* and *in vitro*. Amitrole inhibits thyroid, liver, kidney, eye and blood catalases and the incorporation of both ^{59}Fe and ^{14}C-aminolevulinic acid into haem.

2.2 TOXICOLOGY - MAN

2.2.1 **Absorption**: Amitrole is absorbed from the gastrointestinal tract. It may be absorbed by inhalation of spray mists and minimally through intact skin.

2.2.2 **Dangerous doses**:

Single: The intentional ingestion of 20 mg/kg amitrole by a female subject did not cause symptoms of poisoning.

Repeated: No published information available.

2.2.3 **Observations in occupationally exposed workers**: A single case report describes the development of a chemical pneumonitis after one exposure to an amitrole spray containing 19% aminotriazole, 17% ammonium thiocyanate, less than 1% sodium diethylsulfosuccinate and less than 1% ethylene oxide.

At an estimated dermal exposure of 340 mg/day/man over a 10 day spraying operation no thyroid dysfunctions were detected.

Prolonged exposure for up to 16 years to unknown levels of amitrole during its production and packaging did not cause thyroid disfunction.

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

2.2.5 **Observations on volunteers**: A single oral dose of 100 mg of amitrole inhibited ^{131}I intake of the thyroid for 24 hours in healthy and hyperthyrotid individuals. A dose of 10 mg produced only slight effects.

Amitrole had no irritant effect in a 4 - 8 hour exposure dermal patch test, and had only slight irritancy after 24 hours exposure.

2.2.6 **Reported mishaps**: In a suicide attempt, a 37-year old woman ingested a formulation of 30% amitrole and 56% diuron. The amitrole dose was estimated to be 20 mg/kg b.w. and no signs of intoxication were observed. Unchanged amitrole was excreted in the urine within a few hours at a concentration of 1 g/L.

2.3 TOXICITY TO NON-MAMMALIAN SPECIES

2.3.1 **Birds**:

Oral LD_{50}

Coturnix quail	>316 mg/kg b.w.

Dietary LC_{50} (5 days)

Japanese quail	>5000 mg/kg diet
Ring-necked pheasant	>5000 mg/kg diet
Mallard duck	>5000 mg/kg diet

2.3.2 **Other species**: *Drosophila melanogaster* (larvae) LC_{50} 40 mg/kg diet. prolongation of development time occurred in this species at doses above 10 mg/kg diet. No mutagenic effect was seen.

3.0 FOR REGULATORY AUTHORITIES - RECOMMENDATIONS ON REGULATION OF COMPOUND

3.1 RECOMMENDED RESTRICTIONS ON AVAILABILITY

Risks associated with dietary exposure led to the cancellation of all food and feed uses of amitrole in 1971 in the United States of America. For definition of categories see "Introduction to Data Sheets".

All liquid formulations over 25%, Category 4.

All other liquid formulations, all solid formulations, Category 5.

3.2 TRANSPORT AND STORAGE

Formulations in Category 4: Should be transported in clearly labelled, rigid and leakproof containers, kept out of reach of children, and away from food and drink.
Storage should be under lock and key and secure from access by children and other unauthorized persons.

Formulations in Category 5: Should be transported and stored in clearly labelled, leakproof containers, out of reach of children, away from food and drink.

3.3 HANDLING

Formulations in Category 4: Protective clothing should be used by all persons handling the compound. Adequate washing facilities should be available at all times during the handling and they should be close to the site of handling. Eating, drinking and smoking should be prohibited during handling and before washing of hands and face after handling.

Formulations in Category 5: No facilities other than those needed for the handling of any chemical are required.

3.4 DISPOSAL AND/OR DECONTAMINATION OF CONTAINERS

All formulations: Containers may be decontaminated (for method see Section 4.3). Decontamination procedures must be especially thorough to avoid subsequent contamination of food and feed crops and decontaminated containers should not be used for transportation or storage of food or drink. Discarded containers that are not decontaminated should be burned or crushed and buried in a deep (more than 0.5 m) dry pit. Care must be taken to avoid subsequent contamination of water sources.

3.5 SELECTION, TRAINING AND MEDICAL SUPERVISION OF WORKERS

Formulations in Categories 4 and 5: Special account should be taken of the workers' ability to comprehend and follow instructions. Training of workers in techniques to avoid contact is essential. Pre-employment and periodic medical examinations are required, including a check-up on thyroid function.

3.6 ADDITIONAL REGULATIONS RECOMMENDED IF DISTRIBUTED BY AIRCRAFT

Amitrole is not usually recommended for distribution by aircraft.

3.7 LABELLING

Formulations in Category 4 - Minimum cautionary statement:

Amitrole is a triazole herbicide. Avoid ingestion and inhalation of amitrole. Avoid skin contact; wear protective clothing and impermeable gloves when handling the material. Wash thoroughly with soap and water after using the product. Keep the material out of reach of children and well away from food stuffs, animal feed and food containers. If poisoning occurs, call a physician. There are no specific antidotes.

Formulations in Category 5 - Minimum cautionary statement: This formulation contains amitrole, it may be poisonous if swallowed. Keep the material out of reach of children and well away from food stuffs, animal feed and food containers.

3.8 RESIDUES IN FOOD

As it is recommended only for non-edible crops, no MRLs are recommended by FAO/WHO Joint FAO/WHO Meeting on Pesticide Residues (JMPR). In 1993 the JMPR established a Temporary Acceptable Daily Intake (TADI) of 0-0.0005 mg/kg b.w.

4.0 PREVENTION OF POISONING IN MAN AND EMERGENCY AID

4.1 PRECAUTIONS IN USE

4.1.1 **General**: Amitrole is a triazole herbicide of low acute mammalian toxicity. It is absorbed from the gastrointestinal tract and may also be absorbed through intact skin or by inhalation of mist during spraying. Due to the goitrogenic effect and carcinogenic action in laboratory tests, use of amitrole in the United States of America has been restricted to non-edible crops or non-crop land.

4.1.2 **Manufacture and formulation - TLV**: 0.2 mg/m^3. Closed systems and forced ventilation are 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, 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 a face mask should be worn, as well as an impermeable hat, clothing, boots, and 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 amitrole 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**: With correct use in agriculture, and in the home gardens, the general population should not be exposed to hazardous amounts of amitrole.

4.2 ENTRY OF PERSONS INTO TREATED AREAS

Unprotected persons may enter treated area once application has dried.

4.3 DECONTAMINATION OF SPILLAGE AND CONTAINERS

Residues in containers should be emptied in diluted form into a dry deep pit (more than 0.5 m), taking care to avoid contamination of groundwaters. Empty containers may be decontaminated by filling them completely with water and by allowing them to stand for 24 hours before emptying. The procedure should be repeated three times. Impermeable gauntlets should be worn during the work and an adequate soakage pit should be provided for the rinsings. Decontaminated containers should not be used for transportation and storage of food or drink. Spillage of amitrole and its formulations should be removed by washing with a water and detergent solution and then rinsing with large quantities of water.

4.4 EMERGENCY AID

4.4.1 Early symptoms of poisoning: Not known.

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 water, and soap if available, and flush with large quantities of water. Vomiting may be induced if a large dose has been ingested provided that the person is conscious.

5.0 FOR MEDICAL AND LABORATORY PERSONNEL

5.1 MEDICAL DIAGNOSIS AND TREATMENT IN CASES OF POISONING

5.1.1 General information: Amitrole is a triazole herbicide of low acute mammalian toxicity which may be absorbed from the gastrointestinal tract, through the intact skin, and by inhalation of aerosols or mists during spray application. Chronic high exposure may cause changes in the thyroid function.

5.1.2 Symptoms and signs: Unknown.

5.1.3 Laboratory: Urinary levels of amitrole could be used as a measure of exposure.

5.1.4 Treatment: Symptomatic.

5.1.5 Prognosis: Unknown.

5.1.6 References to previously reported cases:

Geldmacher-V. Mallinckrodt M, Schmidt HP (1970), Arch Toxikol 27: 13-18.

PIMS (1978) Pesticide Incident Monitoring Service. Summary of reported incidents involving Amitrole. No. 114. Office of Pesticide Programs, USEPA.

5.2 SURVEILLANCE TESTS

Unknown.

5.3 LABORATORY METHODS

(References only are given.)

5.3.1 Detection and assay of compound:

Agrawal BBL, Margoliash E (1970), A spectrophotometric method for the determination of aminotriazole and other aromatic amines. Anal Biochem **34**: 505-516.

Demint RJ, Frank PA, Comes RD (1970), Amitrole residues and rate of dissipation in irrigation water. Weed Sci **18**, 439-442.

Storherr RW, Burke J (1961), Determination of 3-amino-1,2,4-triazole in crops. J Assoc Off Anal Chem **44**: 196-199.

5.3.2 Other tests in case of poisoning: None.

REFERENCES

1. WHO (1994), Environmental Health Criteria 158; Amitrole; Geneva, World Health Organization.

2. WHO (1994), Health and Safety Guide 85; Amitrole; Geneva, World Health Organization.

3. FAO/WHO (1978), Pesticide Residues in Food: 1977 evaluations. FAO Plant Production and Protection Paper 10 Sup, 1978.

4. The Pesticide Manual, A World Compendium (9th edition 1991), Worthing, C.R. and Hance, eds., British Crop Protection Council, 20 Bridport Road, Thornton Heath, CR4 7QG, United Kingdom.

5. IARC (1986), IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans; Some Halogenated Hydrocarbons and Pesticide Exposures, Volume 41, Lyon, IARC.

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