NTERNATIONAL PROGRAMME ON CHEMICAL SAFETY

Health and Safety Guide No. 85

AMITROLE HEALTH AND SAFETY GUIDE



UNITED NATIONS ENVIRONMENT PROGRAMME



INTERNATIONAL LABOUR ORGANISATION



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Health and Safety Guide No. 85

AMITROLE

HEALTH AND SAFETY GUIDE

This is a companion volume to Environmental Health Criteria 158: Amitrole

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INTRODUCTION

The Environmental Health Criteria (EHC) monographs produced by the International Programme on Chemical Safety include an assessment of the effects on the environment and on human health of exposure to a chemical or combination of chemicals, or physical or biological agents. They also provide guidelines for setting exposure limits.

The purpose of a Health and Safety Guide is to facilitate the application of these guidelines in national chemical safety programmes. The first three sections of a Health and Safety Guide highlight the relevant technical information in the corresponding EHC. Section 4 includes advice on preventive and protective measures and emergency action; health workers should be thoroughly familiar with the medical information to ensure that they can act efficiently in an emergency. Within the Guide is a Summary of Chemical Safety Information which should be readily available, and should be clearly explained, to all who could come into contact with the chemical. The section on regulatory information has been extracted from the legal file of the International Register of Potentially Toxic Chemicals (IRPTC) and from other United Nations sources.

The target readership includes occupational health services, those in ministries, governmental agencies, industry, and trade unions who are involved in the safe use of chemicals and the avoidance of environmental health hazards, and those wanting more information on this topic. An attempt has been made to use only terms that will be familiar to the intended user. However, sections 1 and 2 inevitably contain some technical terms. A bibliography has been included for readers who require further background information.

Revision of the information in this Guide will take place in due course, and the eventual aim is to use standardized terminology. Comments on any difficulties encountered in using the Guide would be very helpful and should be addressed to:

> The Director International Programme on Chemical Safety World Health Organization 1211 Geneva 27 Switzerland

THE INFORMATION IN THIS GUIDE SHOULD BE CONSIDERED AS A STARTING POINT TO A COMPREHENSIVE HEALTH AND SAFETY PROGRAMME

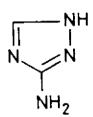
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1. PRODUCT IDENTITY AND USES

1.1 Identity

Common name:

Chemical structure:



amitrole

Molecular formula:	C ₂ H ₄ N ₄
Common synonyms:	aminotriazole; 2-aminotriazole; 3-aminotriazole; 3-amino-S-triazole; 3-amino-1,2,4-triazole; 2-amino-1,3,4-triazole; 3-amino-1H-1,2,4-triazole; AT; 3AT; ATA; 3,A-T; ATZ; AT-90; triazolamine; 1,2,4-triazol-3-amine; 5-amino-1H-1,2,4-triazole
Common trade names:	Amerol; Aminotriazole Weedkiller 90; Aminotriazol Spritzpulver; Amitril; Amitril T.L.; Amitrol; Amitrol 90; Amitrol Plus; Amitrol-T; Amizine; Amizol; Amizol DP; Amizol F; AT Liquid; Azaplant; Azolan; Azole; Azaplant Kombi; Campaprim A1544; Cytrol; Cytrole; Destructol; Diurol 5030; Domatol; Domatol 88; Elmasil; Emisol; Emisol 50; Emosol F; ENT 25445; Exit; Fenamine; Fenavar; Fyrbar; Kleer-Lot; Lancer; Nu-Zinole AA; Orga 414; Pre-Ceed; Radoxone TL; Ramizol; Sapherb; Solution Concentree T271; Ustinex; Vorox; Vorox AA; Vorox AS; Weedar ADS; Weedar AT; Weedazin; Weedazin Arginit; Weedazol; Weedazol GP2; Weedazol Super; Weedex Granulat; Weedoclor; X-All Liquid

PRODUCT IDENTITY AND USES

CAS chemical names:	1H-1,2,4-triazol-3-amine (9CI) 3-amino-S-triazole(8CI)
IUPAC names:	1 <i>H</i> -1,2,4-triazol-3-ylamine 3-amino-1 <i>H</i> -1,2,4-triazole 3-amino-S-triazole
CAS registry number:	61-82-5
RTECS registry number:	XZ3850000

Technical grade amitrole contains a minimum of 95% active ingredient and is formulated as a 250 g/litre solution in water, usually with an equimolar concentration of ammonium thiocyanate, or as a 400 g/kg wettable powder, usually in combination with other herbicides.

1.2 Physical and Chemical Properties

Amitrole is readily soluble in water, methanol, ethanol, and chloroform, sparingly soluble in ethyl acetate, and insoluble in hydrocarbons, acetone, and ether. It forms salts with most acids and bases, and is a powerful chelating agent. It is corrosive to aluminium, copper, and iron.

Further physical and chemical properties of amitrole are given in the "Summary of Chemical Safety Information" (section 6).

1.3 Analytical Methods

Numerous analytical methods have been described for the detection of amitrole. Early methods using paper chromatography for the detection of amitrole in plants have been largely replaced by column chromatography and gas chromatography. Other methods include thin-layer chromatography, high-pressure liquid chromatography, and immunochemistry.

1.4 Production and Uses

Amitrole was first synthesized in 1946, and was commercialized in the 1950s. It is a non-selective herbicide, effective against a very wide spectrum of annual and perennial broad-leaf and grass-type weeds. Its activity is enhanced by the addition of ammonium thiocyanate. It is commonly used

PRODUCT IDENTITY AND USES

as a brush killer, or against non-woody weeds around established apple and pear trees. It is also used on fallow land before planting kale, maize, oilseed rape, potatoes, or wheat. It is also used along roadsides and railway lines and for the control of pond weeds. Amitrole is not approved for use on food plants.

2.1 Identity, Physical and Chemical Properties, and Analytical Methods

Amitrole (3-amino-1,2,4-triazole) is a colourless, crystalline powder. It is thermally stable, and has a melting point of 156-159 $^{\circ}$ C. It is readily soluble in water and ethanol and only sparingly soluble in organic solvents, such as hexane and toluene. Chemically, amitrole behaves as a typical aromatic amine, as well as an S-triazole. A wide range of analytical methods are available for the detection and quantification of amitrole in plants, soil, water, air, and urine.

2.2 Sources of Human and Environmental Exposure

Amitrole does not occur naturally. It is manufactured by the condensation of formic acid with aminoguanidine bicarbonate in an inert solvent at 100-200 °C. It is used as a herbicide with a wide spectrum of activity and appears to act by inhibiting the formation of chlorophyll. It is commonly used around orchard trees, on fallow land, along roadsides and railway lines, or for pond weed control.

2.3 Environmental Transport, Distribution, and Transformation

Amitrole does not enter the atmosphere because of its low vapour pressure. It is readily soluble in water, with a photodegradation half-life of more than one year in distilled water. Photodegradation does occur in the presence of the photosensitizer, humic acid potassium salt, reducing the half-life to 7.5 h.

Amitrole is adsorbed on soil particles and organic matter by proton association. The binding is reversible and not strong, even under favourable acid conditions. Measured K_{∞} values classify amitrole as "highly mobile" in soils of pH > 5 and "medium to highly mobile" at lower pH. There is considerable variation in the leaching of the parent compound through experimental soil columns. Generally, movement is most readily seen in sands; increased organic matter content reduces mobility.

Degradation in soils is usually fairly rapid, but varies with soil type and temperature. Microorganisms (bacteria) that are capable of degrading amitrole have been isolated. The herbicide can act as sole nitrogen source,

but not also as a sole carbon source, for the bacteria. Microbial degradation is probably the major route of breakdown of amitrole; little or no breakdown has been recorded in studies with sterilized soil. However, abiotic mechanisms, including the action of free radicals, have also been proposed for degradation. Laboratory studies have indicated degradation to CO₂, with half-lives of between 2 and 30 days. The results of a single field study suggest that degradation may take longer at lower temperatures and different soil moisture levels; the half-life was about 100 days in a test clay.

Although the parent compound leaches through some soils, degradation products are tightly bound to soil. Since amitrole is degraded rapidly in soil, the high potential of the herbicide to leach does not seem to occur in practice. Occasional damage to trees, reported in early usage, has not been a regular feature of the use of amitrole.

When applied to vegetation, amitrole is absorbed through foliage and can be translocated throughout the plant. It is also absorbed through roots and transported via the xylem to the shoot tips within a few days.

High water solubility, a very low octanol-water partition coefficient, and non-persistence in animals mean that there is no possibility of bioaccumulation of amitrole, or of transport through food-chains.

2.4 Environmental Levels and Human Exposure

Particulates containing amitrole may be released from production plants; atmospheric levels of $0-100 \text{ mg/m}^3$ have been measured close to one plant.

The use of amitrole in waterways and watersheds has led to transitory water concentrations of up to 150 μg /litre. Concentrations in running water fall rapidly to nondetectable levels (<2 μg /litre) within 2 h. Application to ponds gave an initial water concentration of 1.3 mg/litre, falling to 80 μg /litre after 27 weeks. Close to a production plant, river concentrations ranged from 0.5 to 2 mg/litre.

No residues of amitrole have been detected in food following recommended use. Spraying of ground cover around fruit trees did not lead to residues in apples. Wild growing fruit in the vicinity of control areas can develop residues.

There have been no reports of amitrole in drinking-water.

2.5 Kinetics and Metabolism in Laboratory Animals and Humans

Following oral administration, amitrole was readily absorbed from the gastrointestinal tract of mammals. The compound is rapidly excreted from the body, mainly as the parent compound. The main route of excretion in humans and laboratory animals is via the urine, and the majority of excretion takes place during the first 24 h. Metabolic transformation in mammals produces two minor metabolites detectable in the urine of experimental animals. When amitrole aerosol is inhaled, a similar rapid excretion via the urine takes place.

2.6 Effects on Experimental Animals and In Vitro Test Systems

Amitrole has a low acute toxicity when tested in several species, by various routes of administration (LD₅₀s always higher than 2500 mg/kg body weight). Amitrole was found to affect the thyroid after single, short, or long-term exposures. Amitrole is goitrogenic, causing thyroid hypertrophy and hyperplasia, depletion of colloid, and increased vascularity. In long-term studies, these changes precede the development of thyroid neoplasia in rats.

The carcinogenic effects of amitrole on the thyroid are thought to be related to its inhibitory effects on thyroid hormone synthesis, resulting in increased TSH levels and, consequently, continuous stimulation of the gland.

Equivocal results in some tests have been reported on the genotoxic potential of amitrole. In carcinogenicity testing on rats, amitrole does not induce tumours in organs other than the thyroid. However, a high dose of amitrole given to mice caused liver tumours.

Several criteria have been used to assess the early effects of amitrole on the thyroid. The lowest NAOEL derived from these studies was 2 mg/kg in the diet of rats, and assessed on the basis of thyroid hyperplasia.

2.7 Effects on Humans

A single case of contact dermatitis by amitrole has been reported. Amitrole did not cause toxic effects when ingested at a dose of 20 mg/kg. In a controlled study, 100 mg amitrole was found to inhibit iodine uptake by the thyroid at 24 h. Weed control operators exposed dermally to approximately

340 mg amitrole per person per day, for 10 days, had no changes in thyroid function.

2.8 Effects on Other Organisms in the Laboratory and Field

Several studies on the growth of cyanobacteria have shown no effect at concentrations at, or below, 4 mg/litre. No consistent adverse effects on nitrogen fixation have been reported. Bacteria from soil were unaffected by concentrations of 20 mg/litre medium, for nitrogen-fixing *Rhizobium*, and 150 mg/kg, for cellulolytic bacteria. There were no effects on nitrification or soil respiration at 100 mg a.i./kg dry soil, five times the maximum recommended application rate. Reduced nodulation in sub-clover was reported at lower concentrations, up to 20 mg/litre, in culture.

Various unicellular algae have been tested for the growth effects of amitrole. At 0.2–0.5 mg/litre, the growth of *Selenastrum* was reported to be the most sensitive.

Most aquatic invertebrates have shown a high tolerance to technical amitrole: LC50s were > 10 mg/litre for all organisms other than the water flea, *Daphnia magna*, with an acute 48-h EC50 (immobilization) of 1.5 mg/litre. Fish and amphibian larvae are also tolerant to amitrole, with LC50s of > 40 mg/litre. Longer-term studies indicated that young rainbow trout survive concentrations of amitrole of 25 mg/litre for 21 days.

Two earthworm species (*Eisenia* and *Allolobophora*) were unaffected by soil concentrations of amitrole (SP50) and Amitrole T of 100 and 1000 mg/kg, respectively. Carabid beetles were unaffected after direct spraying with amitrole at rates equivalent to 30 kg/ha. Effects on nematodes only occurred at high concentrations of amitrole (LC₅₀ 184 mg/kg). Amitrole was "non-hazardous" to bees in field trials.

The toxicity of amitrole for birds is low, with all reported dietary LC_{50s} being > 5000 mg/kg. Acute oral dosing did not kill any mallard ducks at 2000 mg/kg body weight.

2.9 Evaluation of Human Health Risks and Effects on the Environment

2.9.1 Evaluation of human health risks

General population exposure to amitrole is expected to be minimal, given that it does not persist in the environment, and residues should not occur in food crops. Levels in drinking-water supplies would be expected to be extremely low.

Occupational exposure for weed control operators occurs via the dermal and inhalation routes. However, the results of animal studies and human data indicate that dermal absorption of amitrole is low. Inhalational exposure would be minimized by appropriate breathing apparatus.

In both animals and humans there is a rapid excretion of unchanged amitrole following systemic exposure. Amitrole does not have any teratogenic effects and does not affect reproduction.

The main effect of amitrole in short- and long-term studies on rats is on the thyroid. Amitrole inhibits the production of thyroid hormones T3 and T4, thereby stimulating the pituitary gland to produce more TSH, which in turn activates the thyroid. Consequently thyroid weight increases and the thyroid becomes hyperplastic and hypertrophic. These effects are reversible upon cessation of exposure, even though the extent of this reversal is undefined. Thyroid tumours occur only with long-term exposure at relatively high dose levels in animals already affected by thyroid changes. The mechanism of neoplastic transformation is not understood. However, from all available studies it is clear that hyperplasia always precedes neoplasia, because no tumours are found when the thyroid is not affected. The results of mutagenicity studies are either negative or conflicting and therefore the evidence for amitrole genotoxicity is equivocal. On this basis, it can be concluded that 2 mg/kg diet (equivalent to 0.1 mg/kg body weight per day) is a no-effect level, based on thyroid hyperplasia and iodine uptake, and this value can be used to establish a safe dose for humans.

In carcinogenicity studies on rats, amitrole did not induce tumours in organs other than the thyroid. However, in some mouse studies with high dose levels, liver tumours were also found. Because the mouse is very sensitive to the induction of liver tumours and the dosages are far above any potential

exposure of humans, this is considered of little consequence for the human risk evaluation.

Under normal occupational exposure conditions, it is unlikely that amitrole induces thyroid effects in humans.

Finally, it should be noted that the role of TSH in thyroid carcinogenesis in humans seems to differ from that played in experimental thyroid cancer in rats. This is based on the absence of a correlation between hypothyroidism and thyroid cancer in human epidemiological studies.

2.9.2 Evaluation of effects on the environment

Amitrole has a high potential mobility in soil. The rapid degradation of amitrole in soil, and its retention in most soils by adsorption, makes this potential very unlikely to be realized in most situations. The few reports of effects on non-target vegetation support this view.

Use of amitrole at maximum recommended application rates to control terrestrial weeds would lead to soil residues of up to 20 mg a.i./kg dry soil. Effects on soil microorganisms would not occur at these levels, and soil invertebrates have not been adversely affected at substantially higher concentrations. Amitrole does not present a hazard for birds.

Overspraying of static water bodies during the control of terrestrial weeds would lead to maximum initial water concentrations substantially below reported NOECs for aquatic organisms. Use of amitrole to control aquatic weeds has been reported to lead to water concentrations of about 1 mg/litre that persist for some time. This would not affect fish but could be expected to adversely affect water fleas (NOEC 0.2 mg/litre for reproductive effects).

3. CONCLUSIONS AND RECOMMENDATIONS

3.1 Conclusions

Amitrole does not present a significant risk for human health, when manufactured and used within the confines of good handling procedures. Current restrictions on its use in most countries, particularly its restriction to non-crop uses, will ensure minimum human exposure.

Amitrole is relatively rapidly degraded in the environment with no evidence of bioaccumulation. The available data do not indicate that there are significant effects on the environment. Any effects that do occur appear to be transient.

3.2 Recommendations for the Protection of Human Health and the Environment

Annual monitoring of thyroid function is recommended in workers regularly involved with amitrole, both at the formulation or application stages.

Epidemiological studies should be continued on workers exposed to amitrole.

Use patterns should continue to avoid the risk of contamination of food crops and water supplies, and limits for residues in food and water should be maintained at low levels, e.g., below 0.02 mg/kg in raw agricultural commodities of plant origin (level at, or about, the limit of determination).

4. HUMAN HEALTH HAZARDS, PREVENTION AND PROTECTION, EMERGENCY ACTION

4.1 Human Health Hazards, Prevention and Protection, First Aid

The oral and dermal toxicities of amitrole for mammals are low (rat oral $LD_{50} > 4000 \text{ mg/kg}$, rat dermal $LD_{50} > 2500 \text{ mg/kg}$). An accidental ingestion case (estimated dose 20 mg/kg) produced no clinical symptoms. The potential for skin and eye irritation is slight. A single case study indicated some potential for skin sensitization.

The major health hazard of amitrole is thought to be associated with its goitrogenic activity. Amitrole has the ability to induce thyroid tumours in rats following prolonged exposure, and prolonged thyroid stimulation.

Poisoning by amitrole is unlikely to cause any immediate adverse symptoms. In cases of ingestion, medical attention should be sought.

4.1.1 Advice to physicians

The acute toxicity of amitrole for humans is believed to be low. There is no specific antidote. Treat symptomatically when required. Emesis may be indicated, if a large quantity has been ingested.

If ingestion or inhalation of formulations containing ammonium thiocyanate has occurred, the ammonium thiocyanate would be of more serious toxicological concern than the amitrole. In cases of substantial, recent ingestion, emesis or gastric lavage may be indicated. Haemodialysis is the mainstay of treatment for accidental overdosage with thiocyanate.

4.1.2 Health surveillance advice

Excessive occupational exposure to amitrole may be monitored by means of thyroid function tests (plasma T3 and T4 levels and TSH).

4.2 Explosion and Fire Hazards

Most amitrole formulations do not burn. When strongly heated, amitrole emits highly toxic fumes. Use dry powder, carbon dioxide, alcohol-resistant foam, sand, or earth for dealing with fires. DO NOT use water. Cool nearby drums containing amitrole with water spray.

HUMAN HEALTH HAZARDS, PREVENTION AND PROTECTION, EMERGENCY ACTION

4.3 Storage

Technical amitrole and its formulations should be stored in locked, well-ventilated buildings, preferably specifically used for pesticide storage. Keep products out of reach of children and unauthorized personnel. Do not store near animal feed or foodstuffs.

4.4 Transport

Comply with any local regulations regarding the movement of hazardous goods. Do not load with animal feed or foodstuffs. Before dispatch, ensure that the containers are sound and that labels are securely fixed and undamaged.

4.5 Spillage

Avoid excessive exposure. Keep spectators away from any spillage. Prevent contamination of nearby vegetation and waterways.

Absorb spilled liquid with earth or sand. If available, sawdust, peat, moss, or straw are suitable absorbents; sweep up and place in separate container.

Contain a large spillage by building a barrier of earth or sandbags.

Sweep up any spilled powder with damp sawdust; place in a separate container for disposal.

4.6 Disposal

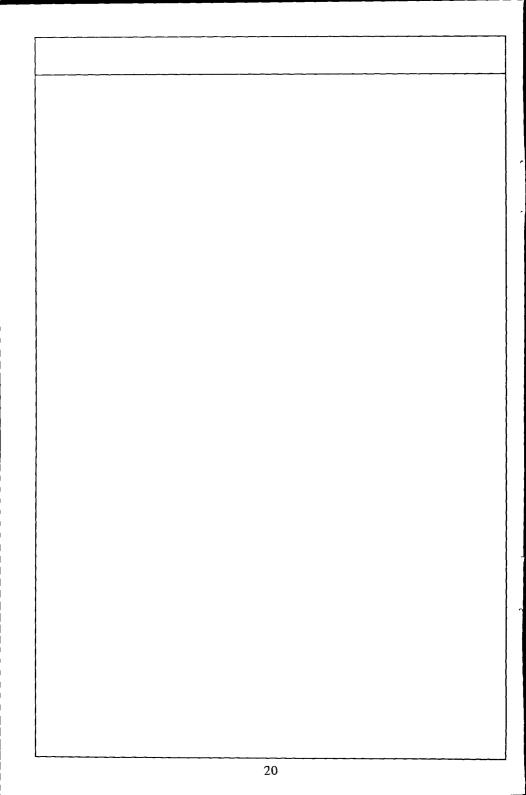
Surplus product, spilled material, contaminated absorbents, containers, etc., should be burnt in an incinerator designed for pesticide disposal. When no incinerator is available, bury in an approved dump or in an area where there is no risk of contamination of ground or surface water. Comply with any local legislation applying to waste disposal.

5. HAZARDS FOR THE ENVIRONMENT AND THEIR PREVENTION

Amitrole has a high potential for leaching. In practice, adsorption on most soils and rapid degradation prevent this mobility. Avoid application to sandy soils with a low organic content, particularly on slopes, and do not apply when rain is imminent.

The toxicity of the herbicide for terrestrial organisms is low and, with recommended use, it should not present any hazard. Amitrole does not bioaccumulate.

Use to control aquatic weeds will lead to concentrations sufficient to kill some aquatic invertebrates, but not fish. These concentrations may persist for several weeks.



6. SUMMARY OF CHEMICAL SAFETY INFORMATION

This summary should be easily available to all health workers concerned with, and users of, amitrole. It should be displayed at, or near, entrances to areas where there is potential exposure to amitrole, and on processing equipment and containers. The summary should be translated into the appropriate language(s). All persons potentially exposed to the chemical should also have the instructions in the summary clearly explained. Space is available for insertion of the National Occupational Exposure Limit, the address and telephone number of the National Poison Control Centre, and local trade names.

SUMMARY OF CHEMICAL SAFETY INFORMATION AMITROLE AMITROLE AMITROLE AMITROLE AMITROLE Chemical formula: C2H4N4 CAS index name: CAS index name: CAS registry number: COL COL CAS registry number: CAS registry number:
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HAZARD/SYMPTOMS	PREVENTION AND PROTECTION	FIRST AID
SKIN: Slight irritant; may cause sensitization	Wear gloves when handling concentrate	Wash off skin with water
EYES: Slight irritant	Avoid contact with eyes	Flush eyes with water
INHALATION: Long-term exposure Avoid breathing spray-mist or dust to spray-mist or dust may be harmful	Avoid breathing spray-mist or dust	
INGESTION: No immediate hazard expected, but long-term ingestion may be harmful	Wash hands before eating, drinking, or smoking	Obtain medical attention, if ingested
ENVIRONMENT: Toxic for vegetation	Do not contaminate vegetation, ponds, or waterways	
SPILLAGE	STORAGE	FIRE/EXPLOSION
Absorb liquid spillage with earth or sand; collect spilled powder with damp sawdust; sweep up, place in closed and suitably labelled container, and dispose of safely; do not contaminate personnel, vegetation, ponds, or waterways	Store in locked storeroom, away from children and unauthorized personnel, and food and animal feed	Some liquid formulations may be flammable; use dry powder, carbon dioxide, or alcohol-resistant foams; cool nearby drums with water spray

SUMMARY OF CHEMICAL SAFETY INFORMATION (continued)	NATIONAL INFORMATION	National Occupational Limit:	National Poison Control Centre:	Local trade names:		
UMMARY OF CHEN			auvery, pury in ap; comply with	Local tr		
S	WASTE DISPOSAL	Burn in high-temperature incinerator, with effluent	scruboing; auern an approved dun local regulations		 	

7. CURRENT REGULATIONS, GUIDELINES, AND STANDARDS

7.1 Previous Evaluations by International Bodies

Amitrole was evaluated by the Joint FAO/WHO Expert Committee on Pesticide Residues (JMPR) in 1974 and 1977. In 1974, the JMPR established a conditional acceptable daily intake (ADI) for man of 0.00003 mg/kg body weight, which was confirmed by the 1977 meeting; however, this concept has been abandoned (WHO, 1990). Amitrole was classified by IARC in Group 2B.

7.2 Exposure Limit Values

The American Conference of Governmental and Industrial Hygienists has set a workplace threshold limit value (TLV) of 0.2 mg/m^3 (time-weighted average for an 8-h day).

No Codex maximum residue limits (MRLs) have been set for amitrole in food. In 1987, the Codex Alimentarius Commission recommended that the uses of amitrole should be restricted to those where residues in food would not be expected to occur. The EEC has set MRLs at the limit of determination (0.05 mg/kg).

7.3 Specific Restrictions

Amitrole has been officially approved for use as a herbicide in many countries. In some countries, specific uses are defined, as well as limitations and precautions.

7.4 Labelling, Packaging, and Transport

The European Community legislation requires labelling as a dangerous substance, using the symbol shown on the next page.

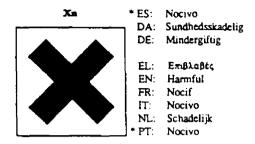
The following standard risk phrases should be used:

R 22 Harmful if swallowed

R 40 Possible risk of irreversible effects

CURRENT REGULATIONS, GUIDELINES, AND STANDARDS

R 48 Danger of serious damage to health by prolonged exposure.



The following standard safety phrases should be used:

S 36 Wear suitable protective clothing

S 37 Wear suitable gloves.

7.5 Waste Disposal

No information available.

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Price: Sw. fr. 5.-Price in developing countries: Sw. fr. 3.50 ISBN 92 4 151085 4