

Itraconazole

sc-205724

Material Safety Data Sheet



The Power is Question

Hazard Alert Code Key:

EXTREME

HIGH

MODERATE

LOW

Section 1 - CHEMICAL PRODUCT AND COMPANY IDENTIFICATION

PRODUCT NAME

Itraconazole

STATEMENT OF HAZARDOUS NATURE

CONSIDERED A HAZARDOUS SUBSTANCE ACCORDING TO OSHA 29 CFR 1910.1200.

NFPA



SUPPLIER

Santa Cruz Biotechnology, Inc.
2145 Delaware Avenue
Santa Cruz, California 95060
800.457.3801 or 831.457.3800

EMERGENCY:

ChemWatch
Within the US & Canada: 877-715-9305
Outside the US & Canada: +800 2436 2255
(1-800-CHEMCALL) or call +613 9573 3112

SYNONYMS

C35-H38-Cl2-N8-O4, "3H-1, 2, 4-triazol-3-one, 4-[4-(4-((2-(2, 4-dichlorophenyl)-, "2(1H-1, 2, 4, -triazol-1-ylmethyl)-1, 3-dioxolan-4-yl)methoxy)phenyl)-", "1-piperazinyl)phenyl]-2, 4-dihydro-2-(1-methylpropyl)", Oriconazole, R-51211, "azole/ triazole fungicide/ antifungal/ antimycotic"

Section 2 - HAZARDS IDENTIFICATION

CHEMWATCH HAZARD RATINGS

		Min	Max
Flammability:	1		
Toxicity:	2		
Body Contact:	2		
Reactivity:	1		
Chronic:	2		
			Min/Nil=0 Low=1 Moderate=2 High=3 Extreme=4



CANADIAN WHMIS SYMBOLS



EMERGENCY OVERVIEW

RISK

Harmful if swallowed.

Irritating to eyes, respiratory system and skin.

Toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment.

POTENTIAL HEALTH EFFECTS

ACUTE HEALTH EFFECTS

SWALLOWED

■ Accidental ingestion of the material may be harmful; animal experiments indicate that ingestion of less than 150 gram may be fatal or may produce serious damage to the health of the individual.

■ Aromatase inhibitors (including triazoles and azoles) produce several side effects including mood swing, depression, weight gain, hot flushes, vaginal dryness, bloating, early onset of menopause. Long-term use may result in bone weakness, increased risk of blood clots, gastrointestinal disturbance, and sweats.

Aromatase inhibitors lower the level of oestrogen in post-menopausal women who have hormone-receptor-positive breast cancers. Prior to menopause oestrogen is mostly produced in the ovaries. Post-menopausal women produce oestrogen from another hormone, androgen. Aromatase inhibitors prevent the enzyme, aromatase from catalysing this reaction. Breast cancer cell growth in post-menopausal women is stimulated by oestrogen.

■ At sufficiently high doses the material may be hepatotoxic (i.e. poisonous to the liver).

EYE

■ Evidence exists, or practical experience predicts, that the material may cause eye irritation in a substantial number of individuals. Prolonged eye contact may cause inflammation characterized by a temporary redness of the conjunctiva (similar to windburn).

SKIN

■ The material may cause mild but significant inflammation of the skin either following direct contact or after a delay of some time. Repeated exposure can cause contact dermatitis which is characterized by redness, swelling and blistering.

■ Skin contact with the material may damage the health of the individual; systemic effects may result following absorption.

■ Open cuts, abraded or irritated skin should not be exposed to this material.

■ Entry into the blood-stream, through, for example, cuts, abrasions or lesions, may produce systemic injury with harmful effects. Examine the skin prior to the use of the material and ensure that any external damage is suitably protected.

INHALED

■ The material can cause respiratory irritation in some persons. The body's response to such irritation can cause further lung damage.

■ Persons with impaired respiratory function, airway diseases and conditions such as emphysema or chronic bronchitis, may incur further disability if excessive concentrations of particulate are inhaled.

CHRONIC HEALTH EFFECTS

■ Long-term exposure to respiratory irritants may result in disease of the airways involving difficult breathing and related systemic problems.

There has been some concern that this material can cause cancer or mutations but there is not enough data to make an assessment.

Limited evidence suggests that repeated or long-term occupational exposure may produce cumulative health effects involving organs or biochemical systems.

Exposure to the material may cause concerns for human fertility, on the basis that similar materials provide some evidence of impaired fertility in the absence of toxic effects, or evidence of impaired fertility occurring at around the same dose levels as other toxic effects, but which are not a secondary non-specific consequence of other toxic effects.

Exposure to the material may cause concerns for humans owing to possible developmental toxic effects, on the basis that similar materials tested in appropriate animal studies provide some suspicion of developmental toxicity in the absence of signs of marked maternal toxicity, or at around the same dose levels as other toxic effects but which are not a secondary non-specific consequence of other toxic effects.

Long term exposure to high dust concentrations may cause changes in lung function i.e. pneumoconiosis; caused by particles less than 0.5 micron penetrating and remaining in the lung.

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Azole fungicides show a broad antifungal activity and are used either to prevent fungal infections or to cure an infection. Therefore, they are important tools in integrated agricultural production. According to their chemical structure, azole compounds are classified into triazoles and imidazoles; however, their antifungal activity is due to the same molecular mechanism. The cell membrane assembly of fungi and yeast is disturbed by blocking the synthesis of the essential membrane component ergosterol. This fundamental biochemical mechanism is the basis for the use of azole fungicides in agriculture and in human and veterinary antimycotic therapies. The enzyme involved is sterol 14[alpha]-demethylase, which is found in several phyla. In mammals, it converts lanosterol into the meiosis-activating sterols (MAS) which regulate or modify cell division. These precursors of cholesterol have been discovered to moderate the development of male and female germ (sexual) cells. Several metabolites of lanosterol have been regarded only as precursors of cholesterol without any biological function in animals. This view dramatically changed recently with the observation that FF-MAS isolated from human follicle fluid and T-MAS isolated from bull testis as well as the MAS-412 and MAS-414 induced resumption of meiosis in cultivated mouse oocytes (Byskov et al. 1995).

Aromatase is another target enzyme of azole compounds. In steroidogenesis, it converts androgens into the corresponding oestrogens. The importance of androgens and oestrogens for the development of reproductive organs, for fertility, and in certain sex steroid-dependent diseases is well known. Therefore, azole compounds can be directed against aromatase to treat oestrogen-responsive diseases. Based on the inhibitory activity of azoles on key enzymes involved in sex steroid hormone synthesis, it is likely that effects on fertility, sexual behavior, and reproductive organ development will occur depending on dose level and duration of treatment of laboratory animals. Several azole

compounds were shown to inhibit the aromatase and to disturb the balance of androgens and estrogens in vivo. In fact, the clinical use of azole compounds in estrogen-dependent diseases is based on this effect. Additionally, azole antifungals developed to inhibit the sterol 14[alpha]-demethylase of fungi and yeast in agriculture and medicine are also inhibiting aromatase. Therefore, these antifungals may unintentionally disturb the balance of androgens and estrogens. Until now, it is not clear whether this effect is compensated by an increased expression of aromatase or by other unknown mechanisms.

The broad use of biologically active compounds in human therapy as well as in nonhuman applications may involve some risks, as exemplified by emerging antibiotic resistance. In agriculture, fungi and yeast are well known to develop resistance to azoles, and some molecular mechanisms of resistance development have been described. The significance of the agricultural azole resistance for human clinical antimycotic therapies has been discussed in Europe, but is not clarified yet. The actual target enzyme of azole antifungals, the fungal sterol 14[alpha]-demethylase, is expressed in many species including humans, and it is highly conserved through evolution. Hence, it seems reasonable to assume that most of the azole antifungals used in agriculture and medicine as well as azoles used in management of breast cancer also act as inhibitors on human sterol 14[alpha]-demethylase to an unknown extent. The toxicologic profiles of individual azole fungicides provide evidence for endocrine effects. In fact, many of these fungicides have effects on prostate, testis, uterus, and ovaries as well as on fertility, development, and sexual behavior. The current database does not allow us to establish causal relationships of these effects with inhibition of sterol 14[alpha]-demethylase and/or aromatase, but the overall view strongly suggests a connection with disturbed steroidogenesis.

Zam et al; Environmental Health Perspectives - 3/1/2003

Some azoles have been associated with prolongation of the QT interval on the electrocardiogram.

Extensive structural activity data from the family of triazole pesticides suggests that may induce hepatocellular adenomas in animal models. The significance of this finding in human carcinogenicity is equivocal.

Exposure to small quantities may induce hypersensitivity reactions characterized by acute bronchospasm, hives (urticaria), deep dermal wheals (angioneurotic edema), running nose (rhinitis) and blurred vision. Anaphylactic shock and skin rash (non-thrombocytopenic purpura) may occur.

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Section 3 - COMPOSITION / INFORMATION ON INGREDIENTS

NAME	CAS RN	%
itraconazole	84625-61-6	>98

Section 4 - FIRST AID MEASURES

SWALLOWED

· IF SWALLOWED, REFER FOR MEDICAL ATTENTION, WHERE POSSIBLE, WITHOUT DELAY. · Where Medical attention is not immediately available or where the patient is more than 15 minutes from a hospital or unless instructed otherwise:

EYE

■ If this product comes in contact with the eyes: · Wash out immediately with fresh running water. · Ensure complete irrigation of the eye by keeping eyelids apart and away from eye and moving the eyelids by occasionally lifting the upper and lower lids.

SKIN

■ If skin contact occurs: · Immediately remove all contaminated clothing, including footwear · Flush skin and hair with running water (and soap if available).

INHALED

· If fumes or combustion products are inhaled remove from contaminated area. · Lay patient down. Keep warm and rested.

NOTES TO PHYSICIAN

■ for poisons (where specific treatment regime is absent):

-----BASIC TREATMENT

 · Establish a patent airway with suction where necessary.
 · Watch for signs of respiratory insufficiency and assist ventilation as necessary.
 Treat symptomatically.

Section 5 - FIRE FIGHTING MEASURES

Vapour Pressure (mmHG):	Negligible
Upper Explosive Limit (%):	Not available.
Specific Gravity (water=1):	~150-350 kg/m3
Lower Explosive Limit (%):	Not available

EXTINGUISHING MEDIA

· Foam.
 · Dry chemical powder.

FIRE FIGHTING

· Alert Emergency Responders and tell them location and nature of hazard.
 · Wear breathing apparatus plus protective gloves.

When any large container (including road and rail tankers) is involved in a fire, consider evacuation by 100 metres in all directions.

GENERAL FIRE HAZARDS/HAZARDOUS COMBUSTIBLE PRODUCTS

- Combustible solid which burns but propagates flame with difficulty.
 - Avoid generating dust, particularly clouds of dust in a confined or unventilated space as dusts may form an explosive mixture with air, and any source of ignition, i.e. flame or spark, will cause fire or explosion. Dust clouds generated by the fine grinding of the solid are a particular hazard; accumulations of fine dust may burn rapidly and fiercely if ignited.
- Combustion products include: carbon monoxide (CO), carbon dioxide (CO₂), hydrogen chloride, phosgene, nitrogen oxides (NO_x), other pyrolysis products typical of burning organic material.

FIRE INCOMPATIBILITY

- Avoid contamination with oxidizing agents i.e. nitrates, oxidizing acids, chlorine bleaches, pool chlorine etc. as ignition may result.

PERSONAL PROTECTION

Glasses:

Safety Glasses.

Chemical goggles.

Gloves:

Respirator:

Particulate

Section 6 - ACCIDENTAL RELEASE MEASURES

MINOR SPILLS

- Remove all ignition sources.
- Clean up all spills immediately.
- Avoid contact with skin and eyes.
- Control personal contact by using protective equipment.
- Use dry clean up procedures and avoid generating dust.
- Place in a suitable, labelled container for waste disposal.

Environmental hazard - contain spillage.

MAJOR SPILLS

- Environmental hazard - contain spillage.

Moderate hazard.

- CAUTION: Advise personnel in area.
- Alert Emergency Responders and tell them location and nature of hazard.

Section 7 - HANDLING AND STORAGE

PROCEDURE FOR HANDLING

- Avoid all personal contact, including inhalation.
- Wear protective clothing when risk of exposure occurs.

Empty containers may contain residual dust which has the potential to accumulate following settling. Such dusts may explode in the presence of an appropriate ignition source.

- Do NOT cut, drill, grind or weld such containers.
- In addition ensure such activity is not performed near full, partially empty or empty containers without appropriate workplace safety authorisation or permit.

RECOMMENDED STORAGE METHODS

- Polyethylene or polypropylene container.
- Check all containers are clearly labelled and free from leaks.

STORAGE REQUIREMENTS

- Observe manufacturer's storing and handling recommendations.

Section 8 - EXPOSURE CONTROLS / PERSONAL PROTECTION

EXPOSURE CONTROLS

Source	Material	TWA ppm	TWA mg/m ³	STEL ppm	STEL mg/m ³	Peak ppm	Peak mg/m ³	TWA F/CC	Notes
US - California Permissible Exposure Limits for Chemical Contaminants	itraconazole (Particulates not otherwise regulated Respirable fraction)		5						(n)

US - Tennessee Occupational Exposure Limits - Limits For Air Contaminants	itraconazole (Particulates not otherwise regulated Respirable fraction)	5	
US - Wyoming Toxic and Hazardous Substances Table Z1 Limits for Air Contaminants	itraconazole (Particulates not otherwise regulated (PNOR)(f)- Respirable fraction)	5	
US - Michigan Exposure Limits for Air Contaminants	itraconazole (Particulates not otherwise regulated, Respirable dust)	5	
Canada - Prince Edward Island Occupational Exposure Limits	itraconazole (Particles (Insoluble or Poorly Soluble) [NOS] Inhalable particles)	10	See Appendix B current TLV/BEI Book

ENDOELTABLE

PERSONAL PROTECTION



RESPIRATOR

Particulate

Consult your EHS staff for recommendations

EYE

- Safety glasses with side shields.
- Chemical goggles.

HANDS/FEET

■ Suitability and durability of glove type is dependent on usage. Important factors in the selection of gloves include: such as:

- frequency and duration of contact,
- chemical resistance of glove material,
- glove thickness and
- dexterity

Select gloves tested to a relevant standard (e.g. Europe EN 374, US F739).

- When prolonged or frequently repeated contact may occur, a glove with a protection class of 5 or higher (breakthrough time greater than 240 minutes according to EN 374) is recommended.
- When only brief contact is expected, a glove with a protection class of 3 or higher (breakthrough time greater than 60 minutes according to EN 374) is recommended.
- Contaminated gloves should be replaced.

Gloves must only be worn on clean hands. After using gloves, hands should be washed and dried thoroughly. Application of a non-perfumed moisturiser is recommended.

Experience indicates that the following polymers are suitable as glove materials for protection against undissolved, dry solids, where abrasive particles are not present.

- polychloroprene
- nitrile rubber
- butyl rubber
- fluorocautchouc
- polyvinyl chloride

Gloves should be examined for wear and/ or degradation constantly.

OTHER

- Overalls.
- P.V.C. apron.
- Barrier cream.
- Skin cleansing cream.
- Eye wash unit.

ENGINEERING CONTROLS

- Local exhaust ventilation is required where solids are handled as powders or crystals; even when particulates are relatively large, a certain proportion will be powdered by mutual friction.
- Exhaust ventilation should be designed to prevent accumulation and recirculation of particulates in the workplace.

Section 9 - PHYSICAL AND CHEMICAL PROPERTIES

PHYSICAL PROPERTIES

Solid.

Does not mix with water.

State	Divided solid	Molecular Weight	705.71
Melting Range (°F)	330.8	Viscosity	Not Applicable
Boiling Range (°F)	Not available	Solubility in water (g/L)	Partly miscible
Flash Point (°F)	Not available	pH (1% solution)	Not applicable
Decomposition Temp (°F)	Not available.	pH (as supplied)	Not applicable
Autoignition Temp (°F)	Not available	Vapour Pressure (mmHG)	Negligible
Upper Explosive Limit (%)	Not available.	Specific Gravity (water=1)	~150-350 kg/m3
Lower Explosive Limit (%)	Not available	Relative Vapor Density (air=1)	>1
Volatile Component (%vol)	Negligible	Evaporation Rate	Not applicable

APPEARANCE

White to off-white or pale yellow, odourless, crystalline powder; does not mix well with water. Soluble in methylene chloride.

Section 10 - CHEMICAL STABILITY

CONDITIONS CONTRIBUTING TO INSTABILITY

- Presence of incompatible materials.
- Product is considered stable.

STORAGE INCOMPATIBILITY

- Avoid reaction with oxidizing agents.

For incompatible materials - refer to Section 7 - Handling and Storage.

Section 11 - TOXICOLOGICAL INFORMATION

ITRACONAZOLE

TOXICITY AND IRRITATION

ITRACONAZOLE:

- unless otherwise specified data extracted from RTECS - Register of Toxic Effects of Chemical Substances.

TOXICITY

IRRITATION

Oral (rat) LD50: >320 mg/kg

Intravenous (rat) LD50: 40 mg/kg

Oral (mouse) LD50: >320 mg/kg

Intravenous (mouse) LD50: 46.4 mg/kg

Oral (dog) LD50: >200 mg/kg

Oral (g.pig) LD50: >160 mg/kg

■ Asthma-like symptoms may continue for months or even years after exposure to the material ceases. This may be due to a non-allergenic condition known as reactive airways dysfunction syndrome (RADS) which can occur following exposure to high levels of highly irritating compound. Key criteria for the diagnosis of RADS include the absence of preceding respiratory disease, in a non-atopic individual, with abrupt onset of persistent asthma-like symptoms within minutes to hours of a documented exposure to the irritant. A reversible airflow pattern, on spirometry, with the presence of moderate to severe bronchial hyperreactivity on methacholine challenge testing and the lack of minimal lymphocytic inflammation, without eosinophilia, have also been included in the criteria for diagnosis of RADS. RADS (or asthma) following an irritating inhalation is an infrequent disorder with rates related to the concentration of and duration of exposure to the irritating substance. Industrial bronchitis, on the other hand, is a disorder that occurs as result of exposure due to high concentrations of irritating substance (often particulate in nature) and is completely reversible after exposure ceases. The disorder is characterised by dyspnea, cough and mucus production.

The material may be irritating to the eye, with prolonged contact causing inflammation. Repeated or prolonged exposure to irritants may produce conjunctivitis.

The material may produce respiratory tract irritation, and result in damage to the lung including reduced lung function.

The material may cause skin irritation after prolonged or repeated exposure and may produce on contact skin redness, swelling, the production of vesicles, scaling and thickening of the skin.

Oral (woman) TDLo: 140 mg/kg/5w - I
Oral (man) TDLo: 240 mg/kg/6w - I
Jaundice, impaired liver function tests, dermatitis after systemic exposure, reproductive system tumours, changes in ovarian weight, changes in adrenal weight, maternal effects, foetotoxicity recorded.

Section 12 - ECOLOGICAL INFORMATION

Toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment.
This material and its container must be disposed of as hazardous waste.
Avoid release to the environment.
Refer to special instructions/ safety data sheets.

Section 13 - DISPOSAL CONSIDERATIONS

Disposal Instructions

All waste must be handled in accordance with local, state and federal regulations.
Puncture containers to prevent re-use and bury at an authorized landfill.
Legislation addressing waste disposal requirements may differ by country, state and/ or territory. Each user must refer to laws operating in their area. In some areas, certain wastes must be tracked.
A Hierarchy of Controls seems to be common - the user should investigate:
· Reduction
· Reuse
· Recycling
· Disposal (if all else fails)
This material may be recycled if unused, or if it has not been contaminated so as to make it unsuitable for its intended use. Shelf life considerations should also be applied in making decisions of this type. Note that properties of a material may change in use, and recycling or reuse may not always be appropriate.
DO NOT allow wash water from cleaning equipment to enter drains. Collect all wash water for treatment before disposal.
· Recycle wherever possible.
· Consult manufacturer for recycling options or consult Waste Management Authority for disposal if no suitable treatment or disposal facility can be identified.

Section 14 - TRANSPORTATION INFORMATION



DOT:
Symbols: G Hazard class or Division: 9
Identification Numbers: UN3077 PG: III
Label Codes: 9 Special provisions: 8, 146,
335, B54,
IB8, IP3,
N20, T1,
TP33
Packaging: Exceptions: 155 Packaging: Non- bulk: 213
Packaging: Exceptions: 155 Quantity limitations: No limit
Passenger aircraft/rail:
Quantity Limitations: Cargo No limit Vessel stowage: Location: A
aircraft only:
Vessel stowage: Other: None
Hazardous materials descriptions and proper shipping names:
Environmentally hazardous substance, solid, n.o.s

Air Transport IATA:

ICAO/IATA Class: 9 ICAO/IATA Subrisk: None
UN/ID Number: 3077 Packing Group: III
Special provisions: A97
Cargo Only
Packing Instructions: 911 Maximum Qty/Pack: 400 kg
Passenger and Cargo Passenger and Cargo
Packing Instructions: 911 Maximum Qty/Pack: 400 kg
Passenger and Cargo Limited Quantity Passenger and Cargo Limited Quantity
Packing Instructions: Y911 Maximum Qty/Pack: 30 kg G
Shipping Name: ENVIRONMENTALLY HAZARDOUS SUBSTANCE, SOLID,

N.O.S. *(CONTAINS ITRACONAZOLE)

Maritime Transport IMDG:

IMDG Class: 9 IMDG Subrisk: None

UN Number: 3077 Packing Group: III

EMS Number: F-A , S-F Special provisions: 179 274 335 909

Limited Quantities: 5 kg Marine Pollutant: Yes

Shipping Name: ENVIRONMENTALLY HAZARDOUS SUBSTANCE, SOLID, N.O.S.

Section 15 - REGULATORY INFORMATION

itraconazole (CAS: 84625-61-6) is found on the following regulatory lists;

"Canada - Prince Edward Island Occupational Exposure Limits","Canada National Pollutant Release Inventory (NPRI)","US - California Permissible Exposure Limits for Chemical Contaminants","US - Michigan Exposure Limits for Air Contaminants","US - Tennessee Occupational Exposure Limits - Limits For Air Contaminants","US - Wyoming Toxic and Hazardous Substances Table Z1 Limits for Air Contaminants"

Section 16 - OTHER INFORMATION

LIMITED EVIDENCE

- Skin contact may produce health damage*.
- Cumulative effects may result following exposure*.
- Limited evidence of a carcinogenic effect*.
- May possibly affect fertility*.
- May possibly be harmful to the foetus/ embryo*.

* (limited evidence).

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- Classification of the preparation and its individual components has drawn on official and authoritative sources as well as independent review by the Chemwatch Classification committee using available literature references.

A list of reference resources used to assist the committee may be found at:

www.chemwatch.net/references.

- The (M)SDS is a Hazard Communication tool and should be used to assist in the Risk Assessment. Many factors determine whether the reported Hazards are Risks in the workplace or other settings. Risks may be determined by reference to Exposures Scenarios. Scale of use, frequency of use and current or available engineering controls must be considered.

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