
SECTION 1 - IDENTIFICATION OF THE SUBSTANCE/MIXTURE AND OF THE COMPANY/UNDERTAKING

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Product identifier	Procabazine
Synonyms	Benzamide, N-(1-methylethyl)-4-[(2-methylhydrazino)methyl]-; 1-methyl-2-(P-(isopropylcarbamoyl)benzyl)hydrazine; N-isopropyl- α -(2-methylhydrazino)-p-tolamide
Trade names	Matulane® (formulated procabazine hydrochloride)
Chemical family	Methylhydrazine derivative
Relevant identified uses of the substance or mixture and uses advised against	Active pharmaceutical ingredient for research and development purposes only; anti-cancer agent
Note	The pharmacologic and toxicologic properties of this substance have not been fully characterized; this SDS will be revisited as more data become available.
Issue Date	11 August 2011

SECTION 2 - HAZARDS IDENTIFICATION

Classification of the substance or mixture

Regulation (EC) 1272/2008 [GHS]	Acute toxicity - oral - Category 4. Irritant (skin) - Category 2. Reproductive Toxicity - Category 1A. Germ Cell Mutagenicity - Category 1B. Carcinogenic - Category 1B. Specific Target Organ Toxicity (repeated exposure) - Category 1. Aquatic toxicity (chronic) - Category 3.
Directive 67/548/EEC or 1999/45/EC	T - R22, R38, R45 (Carc. Cat. 2), R46 (Muta. Cat. 2), R60 (Repr. Cat. 1), R61 (Repr. Cat. 1), R52/53

SECTION 2 - HAZARDS IDENTIFICATION ...continued

Label elements

CLP/GHS hazard pictogram



CLP/GHS signal word

Danger

CLP/GHS hazard statements

H302 - Harmful if swallowed. H315 - Causes skin irritation. H340 - May cause genetic defects. H350 - May cause cancer. H360FD - May damage fertility. May damage the unborn child. H372 - Causes damage to the blood, bone marrow, gastrointestinal tract, nervous system, and testes through prolonged or repeated exposure. H412 - Harmful to aquatic life with long lasting effects.

CLP/GHS precautionary statements

P201 - Obtain special instructions before use. P260 - Do not breathe dust. P270 - Do not eat, drink or smoke when using this product. P273 - Avoid release to the environment. P281 - Use personal protective equipment as required. P302 + P352 - If on skin: Wash with plenty of soap and water. P308 + P313 - If exposed or concerned: get medical advice/attention. P321 - Specific treatment (see First Aid information on product label and/or Section 4 of the SDS). P405 - Store locked up. P501 - Dispose of contents/container to location in accordance with local/regional/national/international regulations.

Other hazards

Procarbazine is an anti-cancer agent that inhibits DNA, RNA, and protein synthesis, and can affect normal, rapidly proliferating cells. It also exhibits monoamine oxidase inhibitory (MAOI) activity. The most common adverse effects associated with use of procarbazine include gastrointestinal disturbances (*e.g.*, anorexia, nausea, and vomiting) and bone marrow suppression, characterized by decreases in platelets and white and red blood cells. Various central nervous system (CNS) effects, resulting from the drug's MAOI activity, may also occur (*e.g.*, dizziness, drowsiness, weakness, sleep disturbances, tremors, changes in blood pressure or heart rate, and numbness in the extremities). Overdosage may cause additional CNS-associated symptoms, which may be manifested 12 hours post exposure and peak at 24-48 hours.

Procarbazine exposure has been identified as an independent risk factor for acute ovarian failure and acute amenorrhea (absence of menstruation) in women. There are case reports of malformations in the offspring of women taking this drug as a part of a combination therapy regimen. Azoospermia (absence of sperm in semen), which can be prolonged, has also been reported in men with procarbazine when used in combination therapy.

Secondary malignancies (including lung cancer and leukemias) have been reported in patients treated with procarbazine in combination therapies.

SECTION 2 - HAZARDS IDENTIFICATION ...continued

US Signal word	Caution
US Hazard overview	Procarbazine is a potent anticancer agent. May be harmful if swallowed. May cause skin irritation. Reproductive/Developmental/Birth defect hazard - can cause adverse reproductive (male and female) effects, developmental effects, and birth defects. Can cause blood, bone marrow, gastrointestinal, nervous system, and testicular damage. Genotoxic. Harmful to aquatic life with long-lasting effects.
Note	This substance is classified as dangerous/hazardous according to Directive 67/548/EEC, Regulation EC No 1272/2008 (EU CLP), and applicable US regulations. The GHS classifications are based on Regulation (EC) 1272/2008.

SECTION 3 - COMPOSITION/INFORMATION ON INGREDIENTS

<u>Ingredient</u>	<u>CAS #</u>	<u>EINECS/ ELINCS#</u>	<u>Amount</u>	<u>EU Classification</u>	<u>GHS Classification</u>
Procarbazine	671-16-9	211-582-2	~100 %	Toxic -T: R22, R38, R45, R46, R60, R61, R52/ 53	ATO4: H302; SI2: H315; RT1A: H360FD; GCM1B: H340; Carc1B: H350; STOT-R1: H372; CA3: H412

Note	The substance listed above is considered dangerous/hazardous. See Section 16 for full text of EU and EU-CLP/GHS classifications. The EU classification is based on Directive 67/548/EEC and the GHS classification is based on Regulation (EC) 1272/2008.
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SECTION 4 - FIRST AID MEASURES

Description of first aid measures

Immediate Medical Attention Needed	Yes
Eye Contact	If easy to do, remove contact lenses, if worn. Immediately flush eyes with copious quantities of water for at least 15 minutes. If irritation occurs or persists, notify medical personnel and supervisor.
Skin Contact	Wash exposed area with soap and water and remove contaminated clothing/shoes. If irritation occurs or persists, notify medical personnel and supervisor.
Inhalation	Immediately move exposed subject to fresh air. If not breathing, give artificial respiration. If breathing is labored, administer oxygen. Immediately notify medical personnel and supervisor.

SECTION 4 - FIRST AID MEASURES ...continued

Ingestion	Do not induce vomiting unless directed by medical personnel. Do not give anything to drink unless directed by medical personnel. Never give anything by mouth to an unconscious person. Notify medical personnel and supervisor.
Protection of first aid responders	See Section 8 for Exposure Controls/Personal Protection recommendations.
Most important symptoms and effects, both acute and delayed	See Sections 2 and 11.
Indication of immediate medical attention and special treatment needed, if necessary	Procarbazine is a potent anticancer agent. Medical conditions aggravated by exposure: blood, bone marrow, gastrointestinal, or CNS disorders. Treat symptomatically and supportively. Management of overdose may include administration of α - and/or β -adrenergic blockers. If accidental exposure occurs to an individual who is also taking one or more concomitant medications, consult the respective package or prescribing information for potential drug interactions.

SECTION 5 - FIREFIGHTING MEASURES

Extinguishing media	Use water spray (fog), foam, dry powder, or carbon dioxide, as appropriate for surrounding fire and materials.
Specific hazards arising from the substance or mixture	No information identified. Emits toxic fumes of carbon monoxide, carbon dioxide, and oxides of nitrogen.
Flammability/Explosivity	No explosivity or flammability data identified. High concentrations of finely divided airborne organic particles can potentially explode if ignited.
Advice for firefighters	Wear full protective clothing and a self-contained breathing apparatus with a full facepiece operated in the pressure demand or other positive pressure mode. Decontaminate all equipment after use.

SECTION 6 - ACCIDENTAL RELEASE MEASURES

Personal precautions, protective equipment and emergency procedures	If product is released or spilled, take proper precautions to minimize exposure by using appropriate personal protective equipment (see Section 8). Area should be adequately ventilated. Do not breathe dust.
Environmental precautions	Do not empty into drains. Avoid release to the environment.

SECTION 6 - ACCIDENTAL RELEASE MEASURES ...continued

Methods and material for containment and cleaning up	DO NOT RAISE DUST. Surround spill or powder with absorbents and place a damp cloth or towel over the area to minimize entry of powder into the air. Add excess liquid to allow the material to enter solution. Capture remaining liquid onto spill absorbents. Place spill materials into a leak-proof container suitable for disposal in accordance with applicable waste disposal regulations (see Section 13). Decontaminate the area twice.
Reference to other sections	See Sections 8 and 13 for more information.

SECTION 7 - HANDLING AND STORAGE

Precautions for safe handling	Follow recommendations for handling potent pharmaceutical agents (i.e., use of engineering controls and/or other personal protective equipment if needed). Avoid breathing dust. Wash thoroughly after handling.
Conditions for safe storage including any incompatibilities	Store at controlled room temperature (20- 25°C) away from incompatible materials. Protect from moisture and damage.
Specific end use(s)	No information identified.

SECTION 8 - EXPOSURE CONTROLS/PERSONAL PROTECTION

Note Wash hands, face and other potentially exposed areas immediately in the event of physical contact.

**Control Parameters/
Occupational Exposure
Limit Values**

<u>Compound</u>	<u>Issuer</u>	<u>Type</u>	<u>OEL</u>
Procarbazine	Sigma-Tau	Occupational Exposure Category/ Band	3 of 4 in a 4-category system. Consult manufacturer for more information.

Exposure/Engineering controls Selection and use of containment devices and personal protective equipment should be based on a risk assessment of exposure potential. Open handling should not be performed when handling potent substances, or substances of unknown toxicity. Material should be handled inside a closed process, ventilated enclosure, isolator or device of equivalent or better control that is suitable for dusts and/or aerosols.

SECTION 8 - EXPOSURE CONTROLS/PERSONAL PROTECTION ...continued

Respiratory protection	Choice of respiratory protection should be appropriate to the task and the level of existing engineering controls. For routine powder handling tasks, an approved and properly worn powered air-purifying respirator equipped with appropriate HEPA filters or combination filters should provide ancillary protection based on the known or foreseeable limitations of existing engineering controls. Use a positive-pressure air-supplied respirator if there is any potential for an uncontrolled release, when exposure levels are not known, or in any other circumstances where air purifying respirators may not provide adequate protection.
Hand protection	Wear nitrile or other impervious gloves if skin contact is possible. Double gloves should be considered. When the material is dissolved or suspended in an organic solvent, wear gloves that provide protection against the solvent.
Skin protection	Wear appropriate gloves, lab coat, or other protective overgarment if skin contact is likely. Base the choice of skin protection on the job activity, potential for skin contact and solvents and reagents in use.
Eye/face protection	Wear safety glasses with side shields, chemical splash goggles, or full face shield, if necessary. Base the choice of protection on the job activity and potential for contact with eyes or face. An emergency eye wash station should be available.
Environmental Exposure Controls	Avoid release to the environment and operate within closed systems wherever practicable. Air and liquid emissions should be directed to appropriate pollution control devices. In case of spill, do not release to drains. Implement appropriate and effective emergency response procedures to prevent release or spread of contamination and to prevent inadvertent contact by personnel.
Other protective measures	Wash hands in the event of contact with this substance, especially before eating, drinking or smoking. Protective equipment is not to be worn outside the work area (e.g., in common areas or out-of-doors).

SECTION 9 - PHYSICAL AND CHEMICAL PROPERTIES

Information on basic physical and chemical properties

Appearance	Solid
Color	White to pale yellow
Odor	Slight odor
Odor threshold	No information identified.
pH	No information identified.
Melting point/ freezing point	223-226°C (procarbazine hydrochloride)

SECTION 9 - PHYSICAL AND CHEMICAL PROPERTIES ...continued

Initial boiling point and boiling range	Not applicable.
Flash point	No information identified.
Evaporation rate	Not applicable.
Flammability (solid, gas)	No information identified.
Upper/lower flammability or explosive limits	No information identified.
Vapor pressure	No information identified.
Vapor density	No information identified.
Relative density	No information identified.
Water solubility	No information identified..
Solvent solubility	No information identified.
Partition coefficient (n-octanol/water)	0.06
Auto-ignition temperature	No information identified.
Decomposition temperature	No information identified.
Viscosity	No information identified.
Explosive properties	No information identified.
Oxidizing properties	No information identified.
Other information	
Molecular weight	221.3
Molecular formula	C ₁₂ H ₁₉ N ₃ O

SECTION 10 - STABILITY AND REACTIVITY

Reactivity	No information identified.
Chemical stability	No information identified.
Possibility of hazardous reactions	No information identified.
Conditions to avoid	No information identified.

SECTION 10 - STABILITY AND REACTIVITY ...continued

Incompatible materials No information identified.

Hazardous decomposition products No information identified.

SECTION 11 - TOXICOLOGICAL INFORMATION

Information on toxicological effects

Route of entry May be absorbed by inhalation, skin contact and ingestion.

Acute toxicity

<u>Compound</u>	<u>Type</u>	<u>Route</u>	<u>Species</u>	<u>Dose</u>
Procabazine	LD ₅₀	Oral	Rat	570 mg/kg
	LD ₅₀	Oral	Mouse	560 mg/kg
	LD ₅₀	IP	Rat	>400 mg/kg
	LD ₅₀	IP	Mouse	614 mg/kg

Irritation/Corrosion Procarbazine hydrochloride was mildly irritating to rabbit eyes and moderately irritating to rabbit skin.

Sensitization No data available.

STOT-single exposure No data available.

STOT-repeated exposure/Repeat-dose toxicity No data available.

Reproductive toxicity No definitive fertility studies have been conducted with procarbazine. Spermatogenesis impairment and sperm/testicular toxicity was noted in male mice following single IP injections of 400 mg/kg and in male rats following either 3 weekly IP injections of 200 mg/kg or single intravenous (IV) bolus doses \geq 500 mg/kg. Overall, procarbazine did cause adverse reproductive effects in males.

Developmental toxicity Oral treatment with 5-10 mg/kg procarbazine during gestation produced eye abnormalities (exclusively before the 12th day of gestation) and limb defects (after the 12th day) in rat offspring. Development of nervous system tumors was noted in rat offspring following IV treatment with 125 mg/kg on day 22 of gestation.

Genotoxicity Procarbazine was positive in *in vitro* rat and *in vivo* mouse micronucleus tests, a mouse lymphoma assay, and an *in vitro* mutagenicity test using Chinese hamster V79 cells. DNA damage was also found *in vitro* in rat liver cells. It was not mutagenic in the Ames bacterial mutagenesis assay. Unscheduled DNA synthesis in rabbit testes was also reported. Overall, procarbazine possesses a high genotoxic potential.

SECTION 11 - TOXICOLOGICAL INFORMATION ...continued

Carcinogenicity	Procarbazine was administered to rats and mice <i>via</i> 3 weekly IP injections at doses of 15-30 and 6-12 mg/kg/dose for up to 26 and 52 weeks, respectively. Significant numbers of malignant tumors were noted in the mammary gland, nose, and brain of rats, and in the blood (leukemias), nose, lungs, and uterus of mice. It is listed as a Group 2A (probably carcinogenic to humans) compound by IARC, a carcinogen by California's Proposition 65, and as "reasonably anticipated to be a human carcinogen" by NTP, based on epidemiological data.
Aspiration hazard	No data available.
Human health data	See "Section 2 - Other Hazards"

SECTION 12 - ECOLOGICAL INFORMATION

Toxicity

<u>Compound</u>	<u>Type</u>	<u>Species</u>	<u>Concentration</u>
Procarbazine	LC ₅₀ /96h	Rainbow Trout	>100 mg/L
	EC ₅₀ /48h	<i>Daphnia magna</i> (crustacea)	>100 mg/L
	ErC ₅₀ /72h	<i>Scenedesmus suspicatus</i> (Algae)	25 mg/L

Persistence and Degradability	Procarbazine hydrochloride is not readily biodegradable.
Bioaccumulative potential	A log K _{OW} of 0.06 was identified for procarbazine.
Mobility in soil	No data available.
Results of PBT and vPvB assessment	Not performed.
Other adverse effects	No data available.
Note	Releases to the environment should be avoided.

SECTION 13 - DISPOSAL CONSIDERATIONS

Waste treatment methods	Dispose of wastes in accordance to prescribed federal, state, and local guidelines, e.g., appropriately permitted chemical waste incinerator. Do not send down the drain or flush down the toilet. All wastes containing the material should be properly labeled. Rinse waters resulting from spill cleanups should be discharged in an environmentally safe manner, e.g., appropriately permitted municipal or on-site wastewater treatment facility.
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SECTION 14 - TRANSPORT INFORMATION

Transport	Based on the available data, this substance is not regulated as a hazardous material/dangerous good under EU ADR/RID, US DOT, Canada TDG, IATA, or IMDG.
UN number	None assigned.
UN proper shipping name	None assigned.
Transport hazard classes and packing group	None assigned.
Environmental hazards	Based on the available data, this substance is not regulated as an environmental hazard or a marine pollutant.
Special precautions for users	Avoid release to the environment.
Transport in bulk according to Annex II of MARPOL73/78 and the IBC Code	Not applicable.

SECTION 15 - REGULATORY INFORMATION

Safety, health and environmental regulations/legislation specific for the substance or mixture	This SDS complies with the requirements under US, EU and GHS (EU CLP - Regulation EC No 1272/2008) guidelines. Consult your local or regional authorities for more information.
Chemical safety assessment	Not conducted.
OSHA Hazardous	Yes. Caution. May be harmful if swallowed. May cause skin irritation. Reproductive/Developmental/Birth defect hazard - can cause adverse reproductive (male and female) effects, developmental effects, and birth defects. Can cause blood, bone marrow, gastrointestinal, nervous system, and testicular damage. Genotoxic. Harmful to aquatic life with long-lasting effects.
WHMIS classification	Not required. Drugs are not subject to WHMIS. This product has been classified in accordance with the hazard criteria of the Controlled Products Regulations and the SDS contains all of the information required by those regulations.
TSCA status	Drugs are exempt from TSCA.
SARA section 313	Not listed.
California proposition 65	Listed as a carcinogen and a developmental toxicant.
Additional information	Procarbazine is considered a hazardous drug by NIOSH.

SECTION 16 - OTHER INFORMATION

Full text of R phrases and EU Classifications

T - Toxic. R22 - Harmful if swallowed.. R38 - Irritating to skin. R45 - May cause cancer. Carc. Cat. 2 - Carcinogenic Category 2. R46 - May cause heritable genetic damage. Muta. Cat. 2 - Mutagenic Category 2. R60 - May impair fertility. R61 - May cause harm to the unborn child. Repr. Cat. 1 - Toxic for reproduction Category 1. R52/53 - Harmful to aquatic organisms, may cause long-term adverse effects in the aquatic environment.

Full text of H phrases, P phrases and GHS classification

ATO4 - Acute Toxicity (Oral) Category 4. H302 - Harmful if swallowed. SI2 - Skin irritant Category 2. H315 - Causes skin irritation. RT1A - Reproductive toxicity Category 1A. H360FD - May damage fertility. May damage the unborn child. GCM1B - Germ Cell Mutagenicity Category 1B. H340 - May cause genetic defects. Carc1B - Carcinogenic Category 1B. H350 - May cause cancer. STOT-R1 - Specific Target Organ Toxicity Following Repeat Exposure Category 1. H372 - Causes damage to the blood, bone marrow, gastrointestinal tract, nervous system, and testes through prolonged or repeated exposure. CA3 - Aquatic toxicity (chronic) - Category 3. H412 - Harmful to aquatic life with long lasting effects.

Sources of data

Information from published literature and internal company data.

Abbreviations

ACGIH - American Conference of Governmental Industrial Hygienists; ADR/RID - European Agreement Concerning the International Carriage of Dangerous Goods by Road/Rail; AIHA - American Industrial Hygiene Association; CAS# - Chemical Abstract Services Number; DNEL - Derived No Effect Level; DOT - Department of Transportation; EINECS - European Inventory of New and Existing Chemical Substances; ELINCS - European List of Notified Chemical Substances; EU - European Union; GHS - Globally Harmonized System of Classification and Labeling of Chemicals; IARC - International Agency for Research on Cancer; IDLH - Immediately Dangerous to Life or Health; IATA - International Air Transport Association; IMDG - International Maritime Dangerous Goods; LOEL - Lowest Observed Effect Level; LOAEL - Lowest Observed Adverse Effect Level; NIOSH - The National Institute for Occupational Safety and Health; NOEL - No Observed Effect Level; NOAEL - No Observed Adverse Effect Level; NTP - National Toxicology Program; OEL - Occupational Exposure Limit; OSHA - Occupational Safety and Health Administration; PNEC - Predicted No Effect Concentration; SARA - Superfund Amendments and Reauthorization Act; STEL - Short Term Exposure Limit; TDG - Transportation of Dangerous Goods; TSCA - Toxic Substances Control Act; TWA - Time Weighted Average; WHMIS - Workplace Hazardous Materials Information System

Revisions

This is the first version of this SDS.

Disclaimer

The above information is based on data available to us and is believed to be correct. Since the information may be applied under conditions beyond our control and with which we may be unfamiliar, we do not assume any responsibility for the results of its use and all persons receiving it must make their own determination of the effects, properties and protections which pertain to their particular conditions.

No representation, warranty, or guarantee, express or implied (including a warranty

SECTION 16 - OTHER INFORMATION ...continued

Disclaimer ...continued

of fitness or merchantability for a particular purpose), is made with respect to the materials, the accuracy of this information, the results to be obtained from the use thereof, or the hazards connected with the use of the material. Caution should be used in the handling and use of the material because it is a potent pharmaceutical product. The above information is offered in good faith and with the belief that it is accurate. As of the date of issuance, we are providing all information relevant to the foreseeable handling of the material. However, in the event of an adverse incident associated with this product, this Safety Data Sheet is not, and is not intended to be, a substitute for consultation with appropriately trained personnel.