

Procarbazine

Safety Data Sheet

Division of Occupational Health and Safety
National Institutes of Health



WARNING!

This compound is absorbed through the intestinal tract. It is toxic, carcinogenic, mutagenic and teratogenic. Avoid formation and breathing of aerosols.

Laboratory operations should be conducted in a fume hood, glove box, or ventilated cabinet.

Avoid skin contact: If exposed, wash with soap and water.

For eye exposure, irrigate immediately with large amounts of water. For ingestion, drink plenty of milk or water. Induce vomiting. For inhalation, remove victim promptly to clean air. Administer rescue breathing if necessary. Refer to physician.

In case of laboratory spill, wear protective clothing during cleanup. Avoid skin contact or breathing of aerosols. Use water to dissolve compound. Wash down area with soap and water. Dispose of waste solutions and materials appropriately.

A. Background

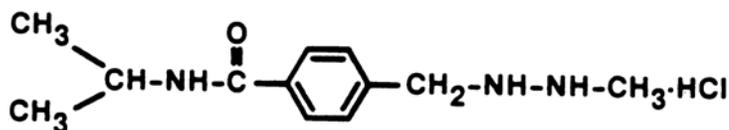
Procarbazine hydrochloride (PCZ) is a white to pale yellow crystalline solid, with a slight odor. It is highly sensitive to ultraviolet light and to oxidation by atmospheric oxygen. PCZ is toxic to man and laboratory animals, producing bone marrow depression and neurotoxicity. It is carcinogenic in animals, suspected of producing leukemia in man, mutagenic, and teratogenic. It is used as a drug in antineoplastic investigations.

B. Chemical and Physical Data

1. Chemical Abstract No.: 366-70-1
2. Synonyms: IBZ, Natulan, MBH, Nathulane, PCZ, NCI-C01810, Matulane, RO-4-6467, Ibenzmetyzin hydrochloride, 1-Benzmetyzin hydrochloride, 2-(p-Isopropylcarbamoyl) benzyl)-1-methylhydrazine hydrochloride, N-Isopropyl-2p-(2-methylhydrazinomethyl) benzamide hydrochloride, N-Isopropyl- α -(2-methylhydrazino)-p-tolumaide hydrochloride, 1-(p-Isopropyl carbamoylbenzyl)-2-methyl hydrazine hydrochloride, p-(N'-Methylhydrazinomethyl)-N-isopropylbenzamide hydrochloride, 1-Methyl-2-(p-isopropyl carbamoylbenzyl)-N-isopropylbenzamide hydrochloride, Benamide, N-(1-methylethyl)-4-[(2-methylhydrazino)methyl]-, monohydrochloride (9C1)

3. Molecular formula, weight and structure:

$C_{12}H_{19}N_3O \cdot HCl$ 257.76



4. Density: No data.
5. Absorption spectroscopy: UV, IR, NMR, fluorescence, and mass spectra are described by Rucki (176).
6. Volatility: No data.
7. Solubility: PCZ is very soluble (but unstable) in water (200 mg/ml at 25°C) and is soluble in methanol and 95% ethanol.
8. Description, appearance, and odor: White to pale yellow crystalline powder with a slight odor.
9. Boiling point: No data.
Melting point: 223°C with decomposition.
10. Stability: PCZ is very sensitive to ultraviolet light. It is stable in the solid state (when protected from UV light and moisture) but is degraded in alcoholic and aqueous solution by autoxidation, which is catalyzed by metal ions such as: Mn^{++} and Cu^{++} .
11. Chemical reactivity: Autoxidation results in formation of the corresponding azo derivative and hydrazone: the latter is further oxidated to yield methyl hydrazine and N-isopropyl-p-formylbenzamide.
12. Flash point: No data.
13. Autoignition temperature: No data.
14. Flammable limits in air: No data.

C. Fire, Explosion, and Reactivity Hazard Data

1. PCZ does not require special fire-fighting procedures or equipment and does not present unusual fire and explosion hazards.
2. No conditions contributing to instability, other than oxidation in the presence of air and light, are known to exist.
3. Heavy metal ions such as Mn^{++} and Cu^{++} are incompatible with PCZ in the presence of air and moisture.
4. Several products of autoxidation of PCZ are carcinogenic, e.g., methyl hydrazine.
5. While there are no data to this effect, it is probably preferable to employ nonspark equipment since gaseous hydrazine derivatives are subject to flaming and explosion when exposed to sparks.

D. Operational Procedures

The NIH Guidelines for the Laboratory Use of Chemical Carcinogens describe operational practice to be followed when potentially carcinogenic chemicals are used in NIH laboratories. The Guidelines should be consulted to identify the proper use conditions required and specific controls to be implemented during normal and complex operations or manipulations involving PCZ.

HZ penetrates various glove materials (Luskus et al., 1980). This factor should be taken into account when handling PCZ.

1. Chemical inactivation: No validated method reported.
2. Decontamination: Turn off equipment that could be affected by PCZ or the materials used for cleanup. If more than 1 g has been spilled or if there is any uncertainty regarding the procedures to be followed for decontamination, call the NIH procedures to be followed for decontamination, call the NIH Fire Department (dial 116) for assistance. Wash surfaces with copious quantities of water. Glassware should be rinsed (in a hood) with water and washed with soap and water. Animal cages should be washed with water.
3. Disposal: No waste streams containing PCZ shall be disposed of in sinks or general refuse. Surplus PCZ or chemical waste streams contaminated with PCZ shall be handled as hazardous chemical waste and disposed of in accordance with the NIH chemical waste disposal system. Nonchemical waste (e.g., animal carcasses and bedding) containing PCZ shall be handled and packaged for incineration in accordance with the NIH medical-pathological waste disposal system. Potentially infectious waste (e.g., tissue cultures) containing PCZ shall be disinfected by heat using a standard autoclave treatment and packaged for incineration, as above. Burnable waste (e.g., absorbent bench top liners) minimally contaminated with PCZ shall be handled as potentially infectious waste and packaged for incineration, as above. Absorbent materials (e.g., associated with spill cleanup) grossly contaminated shall be handled in accordance with the chemical waste disposal system. Radioactive waste containing PCZ shall be handled in accordance with the NIH radioactive waste disposal system.
4. Storage: Store in sealed ampoules or in amber screw-capped glass bottles with Teflon cap liners at room temperature, preferably in a desiccator in a nitrogen atmosphere. Avoid exposure to moisture and light.

E. Monitoring and Measurement Procedures Including Direct Field Measurements and Sampling for Subsequent Laboratory Analysis

1. Sampling: No data for air or water.
2. Separation and analysis: The methods have been reviewed (Rucki, 1976). Spectrophotometric determination of acid solutions at 232 nm has been used, but oxidative decomposition products of PCZ may cause interference. TLC, followed by spraying with Ehrlich's reagent, overcomes this objection. Polarography has also been used.

F. Biological Effects (Animal and Human)

1. Absorption: PCZ is absorbed via the oral route; there are no data on other modes of administration, except for transplacental transmission.
2. Distribution: After oral administration to humans, there is rapid appearance of PCZ in plasma and cerebrospinal fluid, with peak levels in the latter appearing in 30-90 minutes.
3. Metabolism and excretion: PCZ is oxidized to hydrogen peroxide and an azo derivative, which isomerizes to the corresponding hydrazone. This hydrolyzes and the final metabolic product is N-isopropyltere-phthalamic acid (Raaflaub and Schwartz, 1965), which is the major urinary excretion product. Up to 70% of the administered radio activity due to intravenously administered, labeled PCZ is excreted in the urine by man within 24 hours (Miller, 1971).
4. Toxic effects: The acute oral LD50s of PCZ in mice, rats, and rabbits are 1,320, 785, and 147 mg/kg, respectively. Daily dosage of 25 mg/kg administered to monkeys for three weeks was lethal. The target organs in man, when PCZ is administered in chemotherapeutic doses, are the central nervous system (drowsiness or stupor, ataxia, hypotension) and bone marrow, resulting in depression. These

latter symptoms appeared at 3-6 weeks and disappeared within 1-6 weeks after PCZ dosage ceased (Brulé et al., 1965). In dogs and monkeys, there is liver toxicity, as evidenced by increases in BSP retention and of several blood enzyme levels. The mechanism of toxic action appears to involve nucleic acid metabolism.

5. Carcinogenic effects: In animals, PCZ administration results in induction of pulmonary epithelial neoplasia, mammary carcinoma, kidney sarcoma, and lymphocytic leukemia. It is suspected of promoting acute myelocytic leukemia in man.
6. Mutagenic and teratogenic effects: Chromosomal aberrations have been reported in cancer patients and in mice. Teratogenic effects (brain malformations) have been reported in offspring from dams of mice and rats which had received PCZ. Human teratogenicity is suspected but not proven.

G. Emergency Treatment

1. Skin and eye exposure: For skin exposure, remove contaminated clothing and wash skin with soap and water. Avoid raising skin temperature. For eye exposure, irrigate immediately with copious quantities of running water for at least 15 minutes.
2. Ingestion: Drink plenty of milk or water. Induce vomiting.
3. Inhalation: Remove victim promptly to clean air. Administer rescue breathing if necessary.
4. Refer to physician.

F. References

- Brulé, G., J.R. Schlumberger, and C. Griscelli. 1965. N-Isopropyl- α -(2-methylhydrazino)-p-toluamide, hydrochloride (NSC-77213) in treatment of solid tumors. *Cancer Chemother Rep* 44:31-38.
- Luskus, L.J., H.J. Kilian, J.W., J.W., Morky, M.L. Turpin. 1980. Test and Evaluation for Chemical Resistance of Gloves Worn for Protection Against Exposure to H-70 Hydrazine. Report SAM-TR-80-15. USAF School of Aerospace Medicine, Brooks Air Force Base, TX.
- Miller, E. 1971. Development of procarbazine. Pages 3-7 in S.K. Carter, ed. Conference on Procarbazine: Development and Application. US Government Printing Office, Washington, DC.
- Raaflaub, J., and D.E. Schwartz. 1965. Metabolism of α cytostatically active methylhydrazine derivative (Natulan). *Experientia* 21:44-45.
- Rucki, R.J. 1976. Procarbazine hydrochloride. *Analytical Profiles of Drug Substances* 5:403.