PCNU

Safety
Data
Sheet

Division of Occupational Health and Safety
National Institutes of Health

WARNING!

This compound is toxic and may be mutagenic. It is readily absorbed by various body tissues. 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 cold water. Avoid washing with solvents. Avoid rubbing of skin or increasing its temperature.

For eye exposure, irrigate immediately with large amounts of water. For ingestion, drink milk or water. Refer for gastric lavage. 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. Dispose of waster solutions and materials appropriately.

Introductory Note

There is little (or in some instances, no) information in the literature concerning the physical, chemical, and biological properties of PCNU.[A] In what appears below such specific data are identified by an asterisk (*). For the rest, data published here are based on analogies with BCNU or CCNU and professional judgment.

A. Background

PCNU is a solid, stable in pure form and in solution at slightly acid pH, readily decomposed in strong acid and in alkaline solution. It is toxic in mammalian species tested (oral and parenteral toxicity in the mg/kg range) and probably carcinogenic, mutagenic, and teratogenic (although there are no data to this effect; see Introductory Note). It is less lipid soluble than BCNU or CCNU but its lipid solubility is in the range which is considered optimal for the treatment of intracerebral tumors. Toxic side effects due to treatment with PCNU are on the hematopoietic system.

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[A] Abbreviation used in this Data Sheet. Other abbreviations used are BCNU = 1, 3-bis(2-chloroethyl)-1-nitrosourea; CCNU = 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea; MeCCNU = 1-(2-chloroethyl)-3-(4-trans-methylcyclohexyl)-1-nitrosourea.

B. Chemical and Physical Data

1. *Chemical Abstract No.: 13909-02-9
2. *Synonyms: NSC-95466; Urea, N-(2-chloroethyl)-N'(2, 6-dioxo-3-piperidyl)-N-nitrroso-.[A]
3. *Chemical structure, chemical formula and molecular weight:

$C_8H_{10}ClN_40_4$ 261.67

4. Density: No data.
5. *Absorption spectroscopy: Absorbance maxima at 216 (minor) and 233 (major) nm. Fluorescence ($^{\lambda}$ex = 310, $^{\lambda}$em = 375 nm) is too weak for visualization on TLC (Pavlik *et al.*, 1983). Infrared data have been published (Johnston et al., 1966).
6. Volatility: No data; may be regarded as essentially non-volatile.
7. *Solubility: Water solubility is somewhat higher (approx. 1 mg/ml) than that of BCNU, CCNU, and Me-CCNU (US DHHS, 1984); this is also reflected in a lower octanol-water partition co-efficient (log P = 0.31) than for the above-named compounds (Hansch *et al.*, 1972). Slightly more soluble in 95% ethanol (2-3 mg/ml) and chloroform (1-3 mg/ml).
8. Description: No data but probably a white powder.
9. Boiling point: No data; melting point: 154ºC with decomposition (Johnston *et al.*, 1966).
10. Stability: No data; in analogy with related chloroethylnitroso-ureas, PCNU may be expected to be stable in dry form in unopened vials for several years. Storage at refrigerator temperature is recommended. It is likely to be decomposed in alkaline solution. Solutions in 3% methanol decomposed 4, 6.5, 15, and 38% in 1, 3, 6, and 24 hours (temperature not stated).
11. Chemical reactivity: In contrast with BCNU, CCNU, and Me-CCNU, the rate of decomposition in aqueous solution of PCNU is not influenced by the addition of serum albumin or lipoprotein (Levin *et al.*, 1981). Nevertheless the decomposition in plasma (t ½ = 15.4 min) is higher than in phosphate buffer, suggesting an influence of a plasma component other than albumin (Smith *et al.*, 1983).
12. Flash point: No data.
13. Autoignition temperature: No data.
14. Explosive limits in air: No data.

C. Fire, Explosion, and Reactivity Hazard Data

1. PCNU is likely to be inactivated under conditions of fire. Fire-fighting personnel should wear protective clothing and face masks.
2. Flammability is likely to be low.
3. Conditions contributing to instability are alkali and elevated temperatures.

[A] Chemical Abstracts name, used for listing in 9th Decennial Index and subsequently.

4. Hazardous decomposition products under conditions of fire have not been identified but are likely to include hydrochloric acid and nitrogen oxides.

D. Operational Procedures

The NIH Guidelines for the Laboratory Use of Chemical Carcinogens describe operational practices to be followed when potentially carcinogenic chemicals are used in NIH laboratories. The NIH 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 PCNU.

It should be emphasized that this data sheet and the NIH Guidelines are intended as starting points for the implementation of good laboratory practices when using this compound. The practices and procedures described in the following sections pertain to the National Institutes of Health and may not be universally applicable to other institutions. Administrators and/or researchers at other institutions should modify the following items as needed to reflect their individual management system and current occupational and environmental regulations.

Solutions of PCNU do not penetrate glove materials such as latex or thick PVC but do penetrate thin PVC (Laidlaw *et al.*, 1984).

1. Chemical inactivation: No validated method reported.
2. Decontamination: Turn off equipment that could be affected by PCNU or the materials used for cleanup. If there is any uncertainty regarding the procedures to be followed for decontamination, call the NIH Fire Department (dial 911) for assistance. Wipe off surfaces with ethanol, then wash with copious quantities of water. Glassware should be rinsed (in a hood) with ethanol, followed by soap and water. Animal cages should be washed with water.
3. Disposal: No waste streams containing PCNU shall dispose of in sinks or general refuse. Surplus PCNU or chemical waste streams contaminated with PCNU 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 PCNU 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 PCNU 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 PCNU 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 PCNU shall be handled in accordance with the NIH radioactive waste disposal system.
4. Storage: Store solid PCNU in unopened vials, preferably under refrigeration. Avoid exposure to light and moisture. Store working quantities of PCNU and its solutions in an explosion-safe refrigerator in the work area.

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

1. Sampling: No specific data; as for other chloroethylnitrosoureas, blood samples should be cooled immediately with ice, centrifuged while cold, and extracted (usually with ether).
2. Analysis: Very few methods specific for PCNU have been published. The colorimetric methods based on liberation of nitrous acid with the Griess or Bratton-Marshall reagent (Loo and Dion, 1965; DeVita *et al*., 1967) may be applicable but their sensitivity will have to be checked. Derivation by conversion to methyl-carbamate, with a lower detection limit of 100 ng/ml plasma (Weinkam and Liu, 1982) or with trifluoroacetic anhydride are deemed not to be sufficiently sensitive for PCNU. A

specific method with detection limits of less than 1 ng/ml plasma using ether extraction, thin layer chromatography followed by negative chemical ionization mass spectrometry has been developed (Smith *et al*., 1983). Analysis for radioactivity of PCNU labeled with ^{14}C in the 2-chloroethyl group after ether extraction and thin layer chromatography has been described (Rahman *et al*., 1984).

F. Biological Effects (Animal and Human)

Absorption: No data, but can be expected to be effective via the intravenous or intraperitoneal route.

Distribution and pharmacokinetics: Very few studies dealing with PCNU have been reported. Disappearance of intravenous ^{14}C-labeled PCNU from plasma is biphasic (t ½ = 21.7 min and 27.4 hours) in the mouse and is below detectable limits in vivo in 4 hours. High levels of radioactivity are found 5 min after administration in kidney, lung, liver, brain, heart, and spleen. It is interesting to note that 50-60% of the radioactivity in the brain, heart, and spleen is in the form of intact PCNU, whereas in the liver, which is probably the site of PCNU metabolism, only 7% of the radioactivity is in the form of intact PCNU (Rahman *et al.*, 1984). A comparative pharmacokinetic study of PCNU and BCNU in rats and patients indicates that PCNU should be a better chemotherapeutic agent in rats (Levin *et al.*, 1981).

Metabolism and excretion: The studies quoted above indicate that PCNU is metabolized in the animal body but no products of metabolism have been identified. Excretion of the PCNU (and its metabolites) by radioactivity measurements is primarily in the urine (62% in 24 hours) with little fecal excretion (4%) (Woolley et al., 1981; Rahman et al., 1984).

Toxic effects: The only published actue LD50 data for PCNU are 35.7 and 22 mg/kr in the mouse for oral and intravenous administration (NIOSH, 1984) which would indicate that PCNU is slightly more toxic than other 2-chloroethlynitrosoureas. Toxic effects are myelosuppression with anemia, leucopenia, and thrombocytopenia with no evidence of liver, kidney, or lung involvement (Woolley *et al.*, 1981). The mechanism of toxic action of compounds of this class has been ascribed to alkylation and carbamoylation of DNA and proteins; a comparative study of PCNU, BCNU, CCNU, and Me-CCNU shows that relative antitumor and alkylating activity decreases, and carbamoylating activity increases, in the order shown. Since antitumor activity was measured in rats using intracerebral injection of 9L sarcoma cells this would indicate that PCNU is a superior drug for cerebral tumors (Levin and Kabra, 1974). This is in agreement with earlier conclusions by Hansch *et al.* (1972) based on relative lipid-water solubilities of these drugs.

Carcinogenic effects: No data.

Mutagenic and teratogenic effects: No data. However, other 2-chloroethylnitrosoureas are mutagenic.

G. Emergency Treatment

1. Skin and eye exposure: For skin exposure, remove contaminated clothing and wash skin with soap and water. Skin should not be rinsed with organic solvents. Avoid rubbing of skin or increasing its temperature. For eye exposure, irrigate immediately with copious quantities of running water for at least 15 minutes. Obtain opthalmological evaluation.
2. Ingestion: Drink plenty of water or milk. Induce vomiting. Refer for gastric lavage.
3. Inhalation: Remove victim promptly to clean air. Administer rescue breathing if necessary.
4. Refer to physician.

H. References

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