

Safety Data Sheet

BCNU (Carmustine)

Division of Safety
National Institutes
of Health



WARNING!

THIS COMPOUND IS TOXIC, CARCINOGENIC, TERATOGENIC, MUTAGENIC, AND EMBRYOTOXIC. IT IS ABSORBED BY VARIOUS BODY TISSUES, THROUGH THE SKIN AND RESPIRATORY AND INTESTINAL TRACTS AND TRANSPLACENTALLY. IT MAY IRRITATE THE SKIN AND EYES. 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. REFER TO PHYSICIAN.

IN CASE OF LABORATORY SPILL, WEAR PROTECTIVE CLOTHING DURING CLEANUP. AVOID SKIN CONTACT OR BREATHING OF AEROSOLS. DISPOSE OF WASTE SOLUTIONS AND MATERIALS APPROPRIATELY.

A. Background

BCNU (carmustine) is a light yellow powder, melting to an oily liquid at 30-32°C, stable in pure form and in solution at slightly acid pH, readily decomposed in alkaline solution. It is toxic in all mammalian species tested (oral and parenteral LD50 in the mg/kg range) and carcinogenic, mutagenic, teratogenic, and embryotoxic. Because of its high lipid solubility, which permits penetration of the "blood-brain barrier", its major use alone or

Issued: 8/86

Prepared by the Environmental
Control and Research Program

in combination with other therapeutic agents, is as an antineoplastic in the treatment of primary and metastatic brain tumors in addition to that of Hodgkin's lymphoma and multiple myelomas. Toxic side effects are on the hematopoietic system, the gastrointestinal tract, the liver, and possibly on the pulmonary system. Its mechanism of action consists of alkylating and carbamoylating reactions with nucleic acids.

General reviews include: Carter et al. (1972), Schabel (1976), IARC (1981).

B. Chemical and Physical Data

1. Chemical Abstract No.: 154-93-8
2. Synonyms: BCNU; BiCNU; bis(2-chloroethyl) nitrosourea; N,N'-bis(2-chloroethyl) nitrosourea; carmustin; carmustine; Nitrumon; NCI-CO4773; NSC 409962; Urea, N,N'-bis(chloroethyl)-N-nitroso-^A
3. Chemical structure and molecular weight:
$$\begin{array}{c} \text{NO O} \\ | \quad || \\ \text{ClCH}_2\text{CH}_2\text{N}-\text{C}-\text{NHCH}_2\text{CH}_2\text{Cl} \end{array}$$

$\text{C}_5\text{H}_9\text{Cl}_2\text{N}_3\text{O}_2$; 214.04
4. Density: No data.
5. Absorption spectroscopy: Weak chromophore with $\lambda_{\text{max}} = 232 \text{ nm}$.
6. Volatility: No data.
7. Solubility: Slightly soluble in aqueous solution [1 g in 250 ml saline (Carter et al., 1972)]; soluble in ethanol [450 mg per ml (Davignon et al., 1973)]. Highly soluble in lipids and nonpolar organic solvents. Formulations for parenteral injection are usually in absolute ethanol which is diluted with sterile water (Davignon et al., 1973) or in a 1:1 mixture of ethanol with Cremophor EL (Sigma) (a surfactant based on polyethoxylated ricinus oil) and then diluted with saline (e.g., Fiebig et al. 1980).
8. Description: Light yellow powder which melts to an oily liquid.
9. Boiling point: No data. Melting point: 30-32°C.

^AChemical Abstract name, used for listing in 7th Decennial Index and subsequently.

10. **Stability:** Previous work on the stability of BCNU in aqueous solution has been reviewed recently (Bosanquet, 1985). Dry BCNU in unopened vials is stable for at least two years at refrigerator temperature. It is also stable in solution in nonpolar organic solvents. Its aqueous solution is most stable at pH 3.5-4 (10% decomposition in 5 hr at room temperature); stability decreases moderately at lower pH, and markedly at higher pH, with an approximately three-fold increase in decomposition rate per unit pH increase between pH 5 and 8. Solutions of BCNU in 5% dextrose, suitable for infusion, are far less stable in plastic (time for 10% decrease = 0.6 hr) than in glass containers (7.7 hr) (Benvenuto et al., 1981). It is recommended that BCNU not be added to infusion solutions containing sodium bicarbonate (Colvin et al., 1980). A scheme for its decomposition in aqueous solution has been proposed (Colvin et al., 1976; Chatterji et al., 1978). See also Chemical reactivity, below.
11. **Chemical reactivity:** The decomposition of BCNU is markedly increased in the presence of proteins (e.g., the half-times of disappearance from Ringer solution, pH 7.4, volunteer sera and patient sera were 51.4, 11.6, and 15.6 min, respectively [Levin et al., 1978a]); the mechanism appears to be catalysis by serum albumin of the conversion of BCNU to reactive species [2-chloroethylazohydroxide and 2-chloroethylisocyanate (Weinkam et al., 1980)]. BCNU interacts with DNA by cross-linking (Lown and McLaughlin, 1979; Lown et al., 1979), and carbamoylates free amino groups of peptides and proteins (Wheeler et al., 1975).

2. **Flash point:** No data.
3. **Autoignition temperature:** No data.
4. **Explosive limits in air:** No data.

Fire, Explosion, and Reactivity Hazard Data

1. BCNU 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 acid, alkali, and elevated temperatures.
4. **Hazardous decomposition products** under conditions of fire are likely to include hydrochloric acid and nitrogen oxides.

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 BCNU.

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.

Solutions of BCNU penetrate various glove materials (Laidlaw et al., 1984; Connor et al., 1984). This factor should be taken into account when handling BCNU.

1. Chemical inactivation: No validated method reported.
2. Decontamination: Turn off equipment that could be affected by BCNU or the materials used for cleanup. Call the NIH Fire Department (dial 116) 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 BCNU shall be disposed of in sinks or general refuse. Surplus BCNU or chemical waste streams contaminated with BCNU 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 BCNU 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 BCNU 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 BCNU 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 BCNU shall be handled in accordance with the NIH radioactive waste disposal system.

4. Storage: Store solid BCNU in unopened vials, preferably under refrigeration. Avoid exposure to light and moisture. Store working quantities of BCNU and its solutions in an explosion-safe refrigerator in the work area. See B10 for further information.

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

1. Sampling: It is important that blood samples be immediately cooled in ice, centrifuged while cold, and then extracted. Tissue samples are frozen and homogenized (Lee and Workman, 1983).
2. Analysis: Early analyses were based on colorimetry, employing the Friess or Bratton-Marshall reagent after acid liberation of nitrous acid in the presence of sulfanilamide (Loo and Dion, 1965; DeVita et al., 1967). This method is capable of measuring plasma levels down to 1 $\mu\text{g/ml}$, a sensitivity which, because of the fast disappearance of intact BCNU from the blood stream, is not sufficient for monitoring patients for more than 5-10 minutes after oral or intravenous administration (Levin et al., 1978). In addition, the method is not specific for BCNU but also measures active metabolites (Weinkam and Liu, 1982) unless further modified by extraction (Kari et al., 1980) or thin-layer chromatography (DeVita et al., 1967). Differential pulse polarography (Russo et al., 1981, 1984) has a detection limit of 20 ng and is more specific. A convenient and rapid method is high-pressure liquid chromatography with a detection limit of about 100-200 ng/ml whole blood (Krull et al., 1981). Chemical ionization-mass spectrometry, with a detection limit of 50 ng/ml has been described (Weinkam et al., 1978) and used in pharmacokinetic studies (Levin et al., 1978). Sensitivity and specificity have been further enhanced by derivatization methods, either by reaction with methanol to form O-methylcarbamate (Weinkam and Liu, 1982), with trifluoroacetic anhydride (Smith et al., 1981), followed by gas chromatography-mass spectrometry, the latter with a sensitivity of 1-3 ng/ml plasma. A modification of this method, employing methane chemical ionization (Smith and Cheung, 1982) and indicating even higher sensitivity, was actually developed for chloroethyl cyclohexyl nitrosourea (Smith and Cheung, 1982) but there is no reason why it should not apply to BCNU also.

Biological Effects (Animal and Human)

Absorption: BCNU is quickly absorbed and produces biological effects after parenteral (intravenous, intraperitoneal) injection and by ingestion. Percutaneous absorption, with effects on the hematopoietic system of patients has also been noted (Zackheim et al., 1977a, 1977b).

Distribution and pharmacokinetics: Because of the rapid chemical and biochemical decomposition of BCNU in plasma and tissues shortly after administration, distribution data, based on experiments with BCNU labeled with ^{14}C in either ethylene or carbonyl groups, refer to hydrolysis products rather than to intact BCNU. Significant quantities are found in all tissues and are similar regardless of type of label or route of administration. Highest values are found in liver, kidney, and lung, with lower amounts in heart, spleen, brain and muscle. This activity drops quickly after the initial hours but brain tissue retains activity for longer periods of time than other tissues (Wheeler et al., 1964; Zackheim et al., 1977b; Levin et al., 1978a,b). In man, data on plasma disappearance of BCNU support a two-compartment open model (Levin et al., 1978a; Russo et al., 1981).

Metabolism and excretion: Very little has been published concerning the metabolism of BCNU. Because of its rapid disappearance from plasma after oral or parenteral administration it has been assumed that its fate in vivo is similar to its decomposition in aqueous solution. Schemes for this decomposition, including the suggested mechanisms for the non-specific catalysis of decomposition by serum proteins (see also B11) have been published (Colvin et al., 1974, 1976; Wheeler et al., 1975, Weinkam et al., 1980) and these indicate the formation of chloroethyl carbonium ion as an alkylating agent, and 2-chloroethyl isocyanate as a carbamoylating agent. Excretion of radioactivity from ^{14}C -labeled BCNU is mostly via urine although up to 10% has been accounted for in respiratory CO_2 (DeVita et al., 1967). Other volatile compounds (vinyl chloride, acetaldehyde, dichloroethane, and chloroethanol) have been identified in the aqueous decomposition of BCNU (Colvin et al., 1974) but there are no data which would indicate their liberation in the animal body.

Toxic effects: The acute LD50 of BCNU is between 14 and 30 mg/kg for the mouse and rat via the oral, intravenous, intraperitoneal, or subcutaneous route when observed for a 30 day period. Prolongation of this period increases the mortality; for instance, all doses above the LD1 in rats (10 mg/kg) result in 100% mortality (Thompson and Larson, 1972). As with other alkylating agents, no deaths are observed earlier than 4-5 days after administration of even massive doses.

The toxic effects in man and higher mammals have been reviewed (Oliverio, 1973; Perry and Yarboro, 1984) and consist of delayed bone marrow (resulting in thrombocytopenia), cardiopulmonary, gastrointestinal, renal, and hepatic effects in the dog, and (with the exception of cardiopulmonary effects) in the monkey. Effects on spermatogenesis in mice (Meistrich et al., 1982) have also been noted. Hemorrhagic inflammation and skin ulceration occurs in guinea pigs after intradermal injection, similar to what might occur in patients upon extravasation (Barr et al., 1981).

The mechanism of toxic (and anticarcinogenic) action consists of alkylation and cross-linking of DNA (Connors and Hare, 1975; Lown and McLaughlin, 1979) which results in decrease or lack of incorporation of precursors into DNA and RNA and inhibition of protein synthesis.

5. Carcinogenic effects: The literature through 1980 has been summarized (IARC, 1981). Intraperitoneal or intravenous BCNU produces lung tumors, and intraperitoneal BCNU produces intraabdominal tumors in the rat; there is also low neurotropic carcinogenic activity (Zeller et al., 1982). Data in man are difficult to interpret since reports deal mainly with patients under treatment with BCNU in combination with radiation and/or other antineoplastics.
6. Mutagenic and teratogenic effects: BCNU is mutagenic in the Ames test (Franza et al., 1980) and in Chinese hamster cells (Bradley et al., 1980). It is teratogenic in the rat and rabbit (Weiss et al., 1973; Thompson et al., 1974).

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. Since BCNU is readily absorbed through the skin, 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 ophthalmological 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.

References

- Barr, R.D., S.G. Benton, and L.W. Belbeck. 1981. Soft-tissue necrosis induced by extravasated cancer chemotherapeutic agents. *J Natl Cancer Inst* 66:1129-1136.
- Benvenuto, J.A., R.W. Anderson, K. Kerkof, R.G. Smith, and T.L. Loo. 1981. Stability and compatibility of antitumor agents in glass and plastic containers. *Am J Hosp Pharm* 38:1914-1918.
- Bosanquet, A.G. 1985. Stability of solutions of antineoplastic agents during preparation and storage for in vitro assays. General considerations, the nitrosoureas and alkylating agents. *Cancer Chemother Pharmacol* 14:83-95.
- Bradley, M.O., N.A. Sharkey, K.W. Kohn, and M.W. Layard. 1980. Mutagenicity and cytotoxicity of various nitrosoureas in V-79 Chinese hamster cells. *Cancer Res* 40:2719-2725.
- Carter, S.K., F.M. Schabel, Jr., L.E. Broder, and T.P. Johnson. 1972. 1,3-Bis(2-chloroethyl)-1-nitrosourea (BCNU) and other nitrosoureas in cancer treatment: A review. *Adv Cancer Res* 16:273-332.
- Chatterji, D.C., R.F. Greene, and J.F. Gallelli. 1978. Mechanism of hydrolysis of halogenated nitrosoureas. *J Med Chem* 67: 1527-1532.
- Colvin, M., J.W. Cowens, R.B. Brundrett, B.S. Kramer, and D.B. Ludlum. 1974. Decomposition of BCNU (1,3-bis[2-chloroethyl]-1-nitrosourea) in aqueous solution. *Biochem Biophys Res Commun* 60:515-520.
- Colvin, M., R.B. Brundrett, W. Cowens, I. Jardine, and D.B. Ludlum. 1976. A chemical basis for the antitumor activity of chloroethyl-nitrosoureas. *Biochem Pharmacol* 25:695-699.
- Colvin, M., J. Hartner, and M. Summerfield. 1980. Stability of carmustine in the presence of sodium bicarbonate. *Am J Hosp Pharm* 37:677-678.
- Connor, T.H., J.L. Laidlaw, J.C. Theiss, R.W. Anderson, and T.S. Matney. 1984. Permeability of latex and polyvinyl chloride gloves to carmustine. *Am J Hosp Pharm* 41:676-679.
- Connors, T.A. and J.R. Hare. 1975. Studies of the mechanism of action of the tumour-inhibiting nitrosoureas. *Biochem Pharmacol* 24:2133-2140.

- Davignon, J.P., K.W. Yang, H.B. Wood, Jr., and J.C. Cradock. 1973. Formulation of three nitrosoureas for intravenous use. *Cancer Chemother Rep*, Pt. 3, 4(3):7-11.
- DeVita, V.T., C. Denham, J.D. Davidson, and V.T. Oliverio. 1967. The physiological disposition of the carcinostatic 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) in man and animals. *Clin Pharmacol Ther* 8:566-577.
- Fiebig, H.H., G. Eisenbrand, W.J. Zeller, and R. Zentgraf. 1980. Anticancer activity of new nitrosoureas against Walker carcinosarcoma 256 and DMBA-induced mammary cancer of the rat. *Oncology* 37:177-183.
- Franza, B.R., Jr., N.S. Oeschger, M.P. Oeschger, and P.S. Schein. 1980. Mutagenic activity of nitrosourea antitumor agents. *J Natl Cancer Inst* 65:149-154.
- IARC. 1981. International Agency for Research on Cancer. Bis-chloroethyl nitrosourea (BCNU). *IARC Monographs* 26:79-95.
- Kari, P., W.R. McConnell, J.M. Finkel, and D.L. Hill. 1980. Distribution of Bratton-Marshall-positive material in mice following intravenous injections of nitrosoureas. *Cancer Chemother Pharmacol* 4:243-248.
- Krull, I.S., J. Strauss, F. Hochberg, and N.T. Zervas. 1981. An improved trace analysis for N-nitrosoureas from biological media. *J Anal Toxicol* 5:42-46.
- Laidlaw, J.L., T.H. Connor, J.C. Theiss, R.W. Anderson, and T.S. Mætney. 1984. Permeability of latex and polyvinyl chloride gloves to 20 antineoplastic drugs. *Am J Hosp Pharm* 41:2618-2623.
- Lee, F.Y.F and P. Workman. 1983. Modification of CCNU pharmacokinetics by misonidazole - A major mechanism of chemosensitivity in mice. *Brit J Cancer* 47:659-669.
- Levin, V.A., W. Hoffman, and R.J. Weinkam. 1978a. Pharmacokinetics of BCNU in man: A preliminary study of 20 patients. *Cancer Treat Rep* 62:1305-1312.
- Levin, V.A., P.A. Kabra, and M.A. Freeman-Dove. 1978b. Relationships of 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) and 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU) pharmacokinetics of uptake, distribution and tissue/plasma partitioning in rat organs and intracerebral tumors. *Cancer Chemother Pharmacol* 1:233-242.

- Loo, T.L. and R.L. Dion. 1965. Colorimetric method for the determination of 1,3-bis(2-chloroethyl)-1-nitrosourea. *J Pharm Sci* 54:809-810.
- Lown, J.W. and L.W. McLaughlin. 1979. Mechanism of action of 2-haloethylnitrosoureas on deoxyribonucleic acid. Nature of the chemical reactions with deoxyribonucleic acid. *Biochem Pharmacol* 28:2123-2128.
- Lown, J.W., L.W. McLaughlin, and J.A. Plambeck. 1979. Mechanism of action of 2-haloethylnitrosoureas on deoxyribonucleic acid. Nature of the intermediates from nitrosourea decomposition. *Biochem Pharmacol* 28:2115-2121.
- Meistrich, M.L., M. Finch, M.F. DuCunha, U. Hacker, and W.W. Au. 1982. Damaging effects of fourteen chemotherapeutic drugs in mouse testis cells. *Cancer Res* 42:122-131.
- Oliverio, V.T. 1973. Toxicology and pharmacology of the nitrosoureas. *Cancer Chemother Rep, Pt. 3*, 4(3):13-20.
- Perry, M.C. and J.W. Yarbro. 1984. Toxicity of Chemotherapy. Grune and Stratton, Orlando, FL.
- Russo, R., I. Bartošek, E. Piazza, A.M. Santi, A. Libretti, S. Garattini. 1981. Differential pulse polarographic determination of BCNU pharmacokinetics in patients with lung cancer. *Cancer Treat Rep* 65:555-562.
- Russo, R.G., M.T. Cattaneo, and I. Bartošek. 1984. Pharmacokinetics of nitrosoureas: Comparison of 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) and 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU) after oral and intravenous administration to rats. *Tumori* 70:499-502.
- Schabel, F.M., Jr. 1976. Nitrosoureas: A review of experimental antitumor activity. *Cancer Treat Rep* 60:665-698.
- Smith, R.G., S.C. Blackstock, L.K. Cheung, T.L. Loo. 1981. Analysis for nitrosourea antitumor agents by gas chromatography - mass spectrometry. *Anal Chem* 53:1205-1208.
- Smith, R.G. and L.K. Cheung. 1982. Determination of two nitrosourea antitumor agents by chemical ionization gas chromatography - mass spectrometry. *J Chromatogr* 229:464-469.

- Thompson, G.R. and R.E. Larson. 1972. A toxicologic comparison of the potency and activity of 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) and 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU) in mice and rats. *Toxicol Appl Pharmacol* 21:405-413.
- Thompson, D.J., J.A. Molello, R.J. Strebing, I.L. Dyke, and V.B. Robinson. 1974. Reproduction and teratology studies with oncolytic agents in the rat and rabbit. I. 1,3-bis-(2-chloroethyl)-1-nitrosourea (BCNU). *Toxicol Appl Pharmacol* 30:422-439.
- Weinkam, R.J., J.H.C. Wen, D.E. Furst, and V.A. Levin. 1978. Analysis for 1,3-bis(2-chloroethyl)-1-nitrosourea by chemical ionization mass spectrometry. *Clin Chem* 24:45-49.
- Weinkam, R.J., T.-Y.J. Liu, and H.-S. Lin. 1980. Protein mediated chemical reactions of chloroethylnitrosoureas. *Chem-Biol Interactions* 31:167-177.
- Weinkam, R.J. and T.-Y.J. Liu. 1982. Quantitation of lipophilic chloroethylnitrosourea cancer chemotherapeutic agents. *J Pharm Sci* 71:153-157.
- Weiss, E. deC., H. Cravioto, J.F. Weiss, and J. Ransohoff. 1973. Pathologic effects in rats surviving prenatal and neonatal administration of 1,3-bis(2-chloroethyl)-1-nitrosourea. *J Natl Cancer Inst* 51:1363-1365.
- Wheeler, G.P., B.J. Bowdon, and T.C. Herren. 1964. Distribution of C^{14} from C^{14} labeled 1,3-bis(2-chloroethyl)-1-nitrosourea (NSC-409962) in tissues of mice and hamsters after intraperitoneal administration of the agent. *Cancer Chemother Rep* 42:9-12.
- Wheeler, G.P., B.J. Bowdon, and R.F. Struck. 1975. Carbamoylation of amino acids, peptides and proteins by nitrosoureas. *Cancer Res* 35:2974-2984.
- Zackheim, H.S., R.J. Feldmann, C. Lindsay, and H.I. Maibach. 1977a. Percutaneous absorption of 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU, carmustine) in mycosis fungoides. *Brit J Dermatol* 97:65-67.
- Zackheim, H.S., R.J. Feldmann, C. Lindsay, and H.I. Maibach. 1977b. Distribution of ^{14}C after topical application of ^{14}C -labeled 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) in mice. *Experientia* 33:753-754.
- Zeller, W.J., S. Ivankovic, M. Habs, and D. Schmähl. 1982. Experimental chemical production of brain tumors. *Ann NY Acad Sci* 381:250-263.