CHEMICAL HAZARD INFORMATION PROFILE

DRAFT REPORT

Semicarbazide

CAS NO. 57-56-7

April 27, 1982

DISCLAIMER

This document is a preliminary draft. It has not been released formally by the Office of Toxic Substances, Office of Pesticides and Toxic Substances, U.S. Environmental Protection Agency, and should not at this stage be construed to represent Agency policy. It is being circulated for comments on its technical merit and policy implications.

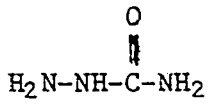
This report represents a preliminary assessment of the subject chemical's potential for injury to human health and the environment and therefore may not reflect all available information on the subject chemical. Any recommendations based on this report are tentative and should not be construed as final Agency policy with respect to the subject chemical.

I. Summary of Available Data

Many sources use semicarbazide and semicarbazide hydrochloride (CAS No. 563-41-7) interchangeably without clear indication as to which is being discussed. Where it is clear, the compound is named within the text; however, from available information, it seems that the biological action of both are the same. Therefore production figures and exposure data are provided for both compounds.

A. Chemical Identity

1. CAS Registry Number: 57-56-7 C_5N_3O
2. Chemical Name: Hydrazinecarboxamide (9 CI); isosemicarbazide (8 CI)
3. Synonyms: Carbamic acid, hydrazide; carbazamide; carbazimidic acid; aminocarbonylhydrazine; semicarbazide; aminourea; carbamylhydrazine; carbamoylhydrazine
4. Structural Formula:



B. Physical and Chemical Properties

5. Molecular Weight: 75.07
6. Physical State: Solid (Weast and Astle 1981-1982)
7. Melting Point (°C): 96 (Weast and Astle 1981-1982)
8. Boiling Point (°C): Not available
9. Solubilities:
   a) Water: Very soluble (Radding et al. 1977, Weast 1970-1971)
   b) Nonaqueous Solvents: Slightly soluble in alcohol; insoluble in ether, benzene, or chloroform (Radding et al. 1977, Weast 1970-1971)
10. Dissociation Constant: 2.7×10^{-11} (pKa: 10.57) (Lange and Forker 1946)
11. Partition Coefficient (log P): -2.53 for octanol/water (Radding et al. 1977)
12. Density: Not available
13. Volatility: Not available
14. Reactivity: Though no specific information is given for semicarbazide, hydrazines in general are oxidized in water by molecular oxygen to diimides and then to nitrogen. This reaction could possibly be catalyzed by metal ions:

$$RNHNH_2 \longrightarrow [RN = NH] \longrightarrow RH + N_2 + H_2O$$

(Wagnerona et al. 1973, as reviewed in Radding et al. 1977).

Semicarbazide, in reaction with aldehydes and ketones, yields semicarbozones (Fishbein 1979).

C. Exposure

1. Worker Exposure Considerations

a. Production

The U.S. International Trade Commission did not report semicarbazide production for the years of 1975-1980 implying an annual production of less than 5,000 lbs (or less than $5,000.00 in sales) in 1976-1980 and less than 1,000 lbs (or less than $1,000.00 in sales) in 1975 (USITC 1977-1981, as reviewed in USEPA 1982). Semicarbazide hydrochloride production was also not reported in the years 1975-1980.

The nonconfidential file of the TSCA Chemical Substance Inventory (USEPA 1978) indicates that in 1977 the Fairmont Chemical Company, Newark, NJ, manufactured between 100,000 and 1,000,000 lbs of the free base semicarbazide and 100,000 to 1,000,000 lbs of the HCl salt, for a total of 200,000 to 2,000,000 lbs. Chem-Sources-U.S.A. (1982) does not list a current producer for semicarbazide but it does list the Fairmont Chemical Company as a current manufacturer of the hydrochloride.

b. Imports

Separate data on the importing of semicarbazide were not given by the U.S. Bureau of the Census in the years 1975-1980 (USEPA 1982). However, according to the TSCA Chemical Substances Inventory, semicarbazide hydrochloride was imported in 1977 by Aceto Chemical Company, Inc., Flushing, NY (10,000-100,000 lbs) and Sobin Chemicals, Inc., Boston, MA (0-1,000 lbs) (USEPA 1978).

c. Exports

No information was available.

d. Process Type

The following methods can be used for the production of semicarbazide: (1) reaction of hydrazine and urea (Durham 1965, as reviewed in Schiessl 1980); (2) action of potassium cyanate on hydrazine sulfate (Thiele and Strange 1894, as reviewed in Udupa et al. 1966); (3) action of hydrazine hydrate on urea (Rossel and Frank 1894, as reviewed in Udupa et al. 1966); (4) heating hydrazine ammonium carbonate (Fichter and Beeker 1912, as reviewed in Udupa et al. 1966); (5) reduction of nitrourea with zinc dust and hydrochloric acid (Thiele and Heusser 1896, as reviewed in Udupa et al. 1966); (6) electrolytic reduction of nitrourea (Udupa et al. 1966); (7) reaction of carbon monoxide with *N,N*-dialkylhydrazine in the presence of selenium yielding 3,3-dialkylselenocarbazic acid and hydrazine - aminolysis followed by oxidation with oxygen gives semicarbazide (Kondo et al. 1974); (8) heating either *N*-chloroguanidine or *N*-hydroxyguanidine-*O*-sulfonic acid with aqueous sodium hydroxide (Ohme and Preuschhof 1969). Schiessl (1980) states that semicarbazide is best made from hydrazine and urea.

e. Workplace Monitoring, and Determination Methodology

Colorimetric determination of hydrazines, and by analogy, semicarbazide, can be accomplished by the formation of colored azines with salicylaldehyde or *p*-dimethylaminobenzaldehyde (Feigl 1966, as reviewed in Schiessl 1980). The *p*-dimethylaminobenzaldehyde method is suitable for quantitative determination in the ppm range and is also used for determination in waste waters and in air by absorption from a known volume of air in a acidified solution of *p*-dimethylaminobenzaldehyde.

f. Worker Exposure

No data were found.

g. Industrial Uses

Semicarbazide has been used as an intermediate in the production of sulfonyl-semicarbazides such as 4-methyl-benzenesulfonyl 2-(aminocarbonyl)-hydrazide and 4,4'-oxybisbenzenesulfonyl bis [2-(aminocarbonyl)hydrazine] which are useful in the foaming of rubber (Schiessl 1980, as reviewed in USEPA 1982).

Miscellaneous uses of semicarbazide include the following: (1) determination of acetaldehyde in biological specimens (Stowell et al. 1980, as reviewed in NLM printout 1982, Stowell 1979, Anderson et al. 1978, as reviewed in Chem. Abstr. 89:101066u); (2) in removing labile glycohemoglobin (Nathan et al. 1981, as reviewed in NLM printout 1982); (3) in laboratory experiments involving enzymes (Lee 1979, Denk et al. 1978, Roth and Gillis 1975, Sladek 1973); (4) in investigations of morphine analgesia (Yoneda et al. 1976); (5) in investigations of mescaline metabolism (Roth et al. 1976); and (6) in studies of nerve transmission (Capek and Esplin 1977).

Semicarbazide has also been suggested for use in preventing discoloration of wood (Minemura 1977, as reviewed in CAB Abstr. 1982); as a cross-linking agent for oxidized ethylene polymers and acrylic fibers (Kehr 1970, Zharkova et al. 1969 as reviewed in Fishbein 1979); as a stabilizer for ethylenevinyl-acetate polymers (Meincke 1970, as reviewed in Fishbein 1979); in the synthesis of plant growth regulators (Roechling et al. 1975, as reviewed in Fishbein 1979); in the preparation of anion-exchangers from polyethylene-polyamines (Samborskii et al. 1974, as reviewed in Fishbein 1979); and in phosphors (Isojima et al. 1974, as reviewed in Fishbein 1979).

Thiosemicarbazides and thiosemicarbazide derivatives have been studied as meat tenderizers (Sekoguchi et al. 1978, as reviewed in Biol. Abstr. 65:70253) and as antimicrobial agents (Bu 1975, as reviewed in Biol. Abstr. 63:31098; Ohmori et al. 1978, as reviewed in Chem. Abstr. 63:46850). Semicarbazide hydrochloride is useful in the preparation of drugs, e.g., nitrofurazone (Hoover 1975, as reviewed in USEPA 1982).

The classification of the uses of semicarbazide and semicarbazide hydrochloride in accordance with the Chemical Use Standard Encoding System (ChemUSES) (Goen et al. 1980, as reviewed in USEPA 1982) is as follows:

290 (Organic intermediate)/28.14.14-6 (Plastics and rubber chemicals)

290 (Organic intermediates)/28.06-4 (Drugs)

238 (Analytical and product testing agents)/
28.02.02.06-8 (Aldehydes);
28.02.02.05-7 (Ketones)

374 (Reagents)/28.02-0 (Organic chemicals)

h. Processors

Uniroyal, Inc., Middlebury, CT may use semicarbazide in the production of the blowing agents 4-methyl-benzenesulfonyl 2-(aminocarbonyl) hydrazide and 4,4'-oxybisbenzenesulfonyl bis[2(aminocarbonyl)hydrazide] (USEPA 1982). Also Morton-Norwich Products, Inc., The Norwich-Eaton Company Division, Norwich, NY, may use semicarbazide hydrochloride in the production of nitrofurazone (USEPA 1982).

i. Disposal

No data were available.

2. Consumer Exposure Considerations

No data were found which document consumer exposure to semicarbazide. Consumers could be exposed to semicarbazide as an agent to prevent the discoloration of wood (a use suggested by Minemura 1977, as reviewed in CAB Abstr. 1982). Consumer exposure to derivatives of semicarbazide is possible through their use as pesticides and meat tenderizers [thiosemicarbizides and their derivatives (Ohmori et al. 1978, as reviewed in Biol. Abstr. 63:46850, Sekoguchi et al. 1978, as reviewed in Biol. Abstr. 65:70253)] and in drugs [semicarbazide hydrochloride (Hoover 1975, as reviewed in USEPA 1982)]. Davis et al. (1978) reported that the photolytic decomposition of the drug indapamide yields semicarbazide suggesting possible exposure to individuals using the drug.

3. Environmental Exposure

a. Environmental Release

No information was found on the release of semicarbazide into the environment.

b. Environmental Fate

i. Persistence

No data were found on the fate of semicarbazide in the environment; however, in water, simple hydrazine derivatives can be oxidized by molecular oxygen to give diimides and subsequently nitrogen (Radding et al. 1977; also see section II.B.14). The octanol/water partition coefficient (log P) of -2.53 suggests that bioaccumulation will not be significant Radding et al. 1977).

ii. Transport

No data were available, documenting the environmental transport of semicarbazide; however, Radding et al. (1977) indicate that simple hydrazine derivatives are polar, nonvolatile, and soluble in water and therefore, will not readily transfer to the atmosphere from water nor are they likely to adsorb to sediments in significant amounts. It should be noted, however, that some amines do bind well to soil via ion-exchange or other mechanisms.

c. Environmental Occurrence

No data were available.

D. Human Health Effects

1. Metabolism

No information was found on the metabolism of semicarbazide. It should be noted that if semicarbazide hydrochloride enters the body, dissociation to semicarbazide will occur.

2. Lethality

Semicarbazide is very toxic when administered acutely to mice and rats via oral, intraperitoneal, subcutaneous and intravenous routes. Some LD_{50} values are listed in Table 1.

TABLE 1. Lethality

Route	Species	LD_{50} (mg/kg)	Reference
Oral	Mouse	176	Lewis 1979
Intraperitoneal	Mouse	123	Lewis 1979
Intraperitoneal	Rat	140	Lewis 1979
Subcutaneous	Rat	173	Lewis 1979
Subcutaneous	Mouse	105	Lewis 1979
Intravenous	Mouse	126	Lewis 1979

3. Carcinogenicity

Mori et al. (1960) designed an experiment to determine the minimum dose of various compounds, including semicarbazide, required to induce pulmonary adenomas in strain dd mice. Female mice, 1½ to 2 months old, were fed a diet containing 0.1% semicarbazide hydrochloride for seven months and were killed for tumor evaluation. Lung nodules were counted macroscopically. Six of eight surviving mice developed tumors (75% incidence) averaging one nodule per mouse. Control dd mice had a tumor incidence of 5% and averaged 0.05 nodules per mouse. Structural comparisons of semicarbazide hydrochloride with other chemicals which gave positive results demonstrated the presence of the carbamyl group in each compound.

Weisburger et al. (1981) investigated the carcinogenic potential of semicarbazide hydrochloride in Charles River CD rats. The compound was administered continuously in the diet at either 1000 ppm (the maximum tolerated dose as determined by range finding studies) or 500 ppm for 18 months, after which time the animals were observed for 6 months. Each dose was given to 26 male and 26 female rats, a total of 104 animals. In the high dose group treatment was discontinued at week 32 because of the large number of deaths. Comprehensive pathological examinations revealed no evidence of tumorigenicity at either dose level.

Toth et al. (1975) administered 0.0625% semicarbazide hydrochloride in the drinking water to 50 female and 50 male Swiss albino mice for life, beginning at six weeks of age. The average daily intake was 3.3 mg for a female and 4.8 mg for a male. An untreated control group of 100 female and 100 male mice were also maintained. All organs were examined macroscopically and histological examination was conducted on the liver, spleen, kidney, bladder, thyroid, heart, pancreas, testis, brain, nasal turbinates and at least four lobes of the lungs of each mouse as well as on those organs showing gross pathological changes.

The results are shown in Table 2. The development of tumors of the lungs and blood vessels was significantly enhanced by continuous lifetime feeding of the compound. In comparison with the controls, the incidence of lung neoplasms in the test group rose from 22% (in the controls) to 40% while the incidence of blood vessel tumors increased from 5 to 12%. The other types of tumors listed in Table 2 occurred in low incidences and their appearance could not be attributed to the treatment.

Parodi et al. (1981) tested sixteen hydrazine derivatives, including semicarbazide, for in vivo DNA-damaging activity using the alkaline elution assay. The assay, which measures single-strand breaks in DNA is thought to be somewhat predictive of carcinogenic potency. Eleven non-inbred male Swiss albino mice 2 to 3 months old were injected intraperitoneally with a total of 3.28 mmol/kg semicarbazide either as a single administration of the LD_{50} twice, or by daily administration of one-third the LD_{50} for 5 successive days. DNA damage was evaluated by the alkaline elution method using lung and kidney preparations. The results indicated that semicarbazide did not cause DNA damage.

4. Mutagenicity

Sixteen hydrazine derivatives, including semicarbazide, were tested for mutagenic activity in the Ames test (Parodi et al. 1981). *Salmonella typhimurium* strains TA 1535, TA 100, TA 1537, TA 1538, and TA 98 were used in a plate incorporation test and a spot test. In the spot test 10 µℓ of a 10% solution (1 mg/plate) of semicarbazide was assayed whereas 100 µℓ (8.3 - 133 µmol/plate) was tested in the plate incorporation test; in both tests mutagenic activity was assessed with and without metabolic activation. Semicarbazide did not demonstrate any mutagenic activity in the spot test and was only weakly mutagenic in the plate incorporation test and in only strain TA 1535. The mutagenic activity was optimal at 67 µmol/plate and was only present without metabolic activation; addition of S-9 mix abolished activity.

Injections of 0.005 mℓ of 0.1M semicarbazide hydrochloride into adult male grasshoppers (*Spachosternum prasiniferum*) caused chromatid and chromosome breaks, translocations, fragments, and bridges in spermatocyte chromosomes (Bhattacharya 1976). It was suggested that semicarbazide acts similarly to hydroxylamine in liberating all the four base pairs from DNA, resulting in the breakage of the sugar-phosphate backbone.

Hayatsu et al. (1966) demonstrated that, in vitro, semicarbazide replaces the C-4 amino group of cytidine and deoxycytidine with a semicarbazide residue. The addition of bisulfite as a catalyst increased the rate of reaction, which was absolutely specific for cytosine nucleotides and nucleosides that are located in the single-stranded region of a nucleic acid (Hayatsu 1976).

Hayatsu (1977) also demonstrated inactivation of, and mutation in, bacteriophage lambda as a result of the co-operative action of semicarbazide and bisulfite upon DNA. In his experiment, bacteriophage strain lambda papa and its host bacteria, *Escherichia coli*, were treated with 1M-sodium bisulfite in the presence of 1M-semicarbazide at 37°C and pH5. Inactivation of the phage took place rapidly, accompanied by induction of the "clear" mutation. Inactivation was faster to the extent of 0.002 in the survivors in 30 min with the combination

TABLE 2. Tumor distribution in semicarbazide hydrochloride (CH)-treated and control Swiss mice

Treatment	Number of Animals	Sex	Animals with: Lung tumors No.	%	Latent periods*	Blood vessel tumors No.	%	Latent periods*	Other Tumors +
0.0625% CH in drinking water daily for life	50	F	25	50	89 (50-111)	9	18	92 (74-107)	5 Malignant lymphomas (54,73,75,91,107) 5 Malignant histiocytoma (104) 1 Sarcoma of glandular stomach (52) 1 Papilloma of forestomach (105)
	50	M	15	30	75 (20-111)	3	6	81 (64-93)	2 Hepatomas (7,71) 1 Hibernoma (111) 1 Malignant lymphoma (79)
Untreated Control	99	F	21	21	95 (60-122)	5	5	113 (97-130)	24 Malignant lymphomas (31,36,68,69,71,79, 80,80,90,94,96,97,101,102,103,105,106, 109,115,118,122,123,130) 2 Adenocarcinomas of breast (73,93) 2 Adenocarcinomas of ovaries (104,106) 1 Adenoma of thyroid (116) 1 Papilloma of skin (109) 1 Malignant histiocytoma (58) 1 Papillary adenoma of ovary (103) 1 Fibrosarcoma, subcutaneous (44) 1 Papilloma of esophagus (103) 1 Leiomyosarcoma of uterus (81) 1 Adenoma of glandular stomach (115)
	99	M	23	23	92 (53-125)	6	6	88 (65-105)	12 Malignant lyphomas (40,57,76,88,93,94, 95,97,102,107,116,126) 1 Fibrosarcoma, subcutaneous (82) 1 Adenocarcinoma of duodenum (113) 1 Malignant histiocytoma (101) 1 Carcinoma of skin (122) 1 Adrenocortical adenoma (130) 1 Papilloma of esophagus (63) 1 Papilloma of forestomach (63)

* Age in weeks (average and range)
+ Latent period given in parenthesis.

Source: Adapted from Toth et al. 1975, p. 19.

of bisulfite and semicarbazide than with either of the two alone; a similar enhancement was seen in the mutation frequency (100 mutants/10^4 survivors after 30 min).

The phage was then reactivated by 1M-sodium phosphate at pH7; reactivation did not significantly alter the freqency of mutation. It was concluded that the cooperativity between bisulfite and semicarbazide in inactivation and mutagenesis of bacteriophage lambda is similar to that of their chemical reaction with cytosine, suggesting that the effects produced on the phage were caused by the modification of cytosine.

In a similar study, Levinson and Helling (1976) found that the infectivity of intact lambda phage and transfection by lambda DNA were inactivated by exposure to a copper complex of semicarbazide. Their results indicated that the inactivation was due to action on DNA.

5. Teratogenicity/Reproductive Effects

a. Type Test: Teratogenicity

Species: Golden Syrian hamster (5-6 pregnant hamsters/group)

Dose/Route: 100, 150 or 200 mg/kg, by gavage, on day 7 of gestation.

Results: Doses of 150 and 200 mg/kg resulted in the death of all females, generally within 48 hours of administration. The animals of the 100 mg/kg group were killed on day 14 or gestation. This dose resulted in the following fetal effects: 1% mortality, 16.5% growth retardation, 5% malpositioned limbs, but no visceral or skeletal abnormalities. No gross external, skeletal or visceral abnormalities were found among litters of untreated or vehicle-treated controls. The authors concluded that semicarbazide appeared to be mildly teratogenic early (day 7) in gestation, but had significant maternal toxic effects at the dose levels tested (Wiley and Joneja 1978).

b. Type Test: Teratogenicity

Species: Sprague-Dawley rat

Dose/Route: See Table 3.

Results: See Table 3. The authors concluded that semicarbazide produced high incidences of cleft palate at 50 mg/day when given on gestation days 10-16; there was also an increased incidence of resorptions. 100 mg/day on days 12-15 of gestation produced a significant number of resorptions and cleft palate in 22/22 fetuses; three of nine treated animals died (Steffak et al. 1972).

TABLE 3. Cleft palate in Sprague-Dawley rats produced by multiple oral doses of semicarbazide HCl

No. of females treated	Dose	Days of gestation administered	Resorption		Cleft palate	
	mg/day		No.	%	No.	%
		Semicarbazide				
6[1]	100	12-15	28/50	56	22/22	100
8	50	10-16	26/68	38	40/42	95
3	25	10-16	1/29	3	12/28	43
11	10	12-15	0/107	0	1/107	0
4	5	12-15	1/33	3	1/32	0

[1] Death occurred in 3 additional pregnant rats.

Source: Steffek et al. 1972, p. 33.

c. Type Test: Teratogenicity

Species: Rat

Dose/Route: Dose not specified; intraperitoneal injection on day 10 or day 13.

Results: The authors determined the LD_{50} to be 140 mg/kg and stated that even at sublethal doses there was no effect on the embryonic development of the rat (Von Kreyburg 1967). No further details were given.

d. Type Test: Teratogenicity/Lathyrogenicity

Species: Porton mice

Dose/Route: 150-180 mg, total, in the diet of pregnant mice during the last week of pregnancy.

Results: The minimal doses to produce aortic rupture or spinal kyphosis in the offspring of treated mothers were 180 and 150 mg, respectively. No maternal deaths were observed (McCallum 1965).

e. Type Test: Teratogenicity

Species: Rat

Dose/Route: 50 mg/kg × 2 on day 7 of gestation or 75 mg × 2/day on days 8-15; subcutaneous injection.

Results: No fetal effects were observed when semicarbazide was the sole treatment. However, when the pregnant animals were fed a pyridoxine-deficient diet in combination with the semicarbazide injections, the fetuses were dead and mummified. These effects were attributed to an inhibition of histamine formation induced by the treatments (Kahlson and Rosengren 1959).

f. Type Test: Teratogenicity

Species: White Leghorn chicken (eggs incubated for 0-16 days).

Dose/Route: 1.0 to 5.0 mg/egg; egg yolk injection

Results: Injections at 4-6 days produced malformations which were dose-related and which included shortened and malformed lower beaks, and bent tarsometatarsal and tibiotarsal bones (Neuman et al. 1956).

g. Type Test: Teratogenicity/Lathyrogenicity

Species: Turkey

Dose/Route: 2 mg; yolk sac injection on day 6 of incubation.

Results: The major effects were in the beak (L-shaped deformity of the lower beak, asymmetrical twisting of the upper beak) and spine (slight lateral scoliosis of the cervical spine) (Cameron 1962).

6. Other Effects

Levene (1968) tested chick embryo monolayer cells in culture for changes in morphology and growth after receiving semicarbazide at doses of 0.25 and 1.5 to 4 mM. No effect on cell morphology or on growth as determined by cell counts was observed.

Weisburger et al. (1981) discovered osteolathyrism and osteoporosis in rats administered semicarbazide hydrochloride (see Section II.D.3 for doses, etc.). Signs of the disorder were rough coats, sternum protrusion and bowing of the legs, and stiffness of the joints with bony growths.

In a study designed to study the effect of lathyrogenic agents on soft tissues, weanling male Sprague-Dawley rats were given finely granulated semicarbazide hydrochloride (0.5 or 0.75 g/kg) in a commercial diet and fed ad libitum for 49 days (Lalich 1966). The 0.5 g/kg dose given to 14 rats, reduced the average weight gains from 4.8 g/day to 3.5 g/day. Autopsies revealed minimal deformities of the sternum, femur, and vertebral column. One of the 14 rats died of aortic rupture. When the level of semicarbazide hydrochloride was increased to 0.75 g/kg in the diet of a separate group of 10 rats, weight gains were reduced to 2.7 g/day, and skeletal deformities were considered to be of moderate severity. Aneurysmal dilation and aortic perforations were not seen at the 0.75 g/kg level; however, prolapse of the penis was seen in 4 of 10 rats after the fifth week. Also one of 10 rats died with acute purulent orchitis and gastrointestinal distention.

Stanley et al. (1975) showed that 0.1% by weight of semicarbazide administered to male weanling Sprague-Dawley rats in their diet caused rupturing of the lungs at much lower recoil pressures than those required for controls. Dilatation of terminal air spaces, rupturing of alveolar walls, and mean linear intercept increases were noted. Biochemical analyses revealed reduced cross-linking in lung collagen. It was concluded that semicarbazide selectively impaired the maturation of lung collagen and that the immaturity was associated with a reduction in the tensile strength of lung tissue.

Many studies of the effects of semicarbazide on the central nervous system have been reported. Jenney and Pfeiffer (1958) give the approximate parenteral convulsant dose (CD_{50}) of semicarbazide in mg/kg as follows: man, 40 i.m. (intramuscularly); monkey, 60 i.p. (intraperitoneally); cat, 40 i.p.; dog, 10 i.m.; guinea pig, 75 i.p.; rabbit, 175 i.p.; rat, 150 i.p.; and mouse, 116.4 ± 3.2 i.p. It was found that fasted mice are more sensitive to the convulsant and to its lethal action; the LD_{50} for intraperitoneal injection being as low as 112 ± 5.4 mg/kg after 16 hours of fasting. Killam and Bain (1957) found that semicarbazide induced seizures in Holtzman adult white rats at a dose of 200 mg/kg administered intraperitoneally. This was associated with a decreased level of gamma-aminobutyric acid (GABA) in the brain. GABA is an end product of the ℓ-glutamic acid decarboxylase enzyme system which was found to be inhibited by semicarbazide. Of the hydrazides tested by Killam and Bain (1957), (thiosemicarbazide, furoyl hydrazide, isonicotinic acid hydrazide and semicarbazide) semicarbazide was the least active as a convulsant. Carlton et al. (1965) produced tremors, ataxia, and paresis in white Peking ducks fed 0.1% semicarbazide hydrochloride for 2 weeks. Microscopic lesions included degenerative changes in the nuclei of cerebellar Purkinje cells, motor neurons of the ventral horn of the spinal cord, and neurons of the medulla oblongata.

Other effects of semicarbazide are as follows: (1) inhibition of amine oxidase activity in the rat aorta (Wibo et al. 1980); (2) weakening of rat tail skin tissue by a possible rupture of bonds involving aldehyde functions (Brown et al. 1969); (3) inhibition of mitochondrial Pi-ATP exchange activity and DNP-stimulated ATPase activity in rat liver (Dallam and Chen 1969); (4) inhibition of copper-linked amino oxidases (Sourkes 1980); and (5) inhibition of renal glutamate decarboxylase in the rat (Goodyer et al. 1980).

E. Environmental Effects

1. Metabolism

No data were available.

2. Lethality

No data were available.

3. Reproduction

No data were available.

4. Behavior

No data were available.

5. Growth and Development

Büning-Pfaue and Rehm (1972) showed that bacterial (*Pseudomonas aeruginosa*) metabolism during decanol oxidation in "batch" fermentation is inhibited by semicarbazide; concentrations too low to influence bacterial respiration inhibited growth.

Propionibacterium shermanni bacteria grown in a cobalt-containing medium, and treated with 10 micromoles/mℓ of semicarbazide, was slightly inhibited in its ability to produce vitamin B_{12} (161 µg/g for the treated cells, compared to 207 µg/g for control cells) and markedly inhibited in the production of porphyrins (142.5 µg/g for the treated cells, compared to 238.3 µg/g for control cells) (Bykhovskii et al. 1966).

6. Population and Community Effects

No data were available.

7 Abiotic Effects

No data were available.

8. Other Effects

No data were available.

F. Existing Standards, Recommended Standards, Regulations

No data were available for semicarbazide; however, hydrazine has a TLV of 1 ppm and it is proposed that this be lowered to 0.1 ppm to conform to the European standard (Schiessl 1980).

G. Other Relevant Information

Adamson (1965), knowing that hydroxyurea had shown antitumor activity, studied the antitumor activity of semicarbazide and other analogs of hydroxyurea

against advanced mouse leukemia L1210 in the hope of determining the active group or groups on the molecule. Mouse leukemia L1210 was implanted into CDBA mice and after 5-7 days, treatment with semicarbazide was initiated at doses of 12.5-150 mg/kg (100 mg/kg/day optimal) per group of 10 animals. The results of the studies showed no increase in the median survival time of the mice when treated with semicarbazide.

Grossberg et al. (1966) demonstrated in KB human malignant cells and other primate cells that semicarbazide (0.3 to 20 mM) increases the development of poliovirus. Specifically, the length of the latent period was diminished, the rate of production of virions was increased; and the final yield of virus was increased.

II. Prelimary Risk Assessment

A. Exposure Assessment

Production figures for semicarbazide were not reported by the U.S. International Trade Commission for the years 1975-1980 implying an annual production of less than 1000 lbs in 1975 (or less than $1,000 in total sales) and less than 5000 lbs in 1976-1980 (or less than $5,000 in total sales) (USITC 1977-1981, as reviewed in USEPA 1982). The nonconfidential file of the TSCA Chemical Substances Inventory (USEPA 1978) indicates that in 1977 between 100,000 and 1,000,000 lbs of the free base semicarbazide and 100,000 to 1,000,000 lbs of the HCl salt were manufactured, a total of 200,000 to 2,000,000 lbs.

No studies documenting either worker, consumer, or environmental exposure were available. Semicarbazide has been used as a chemical intermediate, an analytical reagent and a product testing agent (Goen et al. 1980, as reviewed in USEPA 1982). The latter two uses, in particular, suggest the potential for human exposure. Semicarbazide hydrochloride has been used in the preparation of drugs (Hoover 1975, as reviewed in USEPA 1982) and derivatives of semicarbazide (thiosemicarbazides) have been evaluated for use as meat tenderizers (Sekoguchi 1978, as reviewed in Biol. Abstr. 65:70253).

Available information indicates the potential for significant human exposure to semicarbazide but the exposure assessment would be more complete with the following information: quantification of the amount that is used as a chemical intermediate, documentation of the number of workers and levels to which they are exposed, and quantification of the amount of the hydrochloride used in the manufacture of drugs and residues of the compound remaining in the drugs.

B. Human Health Risk Assessment

When given as acute doses, semicarbazide is apparently very toxic as demonstrated in animals [e.g., intraperitoneal LD_{50} in rats is 140 mg/kg (Lewis 1979) and the intraperitoneal convulsant dose (CD_{50}) in rats is 150 mg/kg

(Jenney and Pfeiffer 1958)] and in humans [e.g., intravenous dose of 40 mg/kg caused unspecified central nervous system effects (Lewis 1979) and the intramuscular convulsant dose (CD_{50}) is 40 mg/kg (Jenney and Pfeiffer 1958)].

Osteolathyrism has been observed in rats (Weisburger et al. 1981), and rabbits (Kasanina and Torbenko 1974) as a result of exposure to semicarbazide but according to Barrow et al. (1974) osteolathyrism (not only that induced by semicarbazide) has not been observed in man.

The published data documenting the tumorigenicity of semicarbazide is conflicting. Weisburger et al. (1981) did not observe any evidence of tumorigenicity in rats fed either 1000 or 500 ppm semicarbazide hydrochloride in the diet for 18 months. On the other hand, Mori et al. (1960) and Toth et al. (1975) reported enhanced pulmonary adenoma development in dd and Swiss albino mice, respectively, fed semicarbazide. Toth et al. (1975) also noted an increased incidence of blood vessel tumors (18% compared to 5% in controls) in female mice. The IARC (1976) cites the latter two studies as evidence that semicarbazide hydrochloride is carcinogenic in mice after oral administration. However, it should be noted that most of the tumors observed in these studies seem to represent an increase in the incidences of spontaneously occurring tumors rather than an inductive process.

Semicarbazide has demonstrated mutagenic potential in grasshoppers [chromosome damage (Bhattacharya 1976)] and in *Salmonella typhimurium* strain TA 1535 (Parodi et al. 1981). It should be noted that in the experiments of Parodi the compound gave negative results in strains TA 100, 1537, 1538, and 98 and was only weakly mutagenic in the TA 1535 strain. Also, when the S-9 mix was added no mutagenic activity was observed suggesting that semicarbazide and not a metabolite is responsible for the mutagenic activity.

Teratogenicity has been demonstrated in hamsters, rats, mice, chickens, and turkeys; however, in mammals abnormalities were observed only at high doses. For example, Wiley and Joneja (1978) observed minor teratogenic effects when Golden Syrian hamsters were administered a single oral dose of 100 mg/kg on day seven of gestation and Steffek et al. (1972) observed no incidence of cleft palate in Sprague-Dawley rats orally administered 10 mg/day (40 mg/kg for a 250g rat) on days 12-15 of gestation. Steffek et al. did observe high incidences of cleft palate at a dose of 50 mg/kg (200 mg/kg for a 250g rat) administered on days 10-16 of gestation.

Information available in the literature indicates that semicarbazide may pose a risk to human health. However, a complete human health risk assessment is not possible until the number of workers exposed and the levels at which exposure occurs are known. In addition, further studies on the carcinogenicity of semicarbazide are warranted, preferably using administration routes simulating human exposure.

C. Environmental Risk Assessment

Very little information is available with which to make an environmental risk assessment. No studies were found on the metabolism of semicarbazide by environmental species, or on the lethal, reproductive, or behavioral effects of the compound. Studies in laboratory animals (Lewis 1979) do suggest that semicarbazide, if released into the environment, could be toxic to feral animals. Laboratory studies with bacteria indicate that concentrations of semicarbazide too low to influence respiration inhibit the growth of *Pseudomonas aeruginosa* (Büning-Pfaue and Rehm 1972) and that the ability of *Propionibacterium shermanni* to produce vitamin B_{12} and porphyrins is inhibited (Bykovskii et al. 1966).

No data documenting the fate, effects on aquatic organisms or releases of semicarbazide to the environment are available. However, an octanol/water coefficient (log P) of -2.53 suggests that bioaccumulation is not likely and in water simple hydrazine derivatives are polar, nonvolatile, and soluble, indicating that these compounds will not transfer to the atmosphere at significant rates, or adsorb to sediments in significant amounts (Radding et al. 1977). Radding et al. also states that in water, hydrazines as a class are oxidized by molecular oxygen to diimides and then to nitrogen. Ross et al. (1971, as reviewed in Radding et al. 1977) indicates that this may be the most important process in determining the fate of hydrazines. Also, the solubility in water of semicarbazide suggests that in soil leaching may occur.

Environmental monitoring data and effects on various environmental species would add significantly to the assessment of environmental risk associated with semicarbazide.

III. Summary

According to the nonconfidential file of the TSCA inventory the combined 1977 production of semicarbazide and semicarbazide hydrochloride was in the range of 200,000-2,000,000 lbs. No human or environmental exposure from the chemical was documented; however, some of the uses (e.g., laboratory reagent) suggest that human exposure is possible. If semicarbazide enters the environment, its octanol/water partition coefficient (log P) of -2.53 suggests that bioaccumulation will not occur and by analogy with hydrazines, in water semicarbazide would be oxidized by molecular oxygen to diimides and then to nitrogen.

Semicarbazide is very toxic to animals upon acute oral exposures. In laboratory animals, tumorigenicity was demonstrated in mice but not in rats. It has shown mutagenic activity in the grasshopper and in the Ames test but only in *Salmonella* strain TA 1535 where it was classified as a weak mutagen. Mutagenicity was not detected in TA 1535 when S-9 mix was added. In laboratory animals teratogenicity was demonstrated. Semicarbazide is known to produce osteolathyrism in animals but this effect has not been reported to occur in humans. No data were available concerning the effect of semicarbazide on aquatic organisms. Although the information available in the literature suggests that semicarbazide is teratogenic and lathyrogenic, additional data are required for a complete health risk assessment and include: number of workers exposed; levels of the compound in the workplace and the environment; and additional information relating to carcinogenicity of the compound.

IV. References

A. Literature Cited

Adamson RH. 1965. Activity of congeners of hydroxyurea against advanced leukemia L1210. Biochem. J. 119:456-458.

Anderson RA, Brentzel HJ, Thurman RG. 1978. Determination of micromolar levels of acetaldehyde in biological preparations. Curr. Alcohol. 3:315-331. Reviewed in Chem. Abstr. 89:101066u.

Barrow MV, Simpson CF, Miller EJ. 1974. Lathyrism: a review. Q. Rev. Biol. 49:101-128.

Bhaattacharya AK. 1976. Chromosome damage induced by semicarbazide in spermatocytes of a grasshopper. Mutat. Res. 40:237-242.

Brown L, Harkness MLR, Harkness RD. 1969. Effect of hydrazine and other aldehyde reacting agents on mechanical properties of rat tail skin. Acta Physiol. Acad. Sci. Hung. 36(1-2):157-169.

Bu YC. 1975. Studies on new antimicrobials. Part 1. synthesis of 2-benzothiazolyl thiosemicarbazide derivatives. Korean Cent. J. Med. 29(1):57-61. Reviewed in Biol. Abstr. 63:31098.

Büning-Pfaue H. Rehm H-J. 1972. Production of aldehyde in "batch"-fermentation by *Pseudomonas aeruginosa* growing on decanol. Arch. Mikrobiol. 86: 231-240. (In German).

Bykhovskii V Ya, Zaitseva NI, Mantrova GV. 1966. Effects of carbonyl reagents on vitamin B_{12} and porphyrin synthesis by dormant cells of *Prophionibacterium shermanii*. Dokl. Akad. Nauk. S.S.S.R. 168(6):1415-1418.

Cameron JM. 1962. Experimental lathyrism in turkey embryos. Nature 194: 210-211.

Capek R, Esplin B. 1977. Hemosynaptic depression and transmitter turnover in spinal monosynaptic pathway. J. Neurophys. 40(1):95-105.

Carlton WW, Hunt CE, Newberne PM. 1965. Neural lesions induced in ducklings by isonicotinic acid hydrazide and semicarbazide hydrochloride. Exp. Mol. Pathol. 4:438-448.

Chem Sources — U.S.A. 1982. Semicarbazide and semicarbazide hydrochloride. Ormond Beach, FL: Directories Publishing Company, Inc., p. 596.

Dallam RD, Chen LH. 1969. Carbonyl groups associated with mitochondrial ATP synthesis. Arch. Biochem. Biophys. 134:19-24.

Davis REG, Wells CHJ, Taylor AR. 1979. Photolytic decomposition of indapamide. J. Pharm. Sci. 68(8):1063-1064.

Denk H, Moldeus PW, Schulz RA, et al. 1976. Hepatic organelle interaction. IV. mechanism of succinate enhancement of formaldehyde accumulation from endoplasmic reticulum *N*-dealkylations. J. Cell Biol. 69:589-598.

Durham HN. 1965. U.S. Patents 3,220,892 and 3,223,561. Reviewed in Schiessl 1980.

Feigl F. 1966. Spot tests in organic chemistry, 7th ed. New York: Elsevier Publishing Company, pp. 275-279. Reviewed in Schiessl 1980.

Fichter F, Becker B. 1912. J. Chem. Soc. 102:Abs. i 15. Reviewed in Udupa et al. 1966.

Fishbein L. 1979. Potential industrial carcinogens and mutagens. New York: Elsevier Scientific Publishing Company, pp. 308-330.

Goen R, et al. 1980. Chemical use standard encoding system (ChemUSES). Vol. I and II. Final Report. SRI Project No. CRU-5722. Washington, DC: Office of Pesticides and Toxic Substances. Reviewed in USEPA 1982.

Goodyer PR, Lancaster G, Villeneuve M, Scriver CR. 1980. The relationship of 4-aminobutyric acid metabolism to ammoniagenesis in renal cortex. Biochim. Biophys. Acta 633:191-200.

Grossberg SE, Lwoff M, Lwoff A. 1966. Exaltation of the development of poliovirus by semicarbazide. J. Bacteriol. 92(5):1473-1477.

Hayatsu H. 1976. Reaction of cytidine with semicarbazide in the presence of bisulfite. A rapid modification specific for single-stranded polynucleotide. Biochemistry 15:2677-2682.

Hayatsu H. 1977. Co-operative mutagenic actions of bisulfite and nitrogen nucleophiles. J. Mol. Biol. 15:19-31.

Haytasu H, Takeishi K, Tyunosin U. 1966. The modification of nucleosides and nucleotides. III. A selective modification of cytidine with semicarbazide. Biochim. Biophys. Acta 123:445-457.

Hoover JE (ed). 1975. Remington's pharmaceutical sciences, 15th ed. Easton, PA: Mack Publishing Company, p. 1096. Reviewed in USEPA 1982.

IARC. 1976. International Agency for Research on Cancer. IARC monographs on the evaluation of carcinogenic risk of chemicals to man: some carbamates, thiocarbamates and carbazides, volume 12. Lyon, France: World Health Organization. pp. 209-215.

Isojima T. 1974. Phosphor. Japan Kokai, 74,102,780 (1973). Chem. Abstr. 81:p19153w. Reviewed in Fishbein 1979.

Jenney EH, Pfeiffer CC. 1958. The convulsant effect of hydrazides and the antidotal effect of anticonvulsants and metabolites. J. Pharmacol. Exp. Ther. 122:110-123.

Kahlson G, Rosengren E. 1959. Prevention of foetal development by enzyme inhibition. Nature 184:1238-1239.

Kehr LL. 1970. Carbazate cross-linking agent and thermosetting resins. Chem. Abstr. 73:p26293e. Reviewed in Fishbein 1979.

Killiam KF, Bain JA. 1957. Convulsant hydrazides I: *in vitro* and *in vivo* inhibition of vitamin B_6 enzymes by convulsant hydrazides. J. Pharmacol. 119: 255-262.

Kondo K, Sonoda N, Sakurai H. 1974. A new synthesis of carbonohydrazide, semicarbizide, and carbazate. Chem. Lett. 8:1429-1430.

Lalich LL. 1966. Effect of different lathyrogens upon tissue responses in rats. Proc. Soc. Exp. Biol. Med. 123(1):214-217.

Lange NA, Forker GM (eds.). 1946. Handbook of Chemistry, Sixth Edition. Sandusky, OH: Handbook Publishers, Inc. p. 1383.

Lee T. 1979. Characterization of fatty alcohol: NAD^+ oxidoreductase from rat liver. J. Biol. Chem. 254(8):2892-2896.

Levene CL. 1968. The effect of lathyrogenic compounds on morphology and growth of cultured cells. Lab. Invest. 19(1):25-28.

Levinson W, Helling R. 1976. Inactivation of lambda phage infectivity and lambda deoxyribonucleic acid transfection by *N*-methyl-isatin β-thiosemicarbazone-copper complexes. Antimicrob. Agents Chemother. 9(1):160-163.

Lewis RJ, Tatken RL (eds). 1979. Registry of toxic effects of chemical substances, vol. 2. Washington, DC: U.S. Government Printing Office, p. 516.

McCallum HM. 1965. Experimental lathyrism in tissue culture. J. Pathol. Bacteriol. 89(2):625-636.

Meincke ER. 1970. Color-stabilized copolymers of ethylene and vinylacetate. Ger. Offen., 1,953,693. Chem. Abstr. 73:pj6821t. Reviewed in Fishbein 1979.

Minemura N. 1977. The prevention of the photoinduced discoloration of wood by semicarbazide. J. Hokkaido Forest Products Research Institute 311:18-22. Reviewed in CAB Abstr. 1982.

Mori K, Yasuno A, Matsumoto K. 1960. Induction of pulmonary tumors in mice with isonicotinic acid hydrazid. Gann 51:83-89.

Nathan DM, Avezzano ES, Palmer JL. 1981. A rapid chemical means for removing labile glycohemoglobin. Diabetes 30(8):700-701. Reviewed in NLM printout 1982.

Neuman RE, Maxwell M, McCoy TA. 1956. Production of beak and skeletal malformations of chick embryo by semicarbazide. Proc. Soc. Exp. Biol. Med. 92:578-581.

Ohme R, Preuschhof H. 1969. Mechanism of semicarbazide formation from guanidines. Liebigs Ann. Chem. 721:25-33.

Ohmori K, Nakagawa T, Suzuki T, et al. 1976. Activity of thiosemicarbazides for the control of bacterial leaf blight of rice. J. Pestic. Sci. 1(2):95-100. Reviewed in Biol. Abstr. 63:46850.

Parodi SP, De Flora S, Cavanna M, et al. 1981. DNA-damaging activity *in vivo* and bacterial mutagenicity of sixteen hydrazine derivatives as related quantitatively to their carcinogenicity. Cancer Res. 41:1469-1482.

Radding SB, Liu DH, Johnson HL, Mill T. 1977. Review of the environmental fate of selected chemicals. Washington, DC: Office of Toxic Substances. EPA 560/5-77-003.

Roechling H, Hartz P, Hoerlein G. 1975. Plant-growth regulators. Ger. Offen., 2,332,000. Chem. Abstr. 82:156326q. Reviewed in Fishbein 1979.

Ross DS, Hendry DG, Kirshen NA. 1971. Study of the basic kinetics of decomposition of MMH and MHF and the effects of impurities on their stability. AFRPL-TR-71-114, September 15, 1971. Reviewed in Radding et al. 1977.

Rossel A, Frank L. 1894. J. Chem. Soc. 66:Abs. i 272. Reviewed in Udupa et al. 1966.

Roth JA, Gillis CN. 1975. Multiple forms of amine oxidase in perfused rabbit lung. J. Pharmacol. Exp. Ther. 194:537-544.

Roth RA, Jr, Roth JA, Gillis CN. 1977. Disposition of ^{14}C-mescaline by rabbit lung. J. Pharmacol. Exp. Ther. 200:394-401.

Samborskii IV, Vakulenko VA, Chetverikov AF, Pedikova LN, Nekrasova LG. 1974. Anion-exchangers. USSR Patent 398,570 (1973). Chem. Abstr. 81:p106565a. Reviewed in Fishbein 1979.

Schiessl HW. 1980. Hydrazine and its derivatives. In: Kirk-Othmer Encyclopedia of Chemical Technology, 3rd ed., vol. 12. New York: John Wiley and Sons, pp. 734-771.

Sekoguchi S, Nakamura R, Sato Y. 1978. The effect of thiosemicarbazide administration on the tenderness of meat obtained from mature chickens and on some characteristics of its intramuscular collagen. Poult. Sci. 57(1):104-110. Reviewed in Biol. Abstr. 65:70253.

Sladek NE. 1973. Bioassay and relative cytotoxic potency of cyclophosphamide metabolites generated *in vitro* and *in vivo*. Cancer Res. 33:1150-1158.

Sourkes TL. 1980. Copper, biogenic amines, and amine oxidases. In: Biological roles of copper, Ciba Foundation Symposium 79. New York: Excerpta Medica, pp. 143-156.

Stanley NN, Alper R, Cunningham EL, Cherniack NS, Kefalides NA. 1975. Effects of a molecular change in collagen on lung structure and mechanical function. J. Clin. Invest. 55:1195-1201.

Steffek AJ, Verrusio AC, Watkins CA. 1972. Cleft palate in rodents after maternal treatment with various lathyrogenic agents. Teratology 5:33-40.

Stowell AR. 1979. An improved method for the determination of acetaldehyde in human blood with minimal ethanol interference. Clin. Chim. Acta. 98:201-205.

Stowell A, Hillbom M, Salaspuro M, Lindros KO. 1980. Low acetaldehyde levels in blood, breath and cerebrospinal fluid of intoxicated humans as assayed by improved methods. Adv. Exp. Med. Biol. 132:635-645. Reviewed in NLM printout 1982.

Thiele J, Heusser C. 1896. J. Chem. Soc. 70:Abs i 208. Reviewed in Udupa et al. 1966.

Thiele J, Strange O. 1894. J. Chem. Soc. 66:Abs i 165. Reviewed in Udupa et al. 1966.

Toth B, Shimizu H, Erickson J. 1975. Carbamylhydrazine hydrochloride as a lung and blood vessel tumor inducer in Swiss mice. Europ. J. Cancer 11:17-22.

Udupa KS, Subramanian GS, Udupa HVK. 1966. Electrolytic production of semicarbazide. Bull. Acad. Pol. Sci., Ser. Sci. Chim. 14(11-12):849-854.

USEPA. 1978. U.S. Environmental Protection Agency. Chemical in commerce information system (CICIS). Data retrieved February 1, 1982. Washington, DC: Office of Toxic Substances.

USEPA. 1982. U.S. Environmental Protection Agency. Production exposure profile: semicarbazide. Washington, DC: Office of Toxic Substances.

USITC. 1977-1981. U.S. International Trade Commission. Synthetic organic chemicals. U.S. production and sales (1975-1980). Washington, DC: U.S. Government Printing Office. (USITC Publications 804, 833, 920, 1001, 1099, and 1183). Reviewed in USEPA 1982.

Von Kreyberg T. 1967. Chemical structure and teratogenic effects of a few groups of compounds. Arch. Pharmak. Exp. Pathologie 257:296-298. (In German; partial translation).

Weast RC. 1970-1971. CRC handbook of chemistry and physics. Cleveland, OH: The Chemical Rubber Company, p. C-489.

Weast RC, Astle MJ. 1981-1982. CRC handbook of chemistry and physics. Boca Raton, FL: CRC Press, Inc., p. C-512.

Weisburger EK, Ulland BM, Nam J, Gart JJ, Weisburger JH. 1981. Carcinogenicity tests of certain environmental and industrial chemicals. J. Natl. Cancer Inst. 67(1):75-88.

Wibo M, Duong AT, Godfraind T. 1980. Subcellular location of semicarbazide-sensitive amine oxidase in rat aorta. Eur. J. Biochem. 112:87-94.

Wiley MJ, Joneja MG. 1978. Neural tube lesions in the offspring of hamsters given single oral doses of lathyrogens early in gestation. Acta Anat. 100(3): 347-353.

Yoneda Y, Takashima S, Kuriyama K. 1976. Possible involvement of GABA in morphine analgesia. Biochem. Pharmacol. 25:2669-2670.

Zharkova MA, Kudryavtsev GI, Khudoshev IF, Romanova TA. 1969. Khim. Volokna. 2:49. Reviewed in Fishbein 1979.

B. Secondary Sources Searched

1. Books

Aldrich Chemical Company. 1979-1980. Aldrich catalog handbook of fine chemicals. Milwaukee, WI.

American Conference of Governmental Industrial Hygienists. 1979. TLVs. Threshold limit values for chemical substances in workroom air adopted by ACGIH for 1979. Cincinnati, OH: American Conference of Governmental Industrial Hygienists.

American Conference of Governmental Industrial Hygienists. 1980. Documentation of the threshold limit values for substances in workroom air adopted by ACGIH for 1980, Cincinnati, OH: American Conference of Governmental Industrial Hygienists.

Arena JM. 1979. Poisoning, 4th ed. Springfield: Charles C. Thomas.

Bennett H, ed. 1974. Concise chemical and technical dictionary. New York: Chemical Publishing Co., Inc.

Bretherick L. 1975. Handbook of reactive chemical hazards. Cleveland, OH: CRC Press, Inc.

Browning E. 1965. Toxicity and metabolism of industrial solvents. New York: Elsevier Publishing Company.

Choudhary G, ed. 1981. Chemical hazards in the workplace. American Chemical Society Symposium series 149. Washington, DC: American Chemical Society.

Clayton GD, Clayton FE, eds. 1981. Patty: Industrial hygiene and technology, 3rd ed., vol. IIa and IIb. New York: Interscience Publishers.

Cone MV, Baldauf MF, Martin FM, Ensminger JT. 1980. Chemicals identified in human biological media, a data base, vol. I, part 1. Washington, DC: Office of Pesticides and Toxic Substances. ORNL/EIS-163.

Cone MV, Baldauf MF, Martin FM, Ensminger JT. 1981. Chemicals identified in human biological media, a data base, vol. II, part 1. Washington, DC: Office of Pesticides and Toxic Substances. EPA 560/13-80-036A.

Cone MV, Baldauf MF, Martin FM. 1981. Chemicals identified in human biological media, a data base, vol. III, part 1. Washington, DC: Office of Toxic Substances. EPA 560/5-81-008A.

Dean JA. 1979. Lange's handbook of chemistry, 12th ed. New York: McGraw-Hill Book Company.

DeBruin A. 1976. Biochemical toxicology of environmental agents. New York: Elsevier/North Holland Biomedical Press.

Deichmann WB, Gererde HW. 1969. Toxicology of drugs and chemicals. New York: Academic Press.

Doull J, Klassen CD, Amdur MO, eds. 1980. Casarett and Doull's toxicology, the basic science of poisons, 2nd ed. New York: MacMillan Publishing Company, Inc.

Faith WL, Keys DB, Clark RL. 1975. Industrial chemicals, 4th ed. New York: John Wiley and Sons, Inc.

Fasset DW, Irish DD, eds. 1963. Patty: Industrial hygiene and toxicology, 2nd ed. New York: Interscience Publishers.

Goring CAI, Hamaker JW, eds. 1972. Organic chemicals in the soil environment, vol. 2. New York: Marcel Dekker, Inc.

Gosselin RE, Hodge HC, Smith RP, Gleason MN. 1976. Clinical toxicology of commerical products, 4th ed. Baltimore: Williams and Wilkins Company.

Grant J, ed. 1979. Hackh's chemial dictionary, 4th ed. New York: McGraw-Hill Book Company.

Grant MW. 1974. Toxicology of the eye, 2nd ed. Drugs, chemicals, plants, venoms. Springfield, IL: Charles C. Thomas.

Grayson M, Eckroth D, eds. 1978-1981. Kirk-Othmer encyclopedia of chemical technology, 3rd ed. New York: Wiley-Interscience.

Hamilton A, Hardy H. 1974. Industrial toxicology, 3rd ed. Littleton, MA: PSG Publishing Company, Inc.

Hawley GG. 1981. Condensed chemical dictionary. New York: Van Nostrand Reinhold Company.

International Agency for Research on Cancer. 1974-1981. IARC monographs on the evaluation of carcinogenic risk of chemicals to man, vol. 1-21. Lyon, France: World Health Organization.

International Technical Information Institute. 1975. Toxic and hazardous industrial chemicals safety manual for handling and disposal with toxicity and hazard data. Tokyo, Japan: International Technical Information Institute.

Kent JA, ed. 1974. Riegel's handbook of industrial chemistry, 7th ed. New York: Van Nostrand and Reinhold Company.

Lewis RJ Sr, Tatken RL. 1979. Registry of toxic effects of chemical substances. Cincinnati, OH: National Institute for Occupational Safety and Health.

Lipsett CH. 1963. Industrial wastes and salvage. Conservation and utilization. New York: Atlas Publishing Co., Inc.

Mackison FW, Stricoff RS, Partridge LJ, eds. 1981. NIOSH/OSHA occupational health guidelines for chemical hazards. Washington, DC: U.S. Department of Health and Human Services.

McGraw-Hill Encyclopedia of Science and Technology. 1977. New York: McGraw-Hill Book Company.

Moeschlin S. 1965. Poisoning - diagnosis and treatment. New York: Grune and Straton.

National Academy of Sciences. 1977. Drinking water and health. Washington, DC: National Academy of Sciences.

National Cancer Institute. 1961-1973. Survey of compounds which have been tested for carcinogenic activity. National Institutes of Health, Public Health Service Publication No. 149. Washington, DC: Government Printing Office.

National Cancer Institute. 1978. Survey of compounds which have been tested for carcinogenic activity. Washington, DC: U.S. Government Printing Office. NIH Publication 80-453.

Parke DV. 1968. The biochemistry of foreign compounds. New York: Pergamon Press.

Ross RH, Kemp HT, Ryon MG, Hammons AS, Ensminger JT. 1979. Chemicals tested for phytotoxicity. Oak Ridge, TN: Oak Ridge National Laboratory. ORNL/EIS-155.

Sax NI. 1979. Dangerous properties of industrial materials, 5th ed. New York: Van Nostrand Reinhold Company.

Sax NI. 1981. Cancer causing chemicals. New York: Van Nostrand Reinhold Company.

Searle CE, ed. 1976. Chemical carcinogens. ACS monograph 173. Washington, DC: American Chemical Society.

Shepard TH. 1980. Catalog of teratogenic agents. Baltimore, MD: Johns Hopkins University Press.

Sittig M. 1975. Environmental sources and emissions handbook. Park Ridge, NJ: Noyes Data Corporation.

Sittig M. 1979. Hazardous and toxic effects of industrial chemicals. Park Ridge, NJ: Noyes Data Corporation.

Toxic and hazardous industrial chemicals safety manual. 1975. Tokyo: The International Technical Information Institute.

Union Carbide Corporation. Undated. Toxicology studies. New York.

Vershueren K. 1977. Handbook of environmental data on organic chemicals. New York: Van Nostrand Reinhold Company.

Windholz M, ed. 1976. The Merck index. An encyclopedia of chemicals and drugs. Rahway, NJ: Merck and Company, Inc.

2. Data Bases

File	Number of References	Date of Search
MEDLARS		
TOXLINE	106	January 12, 1982
TOX 65	54	"
TOX 74	170	"
CANCERLINE	29	"
CANCERPROJ	0	"
MEDLINE	24	"
TDB	0	"
RTECS	1	"
EPILEPSY	19	"
CHEMLINE	1	"
BACK 77	21	"
BACK 75	20	"
BACK 72	9	"
BACK 69	9	"
BACK 66	9	"
LOCKHEED/DIALOG		
AGRICOLA 79-PRESENT	2	"
AGRICOLA 70-78	4	"
APTIC	0	"
ASFA	0	"
BA 74-PRESENT	229	"
BA 69-73	190	"
CA SEARCH 67-71	88	"
CA SEARCH 72-76	126	"
CA SEARCH 77-79	102	"
CA SEARCH 80-PRESENT	84	"
CAB	9	"
CHEMICAL INDUSTRY NOTES	0	"
COMPREHENSIVE DISSERTATION ABSTRACTS	1	"
CONFERENCE PAPERS INDEX	5	"
ENVIROLINE	0	"
EXCERPTA MEDICA IN-PROCESS	11	"
EXCERPTA MEDICA 74-79	131	"
EXCERPTA MECICA 80-PRESENT	29	"
NTIS	6	"
PHARMACEUTICAL NEWS INDEX	0	"
POLLUTION ABSTRACTS	2	"
SCISEARCH 74-77	28	"
SCISEARCH 78-80	8	"
SCISEARCH 81-PRESENT	1	"
SSIE	0	"
SDC/ORBIT		
CRECORD	0	"
FEDREG	0	"

C. Search Strategy

Semicarbazide

Search terms included collective index names, synonyms, CAS Registry Number, and CHEMLINE nomenclature. All hits from each data base were "dumped" and the computer printouts were scanned for pertinent references.