

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY  
DEPARTMENT OF PESTICIDE REGULATION  
HUMAN HEALTH ASSESSMENT BRANCH

SUMMARY OF TOXICOLOGY DATA  
HYDROGEN CYANAMIDE

Chemical Code # 2238, Document Processing Number (DPN) # 50660  
SB 950 # Not applicable

Original date: 12/28/87  
Revised: 9/8/93, May 10, 2016

DATA GAP STATUS

Chronic toxicity, rat:	No data gap, no adverse effect
Chronic toxicity, dog:	No data gap, possible adverse effect
Oncogenicity, rat:	Not required at this time
Oncogenicity, mouse:	No data gap, possible adverse effect
Reproduction, rat:	No data gap, no adverse effect
Developmental toxicity, rat:	No data gap, possible adverse effect
Developmental toxicity, rabbit:	No data gap, no adverse effect
Gene mutation:	No data gap, no adverse effect
Chromosome effects:	No data gap, possible adverse effect
DNA damage:	No data gap, no adverse effect
Neurotoxicity:	Not required at this time

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Toxicology one-liners are attached.

All record numbers for the above study types through 125670 (Document No. 50660-0077) were examined. This includes all relevant studies indexed by DPR as of May 3, 2016.

In the 1-liners below:

\*\* indicates an acceptable study.

**Bold face** indicates a possible adverse effect.

## indicates a study on file but not yet reviewed.

File name: t20160510  
 Revised by [REDACTED], 5/10/16

NOTE: The following symbols may be used in the Table of Contents which follows:

- \*\* = data adequately address FIFRA requirement
- † = study(ies) flagged as “possible adverse effect”
- (N/A) = study type not currently required

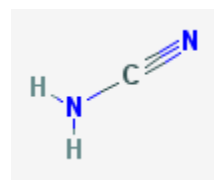
This record contains summaries of studies. Individual worksheets may be useful for detailed assessment.

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Hydrogen Cyanamide structure from <https://pubchem.ncbi.nlm.nih.gov>



## METABOLISM AND PHARMACOKINETICS \*\*

\*\*109; 125670; “Metabolism of [<sup>14</sup>C] Hydrogen Cyanamide in Rats (Preliminary and Definitive Phases)” (author: Struble, C.B., Hazleton Wisconsin, Madison, WI, Lab. Project ID # HWI 6265 101, 8/19/93). Test article: hydrogen cyanamide (radiolabeled: lot # 061H9212, 97% purity, 14.8 mCi/mmol; non-labeled: lot # 111701, 99.7% purity). Regimen: oral: single (1 or 20 mg/kg) or multiple (pretreated with 1 mg/kg/day for 14 days with non-labeled hydrogen cyanamide followed by a final dose of radiolabeled hydrogen cyanamide). Intravenous (iv): single dose (1 mg/kg). There were 5 rats/sex/dose. Radioactivity was rapidly excreted, regardless of the route of administration or dose level. From 67% to 92% was excreted by all routes in the first 24 hours after administration. The main route of excretion was via urine (66.9-97.7%). Fecal excretion of radioactivity was 3 to 4 times higher after an iv dose (13.2-15%) compared with a similar oral dose (2.3-4.2%), suggesting that biliary excretion may play an important role after iv dosing. Elimination of radioactivity as <sup>14</sup>CO<sub>2</sub> was reduced by 30% in animals repeatedly dosed with hydrogen cyanamide as compared with single oral dose. Treatment at 20 mg/kg reduced the percent of radioactivity in expired air, but the opposite result was observed for the percent of dose in the urine. There was no evidence of bioaccumulation after multiple dosing. The major metabolic reaction was acetylation of the nitrogen: N-acetylcyanamide accounted for 58% to 74% of the radioactivity in urine, and for over 80% in feces. High concentrations of radioactivity were found in blood, liver and kidneys. Males were reported to have higher levels

of radioactivity in liver, blood and kidney as compared to females. The study is acceptable (██████, 9/1/93).

50660-0048 92525; “Investigation of the Absorption, Metabolism, and Excretion of Hydrogen Cyanamide in Rat and Human” (authors: Gloxhuber, C. et. al., SKW Trostberg AG, Trostberg, Germany, 9/1/89). The major urinary metabolite of cyanamide in rat and man is N-acetylcyanamide. Rats treated orally with cyanamide (10 mg/kg) demonstrate that 51.5% of the dose was excreted in the urine as N-acetylcyanamide. Similarly, male human volunteers excreted 57.8% of the oral dose (20 mg/kg) in urine as N-acetylcyanamide. The same group of volunteers participated in a skin absorption with dermal application of 20 mg per person. A maximum of 3.5% of this dose was absorbed through the skin and excreted as N-acetylcyanamide in the urine. Additional findings from the literature indicate that cyanamide is metabolized in vitro to cyanide. However, according to experiments performed in vivo, no significant increases in cyanide concentrations in the blood and thiocyanate concentrations in the urine were detected after a 20 mg oral dose. Supplemental. (██████, 8/10/93).

077; 116275; “Metabolism of Hydrogen Cyanamide” (author: Environ Corp., 9/5/91). Hydrogen cyanamide is rapidly absorbed and eliminated following oral administration in rats ( $t_{1/2} = 27.2$  minutes) and dogs ( $t_{1/2} = 62$  minutes). In contrast, absorption through the skin is generally proportional to the dose and increases with the time of exposure. The major urinary metabolite after oral dosing in rat, dog, and man has been identified as N-acetylcyanamide and accounts for 45.6%, 87%, and 87%, of the administered dose, respectively. Blood samples of volunteers collected before and up to 48 hours after intake of hydrogen cyanamide did not show any significant differences in blood levels of cyanide or urinary levels of thiocyanate. Supplemental data. (██████, 8/10/93).

50660-0077 116277 Mertschenk, B. *et al.*, “Urinary excretion of acetylcyanamide in rat and human after oral and dermal application of hydrogen cyanamide ( $H_2NCN$ ),” *Arch. Toxicol.* (1991) **65**: 268-272. This published article, by the group which produced Record No. 50660-0048 092525, above, reported an average of 40% of orally administered hydrogen cyanamide in human volunteers was excreted in urine as acetylcyanamide. There is no reviewable information in this brief report, hence no DPR worksheet. (██████, 5/9/16).

50660-0044 87934 “Health risk evaluation based on clinical observations during the therapeutical use of cyanamide ( $H_2NCN$ ) and calcium cyanamide ( $CaNCN$ ) as an alcohol deterrent agent.” This is a collection of 29 published articles relating to clinical trials of calcium cyanamide as a replacement of disulfuram for alcohol abuse prevention, compiled Dr. Chr. Gloxhuber in 1989. No DPR worksheets. (██████, 5/9/16).

50660-0077 116278 “Pharmacokinetics of cyanamide in dog and rat.” This brief published article does not provide essential new information. No DPR worksheet. (██████, 5/9/16).

Additional brief published articles indexed by DPR Registration Branch, which do not warrant DPR review:

50660-0077 116279, 50660-0077 116280, 50660-0077 116281, 50660-0077 116282, 50660-0004 034913,

## GUIDELINE ACUTE STUDIES ON ACTIVE INGREDIENT

The Product Registration Recommendation Sheet of 7/27/95 notes that the manufactured product is approximately 50% hydrogen cyanamide, so the aqueous solution is equivalent to technical material. The studies below reflect the formulated product, Dormex, or equivalent products.

### Acute oral toxicity, rat \*\*

\*\*50660 003; 34911; Acute Oral Toxicity Study; 811; Rat; Central Institute for Nutrition and Food Research, Zeist, The Netherlands; No study no.; 2/7/73; Cyanamid L 500; 5 animals/sex/group; Dose: 0.20, 0.25, 0.30, 0.35 ml/kg; Mortality: 0.20 (M:1/5, F:0/5), 0.25 (M:4/5, F:0/5), 0.30 (M:5/5, F:2/5), 0.35 (M:5/5, F:1/5); Observations: convulsions; Necropsy: no treatment related lesions in the survivors; LD<sub>50</sub> (M/F): 0.285 ml/kg; Toxicity Category II; Study acceptable. (██████████, 8/2/93)

### Acute dermal toxicity \*\*

\*\*50660 035; 85349; Acute Dermal Toxicity Study; 812; Rabbit; Hazleton Laboratories America, Inc., Vienna, VA; Study No. 2319 122; 2/9/88; aqueous hydrogen cyanamide (50% w/w); 5 animals/sex/group; Doses: 1.0, 2.5, 4.0 ml/kg, 24 hour exposure; Mortality: 1.0 (M:0/5, F:1/5), 2.5 (M/F:5/5), 4.0 (M/F:5/5); Observations: prostrate, depressed, tremors, ataxia; Necropsy: dark red areas in lungs; LD<sub>50</sub> (95% confidence limits) M=1.7 (1.1 to 2.7) ml/kg, F=1.4 (0.9 to 2.2) ml/kg; Toxicity Category II; Study acceptable. (██████████, 8/2/93)

50660 003; 34910; Acute Dermal Toxicity Study; 812; Rabbit; Central Institute for Nutrition and Food Research, Zeist, The Netherlands; No study no.; 6/19/73; Cyanamid L 500; 2 animals/sex/group; Doses: 0, 2.0, 4.0, 6.0 ml/kg, 24 hour exposure; Mortality: 0 (M/F:0/2), 2.0 (M/F:0/2), 4.0 (M:1/2, F:0/2), 6.0 (M/F:2/2); Observations: signs of apathy, dilation of pupils, skin irritation; Necropsy: swollen livers, hemorrhagic erosions in the stomach; Histopathology: acanthosis, parakeratosis, hyperkeratosis, edema in the skin, enlarged periportal hepatocytes, atrophy of splenic white pulp, hemorrhagic erosions in the stomach; LD<sub>50</sub> cannot be determined; Toxicity Category cannot be determined; Study is unacceptable, not upgradeable (number of animals/sex/group less than the recommended number of 5). (██████████, 8/2/93).

### Acute inhalation toxicity, rat \*\*

\*\*50660 003; 34909; Acute Inhalation Toxicity Study; 813; Rat; Central Institute for Nutrition and Food Research, Zeist, The Netherlands; No study no.; 5/22/73; SKW Cyanamid L 500; 5 animals/sex; reported exposure concentration (analytical) 2.0 gm/m<sup>3</sup>; reported particle size 99% less than or equal to 1.5 mm; No mortality; Observations: rapid, shallow respiration during exposure; Necropsy: no treatment related lesions reported; reported LC<sub>50</sub> (M/F) > 2.0 gm/m<sup>3</sup>; Summary Study (information regarding the analytical data and calculations used to determine the exposure concentration, the data collected to determine the particle size distribution, the observation records for the study animals, and the necropsy records for the animals were not included in the report). (██████████, 8/2/93)

**Primary eye irritation, rabbit \*\***

\*\*50660 012; 42360; Primary Eye Irritation Study; 814; Rabbit; Central Institute for Nutrition and Food Research, Zeist, The Netherlands; No study no.; 6/10/74; SKW Cyanamid L 500; 6 animals; Dose: 0.1 ml; 6 animals; Observations: corneal opacity, grade 1 or 2 in all animals at 24 and 48 hours, gradually diminishing and clearing by 7 days; iritis, grade 1 in all animals at 24 and 48 hours, diminishing to grade 1 in 4/6 at 72 hours and clearing by 7 days; conjunctival irritation redness, grade 2 in all animals at 24 and 48 hours, diminishing to grade 1 or 2 in all animals at 72 hours and grade 1 in all animals at 7 days, chemosis grade 2 or 3 in all animals at 24 and 48 hours, diminishing to grade 1 in 5/6 animals at 7 days; Toxicity Category III; Study acceptable. (██████, 7/30/93)

**Primary dermal irritation \*\***

\*\*50660 071; 116268; Primary Dermal Irritation Study; 815; Rabbit; Huntingdon Research Centre Ltd., Huntingdon, Cambridgeshire, England; Lab. No. 891330D/STB 4/SE; 12/22/89; Aqueous Hydrogen Cyanamide 49% w/w; 6 animals; Dose: 0.5 ml, 4 hour exposure; Observations: erythema grade 1 or 2 in all animals at 4 hours post dosing, diminishing to grade 1 in 2 animals at 24 hours, clearing by 48 hours, edema grade 1 in 5/6 animals at 4 hours, clearing by 24 hours; Toxicity Category IV; Study acceptable. (██████, 7/30/93)

50660 012; 42359; Primary Dermal Irritation Study; 815; Rabbit; Central Institute for Nutrition and Food Research, Zeist, The Netherlands; No study no.; No study date; SKW Cyanamide L 500; 6 animals; Dose: 0.5 ml, 4 hour exposure; Observations: erythema grade 1 to 4 for all animals at 4 hours post-dose, grade 2 or 4 for all animals at 52 hours post-dose, edema grade 2 or 3 for all animals at 4 hours post-dose, grade 1 or 2 for all animals post-dose; Toxicity Category cannot be determined; Study is unacceptable and not upgradeable (study was terminated prior to reversal of irritation signs). (██████, 7/30/93)

**Dermal sensitization \*\***

\*\*50660-0147 243788; Skin Sensitization Study; 816; Guinea Pigs; Stillmeadow Inc., Sugar Land, TX Study # 9312-05; Jia, S., 9/29/05; Hydrogen Cyanamide 50%; 30 Guinea Pigs (10/sex induced, 5/sex naïve controls); Method of Buehler; Induction phase: three applications of 0.4 ml of undiluted test substance were applied to a shaved area under a 2.5 x 2.5 cm gauze pad for at least 6 hours per exposure (7 days between each exposure); After a two-week rest period, challenge doses of 0.4 ml of undiluted test article were applied on day 29 to areas clipped free of hair via the patching procedure previously described for a 6-hr exposure; no erythema (score 0) was noted in all test article-induced animals at 24 and 48 hours; score 0 was reported during all observations in the naïve controls; Toxicity Category: Not a Contact Sensitizer. Study is Acceptable. (██████, 1/23/09).

**SUBCHRONIC STUDIES****Oral toxicity, rat: \*\***

003; 34904; Sub Chronic (90 Day) Toxicity Study with Cyanamid L 500 in Albino Rats (Authors: H.P. Til, et al.); 821; Rat; Central Institute for Nutrition and Food Research, Zeist, The Netherlands; Report No. R 4595; 1/24/75; Cyanamid L 500; 10 animals/sex/group; Doses: 0 (I),

20 (II), 60 (III), 180 (IV) ppm; No mortality; Clinical Observations: no treatment related signs, no treatment related effects upon body weights or food consumption; Hematology: slight increase in RBC count (IV M); Clinical Chemistry: no treatment related effects observed; Urinalysis: no treatment related effects observed; Necropsy: no treatment related lesions, relative liver weight slightly increased (IV M), relative thymus weight slightly reduced (IV F); Histopathology: predominantly small follicular lumens without colloid in thyroid (III M, IV M,F); target organ: thyroid; possible adverse effect: increased number of small follicles, lined with cuboidal epithelial cells, disappearance of colloid in thyroid; nominal NOEL = 20 ppm; unacceptable, not upgradeable (no analysis of the test article in the diet was performed). (██████████, 8/4/93)

072; 116269; 28 Day Repeated Dose Oral Toxicity Study with Aqueous Hydrogen Cyanamide in Rats; Author: Osheroff, M.R.; 821; Rat; Hazleton Laboratories America, Inc., Rockville, MD; Study No. 2319 123; 9/9/88; Aqueous Hydrogen Cyanamide (50% A.I. (w/w)); 5 animals/sex/group; Doses: 0 (I), 5 (II), 10 (III), 20 (IV), 40 (V) mg/kg/day a.i., by gavage; Mortality: I (M/F:0/5), II (M/F:0/5), III (M/F:0/5), IV (M:0/5;F:1/5), V (M/F:0/5); Clinical Observations: rough haircoat (V); decreased body weight (IV M, V M,F); food consumption decreased (IV, V M); Hematology: decrease in RBC count (V M), hemoglobin (V M,F), hematocrit (V M,F), and MCH (V M); Clinical Chemistry: increase in BUN (V M), no apparent effect on parameters of thyroid function test; Gross Necropsy: no apparent treatment related lesions, reduced absolute testes weight (IV, V); increased organ/body weight ratio for brain (V M), kidney (IV and V M,F), liver (IV M, V M,F) and thyroid (V M); Histopathology: thyroid decreased colloid, hyperplasia of follicular cells, small, closely packed follicles, apparent dose response; liver bile duct hyperplasia, apparent dose response; kidneys mineralization in tubules (V M); target tissues: thyroid, liver; possible adverse effect: follicular cell hyperplasia in thyroid, bile duct hyperplasia in liver; NOEL < 5 mg/kg/day a.i. (based on histopathological changes in thyroid and bile duct hyperplasia in 5, 10, 20, and 40 mg/kg/day a.i. treated males); Study supplemental. (██████████, 7/30/93)

003; 34905; Range Finding (28 Day) Toxicity Study with Cyanamid L 500 in Albino Rats (Authors: H.P. Til, et al.); 821; Rat; Central Institute for Nutrition and Food Research, Zeist, The Netherlands; Report No. R 4387; 5/21/74; Cyanamid L 500; 10 animals/sex/group; Doses: 0 (I), 100 (II), 300 (III), 1000 (IV), 3000 (V) ppm; Mortality: 0 (M/F:0/10), 100 (M/F:0/10), 300 (M/F:0/10), 1000 (M/F:0/10), 3000 (M:0/10; F:1/10); Clinical Observations: emaciation, decreased activity, reduced body weight gain or body weight loss, reduced food consumption (III, IV, V); Hematology: reduced hemoglobin concentration (IV, V); Necropsy: grossly pale livers (V), increased relative organ weights for liver (IV, V) and kidney (V); Histopathology: hydropic liver cell degeneration, ballooning of liver cells with marked degree of bile duct proliferation (IV, V), slight to moderate enlargement of periportal hepatocytes, scattered liver cell necrosis, occasional hydropic degeneration of liver cells (II, III); target organ: liver; possible adverse effect: marked lesions in the liver; NOEL: < 100 ppm (based on treatment related effects in the liver of the 100 ppm treatment group); Study Supplemental. (██████████, 8/4/93)

### Oral toxicity, mouse:

038; 85352; "6 Week Oral (Drinking Water) Palatability and Dose Range Finding Study in the Mouse" (author: Goodyer, M.J., Hazleton Laboratories Europe, Ltd., North Yorkshire, UK, lab. project ID # 5051 556/2, 5/86); aqueous hydrogen cyanamide (49% a.i.) administered in drinking

water for 6 weeks; mean actual dosage level: male 0, 26.0, 72.3, or 171.1 mg a.i./kg/day, female 0, 37.4, 88.9 or 204.4 mg a.i./kg/day; 6 mice/sex/dose; all animals survived the 6 week treatment period; no treatment related changes in clinical conditions or behavior; slight decrease in mean body weight in high dose males; water consumption for high dose males and females was markedly reduced throughout the treatment period; body weight was unaffected by treatment at the mid dose; however, water consumption at this dose level was slightly reduced; no abnormalities were seen at necropsy; Therefore the mid dose was selected as the high dose for the subsequently chronic study in mice; supplemental; (██████, 8/5/93).

### Oral toxicity, non-rodent: \*\*

\*\* 036; 34903; Sub Chronic (90 Day) Oral Toxicity Study with Alzodef in Dogs (Authors: H.P. Til, et al.); 821; Dog; Netherlands Organization for Applied Scientific Research, Division for Nutrition and Food Research TNO, Zeist, The Netherlands; Project ID# V 82.084/210694; 3/82. 4 animals/sex/dose; Dose: 0 (I), 0.6 (II), 2 (III), 6 (IV) mg/kg/day a.i., by gavage; No mortality; Clinical observations: no treatment related signs, reduced body weight gain (IV F); Hematology: reduced hemoglobin, packed cell volume, RBC count, day 85 (IV M), increased % of monocytes (III F, IV M/F); Urinalysis: no treatment related effects; Function Tests: no treatment effect on liver or kidney, reduced T3 content, day 85 (IV M/F), reduced T4 content, day 85 (IV M); Clinical Chemistry: increased cholesterol level, days 44, 85 (IV F), reduced potassium level, days 44, 85 (IV M); Necropsy: reduced testes weight (IV M); Histopathology: reduced or absent spermatogenesis (II, III, IV); target organ: testes; possible adverse effect: reduced or absent spermatogenesis; NOEL cannot be determined (reduced spermatogenesis in 0.6 mg/kg/day a.i. treatment group); Study acceptable. (██████, 8/3/93)

50660-0036 85350 This is another record number given to 50660-036 34903, above.

### Dermal toxicity, 21/28-day or 90-day:

## CHRONIC STUDIES

### Chronic, rat \*\*

\*\* 043, 105; 85432, 116545; "Chronic Toxicity Study in Rats with Aqueous Hydrogen Cyanamide" (author: Osheroff, M.R., Hazleton Laboratories America, Inc., Rockville, MD, HLA Study # 2319 125, progress report (7/28/89), final report (4/15/91)); 831; aqueous hydrogen cyanamide (50% w/w a.i.) administered by gavage to 20 Sprague Dawley rats/sex/dose for 92 weeks; treatment initiated at 0, 2.5, 7.5, or 30 mg/kg/day a.i. was reduced at the 17th week to 0, 1, 2.5, and 7.5 mg/kg/day a.i., respectively, due to deterioration in general health; high dosed animals were noted to be "hunched" with tremors during weeks 9 to 17; decreases in body weight reported for mid and high dose animals at weeks 4 and 16 and for high dose animals at weeks 52 and 91; compound related histomorphologic alterations consisted of reduced colloid, characterized by microfollicles, in the thyroid of mid and high dose males (7/20, 17/18, respectively vs. 0/20 control) and high dosed females (16/20 vs 3/20 control); reduced plasma levels of triiodothyronine (T3) in high dose males and females and in mid dose males at week 92; thyroxine (T4) was also reduced in high dose males at weeks 14 and 92, while thyrotropin was comparable between control and treated groups; NOEL (M/F) = 1 mg/kg/day a.i. (reduced



body weight and changes in T3 and T4); no adverse effects; acceptable; (██████████), 10/23/90, updated, (██████████), 8/2/93).

### Chronic, dog \*\* †

\*\* **037; 85351**; “Chronic Toxicity Study in Dogs with Aqueous Hydrogen Cyanamide” (author: Osheroff, M.R., Hazleton Laboratories America, Inc., Vienna, VA, HLA Study # 2319 121, 5/10/89); 831; aqueous hydrogen cyanamide (Lot # 07/07/87, 50% w/w) administered in distilled water to 4 dogs/sex/day for 52 weeks; treatment initiated at 0, 0.1, 0.5, or 2.5 mg a.i./kg/day was increased to 0, 0.2, 1.0, or 5.0 mg a.i./kg/day on week 2; no deaths were reported during the course of this study; salivation and tremors were noted in high dose animals and in one mid dose female; possible adverse effect: inflammation and decreased spermatogenic activity were noted in the testes of three high dose dogs; in one dog, inflammation was rather severe in both testes and aspermatogenesis was evident; histological sections of testes with epididymides revealed the presence of immature sperm forms and neutrophil infiltration in the epididymal ducts of one mid-dose dog; significant reduction in thyroxin levels and concomitant signs of decreased metabolic rate in high dose dogs indicate hypothyroidism; thymic atrophy was noted in high-dose males and one high-dose female with demodicosis; NOEL (M/F) = 0.2 mg a.i./kg/day (clinical signs and histopathological findings); acceptable; (██████████), 10/26/90; updated, (██████████), 8/4/93).

### Oncogenicity, rat

50660 004; 34921; “Bioassay of Calcium Cyanamide for Possible Carcinogenicity,” (NCI Frederick Cancer Research Center, DHEW Pub. 79 1710). Calcium cyanamid, 63% commercial formulation with 22% calcium oxide and 12% free carbon, fed in the diet to F344 rats, 20/sex in controls, diets replenished at least 3 times per week; 50/sex in test groups, two doses only; dietary levels up to 400 ppm; no toxicity or carcinogenicity observed; incomplete and unacceptable report (no diet analysis, no individual data supplied, doses too low, 2 studies in same room). Not upgradable; (██████████ and ██████████), 10/28/85.

### Oncogenicity, mouse \*\* †

\*\* **051, 106; 95230, 116548**; “Hydrogen Cyanamide: Up to 104 Week Oral (Drinking Water) Carcinogenicity Study in the Mouse” (Goodyer, M.J., Hazleton UK, North Yorkshire, UK, Lab. Study # 6001 556/3, final report: 5/90, amended final report: 10/1991); 832; Hydrogen Cyanamide (49.9% purity, w/w) administered in drinking water to 60 mice/sex/dose for 104 weeks; mean actual dose levels: males: 0, 10.7, 29.5, or 75.6 mg a.i./kg/day, females: 0, 13.7, 35.2, or 101 mg a.i./kg/day; dose related increase in the incidence of chronic cystitis of the urinary bladder was reported for mid and high dose animals; evidence of kidney degeneration as characterized by atrophic/basophilic tubules, fibrosis/scarring and vacuolar degeneration was detected in high dose animals; possible adverse effect: slight increased incidence of granulosa theca tumors in ovaries in high dose females would have been significant if one of the three granulosa theca tumors in the control group, which was diagnosed as “questionable” due to tissue necrosis, was not included in analysis; comparison of the incidence of ovarian granulosa theca tumors in the present study with the average incidence obtained from historical control data from 1985 to 1990 revealed significant increases in mid and high dose females; NOEL (M) = 10.7 mg/kg/day a.i., (F) = 13.7 mg/kg/day a.i. (based on chronic cystitis of the urinary bladder and ovarian granulosa theca tumors); acceptable; (██████████), 10/26/90; updated, (██████████), 8/3/93).

50660-0038 85353 (preliminary report for 051, 106; 95230, 116548, above).

50660 004; 34921; “Bioassay of Calcium Cyanamide for Possible Carcinogenicity,” (NCI Frederick Cancer Research Center, Pub. 79 1719). Calcium cyanamide, 63%, calcium oxide 22%, free carbon, 12%; fed in the diet to B6C3F1 mice at 0, 500 or 1000 ppm for 100 weeks; Inadequate. Unacceptable (no analyses of diets, no individual data, no body weights, seven other studies in same animal room). Possible oncogenic effect (hemangiosarcomas in males). Considered supplemental data for hydrogen cyanamide; [REDACTED], 10/25/85).

## GENOTOXICITY

### Bacterial reverse mutation assay \*\*

\*\* 50660 020; 63691; “Mutagenicity Test on Hydrogen Cyanamide in the Ames Salmonella/Microsome Reverse Mutation Assay.” (author: Jagannath, D.R., Hazleton Laboratories America, MD, HLA 9583 0 401, 10/21/87); Hydrogen cyanamide (53%, w/v in aqueous solution, lot 02/10/86); Salmonella strains TA1535, TA1537, TA1538, TA98 and TA100, two trials in triplicate, with and without activation by Aroclor 1254 induced rat liver S9 fraction; concentrations of 0.02, 0.04, 0.08, 0.17, 0.42, 0.84, 1.69 and 2.54 mg hydrogen cyanamide per plate based on analyzed amount (0.10 to 15 µl); no adverse effects; no increase in reversion rate reported in either trial with decrease in reversion rate at the highest concentration as evidence of the adequacy of the high concentration; Acceptable. ([REDACTED], 12/21/87; updated, [REDACTED], 8/5/93).

50660 004; 34917; “Evaluation of Two Products CCA and CA in the Salmonella/ microsome Mutagenicity Test.” (author: Willems, M.I., Central Institute for Nutrition and Food Research, The Netherlands, Report # R 5707, 6/78). Salmonella microsome mutagenicity for “CCA” and “CA”, tested at 0 to 1000 µg/plate, in triplicate, with and without activation by Aroclor 1254 induced rat liver S9 fraction; CCA is calcium cyanamide and CA is cyanamide; Unacceptable and not upgradeable (because high concentration not justified, no repeat trial to confirm negative result, no individual plate counts). No adverse effects indicated; No increase in reversion reported. ([REDACTED] and [REDACTED], 10/22/85; updated, [REDACTED], 8/5/93).

### Mutagenicity: *In vitro* mammalian cell assay

#### Mutagenicity: *In vivo* cytogenetics \*\* †

\*\* 50660 020; 63690; “Mutagenicity Test on Hydrogen Cyanamide in an *in vitro* Cytogenetic Assay Measuring Chromosomal Aberration Frequencies in Chinese Hamster Ovary (CHO) Cells.” (author: Ivett, J.L., Hazleton Laboratories America, Inc., Kensington, MD, HLA 9583 0 437, 10/21/87.) Hydrogen cyanamide, 53% w/v aqueous solution, lot 02/10/86, liquid with sp. gravity of 1.06; CHO cells exposed *in vitro* without activation at 0, 42.4, 56.5, 141 or 283 µg/ml for 17.5 hours plus 2.5 hours = 20 hour harvest; with rat liver activation at 0, 438, 875 or 1310 µg/ml, 2 hour treatment and harvest at 20 hours or 0, 321 or 428 µg/ml, total of 10 hours to

harvest; possible adverse effects: increase in aberrations with and without activation; acceptable; (█████, 12/21/87; updated, █████, 8/5/93).

\*\* 50660 020; 63689; “Mutagenicity Test on Hydrogen Cyanamide in the in vivo Mouse Micronucleus Assay.” (author: Ivett, J.L., Hazleton Laboratories America, Inc., Kensington, MD, HLA Study # 10052 0 455, 10/21/87); Hydrogen cyanamide, 53% w/v aqueous solution, lot 7/07/87, liquid; given by oral gavage to 5/sex/test, ICR mice; actual doses from analysis at 0, 31.4, 157.4 or 330.5 mg/kg in water; 2 males in high dose group died within 24 hours; sacrifices at 24, 48 and 72 hours; no positive or negative controls at 48 and 72 hours; no adverse effect; no effect on micronuclei formation; acceptable; (█████, 12/21/87; updated, █████, 8/5/93).

50660-0004 34915 (A 3-page negative mouse micronucleus assay by Menargues *et al.* in a published article). No DPR worksheet. █████, 5/9/16.

50660 004; 34914; “Evaluation of “Kalkstickstoff and “Thioharnstoff” in the Micronucleus Test” (author: Willems, M.I., Central Institute for Nutrition and Food Research, The Netherlands, Report # R 6012, 2/79); Kalkstickstoff (calcium cyanamide, calcium oxide and free carbon with 23% N 50660 007) Tested in Wistar rats by oral gavage at 0, 3.06 and 7.0 %, 5/sex/group, 2 dosings, sacrificed 6 hours after the second dosing; 400 cells/slide with 5 slides per animal; Trenimon as positive control; No adverse effects indicated; Unacceptable (no toxicity reported from high dose, single sacrifice time.) Not upgradable. (█████ and █████, 10/22/85; updated, █████, 8/5/93).

50660 004; 34916; “An Investigation into the Sister Chromatid Exchange Induction in Chinese Hamster Ovary Cells by a Sample of “Kalkstickstoff.” (author: de Raat, W.K., Netherlands Organization for Applied Scientific Research, Report # CL/78/120, 2/2/79) Calcium cyanamide 40 60%, calcium oxide and free carbon (Kalkstickstoff); Chinese hamster ovary cells tested for 1 hour with 0, 10, 50, 250 or 500 µg/ml; 500 µg/ml equivalent to 330 µg/ml calcium cyanamide and was not completely soluble; scored 20 metaphases per slide; No adverse effects indicated; Unacceptable (inadequate number of metaphases scored, single replicate per concentration, exposure of 1 hour not justified), not upgradable. (█████ and █████ 10/22/85; updated, █████, 8/5/93).

### **Mutagenicity: DNA damage \*\***

\*\* 50660 020; 63688; “Mutagenicity Test on Hydrogen Cyanamide in the Rat Primary Hepatocyte Unscheduled DNA Synthesis Assay.” (author: Cifone, M.A., Hazleton Laboratories America, Kensington, MD, HLA # 9583 0 447, 10/21/87.) Hydrogen cyanamide, 53% w/v in aqueous solution; male rat hepatocytes tested at 0, 6.0, 11.9, 23.8, 47.6, 71.4, 95.2, 143 or 190 µg/ml actual content from analysis; triplicate coverslips, scored a total of 150 nuclei per concentration; no adverse effect; negative for unscheduled DNA synthesis; acceptable. (█████, 12/21/87; updated, █████, 8/5/93).

## REPRODUCTIVE TOXICITY, RAT \*\*

\*\* 075; 116273; “Two Generation Reproduction Study in Rats with Aqueous Hydrogen Cyanamide (50% w/w)”, (Author: S.L. Morseth; Hazleton Laboratories America Inc., Vienna, VA; Report No. 2319 126; 4/19/90; Dormex (50% w/w Hydrogen Cyanamide); 0, 1.25, 3.75, 15.0 mg/kg/day of a.i. oral gavage; 26 Charles River rats/sex/dose level both F<sub>0</sub>, F<sub>1</sub>; 2 generations, 1 mating/generation; Adult Effects: no dose related mortalities, 2 animals died due to gavage error; initial high dose levels (7.25 and 30 mg/kg/day of a.i.) resulted in weight loss, decreased food consumption and rough haircoats; dose levels were reduced at week 12, 2 weeks before mating and high dosed rats gained weight but showed reduced fertility and gestation indices; Offspring Effects: high dose group showed decreased day 4 mean litter size and body weights (day 7 day 21), mean pup weight(day 7 day 21) reduced at 3.75 mg/kg level; reduced day 4 viability observed in F<sub>0</sub> and F<sub>1</sub> generations at all treatment levels, however, these observations can only be attributed to treatment and not specific dose levels because of dose level changes; F<sub>1</sub> animals at all treatment levels had decreased growth after weaning and gavage dosing began; lower F<sub>2</sub> neonatal survival in treated groups was attributed to variability not treatment results, pups that were weak, thin, dehydrated, and had dry skin were noted not to occur in a dose related pattern; gross necropsy and histomorphologic findings in adults and offspring were not considered treatment related; no adverse effects indicated; Adult NOEL: 1.25 mg/kg/day a.i. (based on reduced body weight); Developmental NOEL: 1.25 mg/kg/day a.i. (based on reduced body weight); Acceptable. (██████, 8/3/93)

019 63684 “Oral Two Generation Reproduction Study with An Aqueous Cyanamide Solution (Content 49% W/W) in Rats.” (Netherlands Organization for Applied Scientific Research, 10/86, 84 1475). Aqueous cyanamide (49% W/W, no further identification of other 51% or whether calcium or hydrogen form at start); fed in the diet at 0, 20, 60 or 180 ppm to 24/sex/group, two generations, two litters per generation; testicular changes described as partial or complete impairment of spermatogenesis occurred in all groups but particularly in the high dose, F<sub>1</sub> males but fertility was not obviously impaired; body weight gains were decreased in both males and females at 180 ppm; no effect was reported on other reproductive parameters; NOEL (males) < 20 ppm (testicular changes), females = 60 ppm (body weight), reproductive NOEL > 180 (no consistent effects on litter/pup data). Unacceptable, incomplete: no individual data, inadequate description of the test material, mean value only for 10 analyses of the diet in which there was a problem with stability. Upgradeable; (██████, 12/21/87).

## DEVELOPMENTAL TOXICITY

### Rat \*\* †

\*\* 50660-030, 040; 70870, 85355; “Rat Teratology Study with Aqueous Hydrogen Cyanamide,” (Authors: S.L. Morseth, *et al.*); 833; Rat; Hazleton Laboratories America, Inc., Vienna, VA; Study No. 2319 124; 5/2/89. Aqueous Hydrogen Cyanamide (50% (w/w) hydrogen cyanamide) was administered by gavage to 25 Sprague-Dawley rats/group at 0 (Group I), 5 (Group II), 15 (Group III), or 45 (Group IV) mg/kg/day active ingredient. Dosing was from gestation days 6 through day 15. **Maternal effects:** There was no maternal mortality. Clinical observations found hypoactivity in groups III and IV. Body weight gain (gestation days 6-20) was reduced by 23% and by 52% in groups III and IV, respectively. Food consumption during dosing (gestation days 6 through 16) was reduced by 12% and 26% in groups III and IV, respectively. There were

no treatment related changes at necropsy. **Litter effects:** Mean gravid uterine weight was reduced in group IV. There was no treatment effect on post-implantation losses. Mean fetal weight was reduced by 15% in group IV. Incidence of diaphragmatic hernia, a rare malformation, was observed in 5/24 group V litters (total of 7 fetuses), vs. 0/25 in all other litters. There were no other treatment-related malformations. There were increased incidences of several common ossification delays and other skeletal variations in group IV, such as wavy or bent ribs, thickened ribs, and incomplete skull ossification. Group IV also displayed presence of hemicentra and an increase of bipartite vertebral centra. **Conclusions:** Maternal NOEL = 5 mg/kg/day a.i. (based mainly on the reduced food consumption and body weight gain at 15 to 45 mg/kg/day). Developmental NOEL = 15 mg/kg/day a.i. (based on diaphragmatic hernias, in addition to minor skeletal variations and ossification delays, and reduced fetal weight at 45 mg/kg/day a.i.). Study was initially designated as unacceptable but possibly upgradeable (1988), but was later found acceptable upon submission of finalized report with GLP compliance statement, purity and stability of test material (1993). Earlier CDFA/DPR reviews classified this study as showing “no adverse effects,” based on a lower NOEL for maternal than for developmental findings. The 2016 review re-designates the diaphragmatic hernia response as a “possible adverse effect,” with maternal toxicity as a plausible contributing factor. (Reviewers: Rinkus review of draft report, 11/10/88; ██████ review of final report, 8/5/93; ██████, 5/10/16).

50660-0019 63682 van Marwijk, M. W., “Incidence of spontaneous malformations, anomalies and variants in albino rats of the Wistar Strain (cpb:WU: Wistar random),” Civo Institutes (TNO), April 1985. Soft tissue malformations in this series (of 483 dams) did not include any cases of diaphragmatic hernia, noted in the Hazleton study above (Record No. 70870). ██████, 5/9/16. Note that this is not the strain used in the Hazleton developmental toxicity study, above.

### Rabbit \*\*

\*\*50660 004, 039, 076; 34919, 85354, 116274; “Oral Embryotoxicity/Teratogenicity Study with an Aqueous Cyanamid Solution (49%) in New Zealand White Rabbits.”(Author: Koeter, H.B.W.M., and van Marwijk, M.W.; TNO CIVO Division for Nutrition and Food Research, Netherlands; Report No. 84.444/240171; 11/84); Dormex (Batch No. 06/04/91; 49% Hydrogen Cyanamide); 0, 4, 12, 36 mg/kg/day (0, 2, 6, 18 mg/kg/day a.i. respectively) oral gavage; New Zealand White rabbits; at 36 mg/kg: demonstrated very slight maternal toxicity (decreased b.w. gain) and developmental toxicity (increased resorptions, deaths, anomalies and variants, decreased fetal weight); 12 mg/kg dose: increased anomalies and variants; Maternal NOEL = 12 mg/kg/day (6 mg/kg a.i.) (based on decreased body weight gain); Developmental NOEL = 4 mg/kg/day (2 mg/kg a.i.) (based on increased retinal folds); no adverse effects; initially reviewed as unacceptable but possibly upgradeable with submission of additional data; requested information submitted and subsequently reviewed as Acceptable. (██████, 10/23/85; upgraded, ██████, 8/6/93).

## NEUROTOXICITY

### Acute neurotoxicity, rat

## 90-day neurotoxicity, rat

## Developmental neurotoxicity, rat

## Delayed neurotoxicity, hen

## IMMUNOTOXICITY

## ENDOCRINE DISRUPTOR STUDIES

## SUPPLEMENTAL STUDIES

044; 87935; “Cyanamide Induced Liver Cell Injury Experimental Study in the Rat” (author: Vazquez, J.J. and Guillen, F.J., *Laboratory Investigation*, **50**: 385-393, 1984). Cyanamide prepared in saline and administered daily intraperitoneally for 27 weeks at 0, 8, or 16 mg/kg/day; 5-8 Wistar male rats/dose; inclusion bodies, containing large amounts of glycogen, lipid droplets and secondary lysosomes were detected at week 13 of cyanamide treatment; initially hepatocytes bearing inclusion bodies are located predominantly at the periportal areas but moving toward the center of the lobule; prior to the detection of inclusion bodies, cyanamide treatment produced cytoplasmic homogenous areas consisting of glycogen depositions and smooth endoplasmic reticulum tubules; supplemental; (██████, 8/6/93).

044; 87936; “Lack of Hepatotoxicity after Long Term Administration of Cyanamide in Rats: A Histological and Biochemical Study” (authors: Obach, R., *Acta Pharmacol. et Toxicol.* **57**: 279-284, 1985); Cyanamide (Batches S-13 and T-14) prepared daily by dilution in distilled water were administered orally (0, 2, 7, or 25 mg/kg/day for 6 months, 20 Sprague Dawley rats/sex/dose) or intraperitoneally (0, 8, or 16 mg/kg/day for 12 months, 40 male Wistar and 40 male Sprague Dawley rats/dose); no significant histological changes were observed in the liver after oral or intraperitoneal administration; specifically no inclusion bodies in any cyanamide treated rats were detected; however, Sprague Dawley rats treated orally for 6 months showed elevated levels of alkaline phosphatase, bilirubin, and alanine phosphatase at the high dose, whereas only bilirubin was increased in male Wistar rats treated intraperitoneally at 16 mg/kg/day for 12 months; supplemental; (██████, 8/6/93).

50660-0019 63683 “Incidence of tumours in CPB: WU Wistar random rats data of control animals from long-term studies,” Sept. 1996, SKW Trostberg AG. These control data do not have direct application to studies submitted to DPR in support of hydrogen cyanamide, as Wistar strain was not used in the long-term rat studies in this Summary. The above supplementary study in Record No. 87936 used Wistar rats, however. ██████, 5/10/16.

50660-020 63686 “Potential Health Hazards of Dormex (Hydrogen Cyanamide) Exposure: A Literature Review (Draft).” (Authors: Environ's Staff; Environ Corporation, 7/24/87) Review discusses 2 reports on the incidence of cancer in workers in the manufacture of calcium carbimide = cyanamide in Norway and Germany. No cancer excess was noted. It also discussed treatment of alcoholics with calcium cyanamide with changes in the liver (“ground glass hepatocytes”) the only finding other than intended effects of nausea, anorexia, flushing, etc. supplemental: [REDACTED], 12/21/87; updated, [REDACTED], 8/5/93).

50660-0018 Three records (63680, 63673, and 63679) were submitted by CIVO Institutes, containing historical control pathology data for Wistar rats following 3, 12, and 24 months, respectively. [REDACTED], 5/10/16.

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