

Integrated Laboratory Systems

**2-Chloro-6-(trichloromethyl)pyridine (Nitrapyrin)
[CASRN 1929-82-4]**

Review of Toxicological Literature

Prepared for

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EXECUTIVE SUMMARY

Nitrapyrin, an EPA-registered pesticide, is used as a fertilizer additive to control nitrification and prevent loss of soil ammonium nitrogen by delaying nitrification. Nitrapyrin is selectively active against *Nitrosomonas* bacteria, the organisms responsible for nitrification of the ammonium ion to the nitrite ion in the soil. Nitrapyrin is listed on the U.S. Environmental Protection Agency (EPA), Office of Pollution Prevention and Toxics (OPPT) High Production Volume Chemicals list with an annual production volume of ~1.6 to 2.9 million pounds (~720 to 1300 metric tons).

Nitrapyrin was metabolized to 6-chloropicolinic acid (6-CPA) and its glycine conjugate in rats and dogs. Milk from cows fed nitrapyrin did not contain detectable nitrapyrin.

In range-finding acute studies, nitrapyrin was moderately toxic in oral and dermal studies in mice, rats, and rabbits, and in 48-hr and 96-hr tests with aquatic species. It was slightly toxic to mallard ducks and Japanese quail. In subchronic studies, dogs and rats fed nitrapyrin at doses of 15 mg/kg/day for 93 days exhibited no adverse effects. Histopathological examination revealed no organ or tissue changes. Unpublished subchronic dietary studies of nitrapyrin with rats reported possible adverse effects in the kidneys and liver at doses ≥ 40 mg/kg/day; similar studies with dogs indicated adverse effects that may have been secondary to inadequate nutrition due to the low palatability of the diet. The no-observed-effect-level (NOEL) was 10 mg/kg/day for rats and ≤ 15 mg/kg/day for dogs.

Nitrapyrin was not associated with adverse effects in an unpublished chronic 1-year dietary study with dogs fed up to 15 mg/kg/day. Dogs fed a diet of up to 0.2% 6-CPA (2000 ppm) in the diet for 2 years showed degenerative changes in the liver and kidneys at 0.06 and 0.2% CPA. Male mice fed up to 900 mg 6-CPA/kg/day for up to 2 years showed decreased body weight and renal changes at the high dose by 6 months whereas females did not show treatment-related effects.

Nitrapyrin did not cause any clinical toxicity in artificially inseminated female Fischer 344 rats dosed with up to 50 mg/kg/day by gavage on days 6-15 of gestation and did not cause any teratogenic effects in their fetuses. Nitrapyrin caused significant decreases in Sprague-Dawley dam body weight gain at 50 or 120 mg/kg/day and significant decreases in food consumption at 120 mg/kg/day in female rats given nitrapyrin by gavage at doses of 15, 50, and 120 mg/kg/day on days 6-15 of gestation. Developmental delays in the form of ossification variations in the sternbrae and ribs were noted in fetuses from dams treated with 120 mg/kg/day. The NOEL was determined to be 15 mg/kg/day for maternal toxicity and 50 mg/kg/day for developmental toxicity.

An unpublished two-generation reproductive study of nitrapyrin in Fischer 344 rats reported no adverse reproductive or teratogenic effects when rats were fed up to 75 mg/kg/day in the diet. Another unpublished developmental toxicity study in rats observed a possible adverse effect for fetal skeletal development at 50 mg/kg/day but not at 120 mg/kg/day (dosing by gavage).

Nitrapyrin caused significant weight loss and significantly increased liver weights in artificially inseminated female rabbits dosed with 30 mg/kg/day on days 6-18 of gestation. No clinical signs of toxicity were observed in pregnant rabbits at lower doses of 3 or 10 mg/kg/day.

Teratogenic effects were not observed in the fetuses of any of the dose groups. Other oral teratology studies with rats and rabbits reported no adverse effects.

Nitrapyrin was associated with primary renal tumors in male rats given the highest dose tested, 60 mg/kg/day, in the diet for two years. Chronic progressive glomerulonephropathy was observed in both sexes at this dose. A similar study with mice found no adverse effects.

Groups of male and female B6C3F₁ mice were administered diets with 0, 100, 300, or 900 mg/kg/day 6-CPA, the major metabolite of nitrapyrin, for 6, 12, or 24 months. Female mice given the high dose for 2 years showed an equivocal increase in hepatocellular carcinoma because the tumor incidence was slightly elevated (12%) when compared to the historical control range of the test laboratory (0-8%). However, the increase was not statistically significant compared to concurrent controls and controls were within the range of control values reported by other laboratories (0-15%). Treated males did not have an increased tumor incidence at any site.

Rats were given 30, 100, 300, and 1000 ppm 6-CPA in the diet for 2 years. Significant dose-related biliary hyperplasia occurred in female rat livers, but no effects were observed in male rats or controls.

Nitrapyrin was mutagenic in a dose-dependent fashion in *Salmonella typhimurium* strain TA100 in the presence (but not the absence) of Aroclor 1254. It was not mutagenic in strain TA1535, in the presence and absence of Aroclor-1254-induced metabolic activation. An unpublished study reported no increased reversion rate in *S. typhimurium* strains TA97, TA98, TA100, and TA1535. Other unpublished studies found no evidence for an increase in mutation frequency in Chinese hamster ovary cells, unscheduled DNA synthesis in cultured rat hepatocytes, or induction of micronucleated polychromatic erythrocytes in mice.

No information on tumor initiation/promotion or anticarcinogenicity was located. Also, no information was found for cogenotoxicity, antigenotoxicity, immunotoxicity, or structure-activity relationships.

TABLE OF CONTENTS

EXECUTIVE SUMMARY	i
1.0 BASIS FOR NOMINATION	1
2.0 INTRODUCTION	1
2.1 Chemical Identification	1
2.2 Physical-Chemical Properties	1
2.3 Commercial Availability	2
3.0 PRODUCTION PROCESSES AND ANALYSES	2
4.0 PRODUCTION AND IMPORT VOLUMES	2
5.0 USES	2
6.0 ENVIRONMENTAL OCCURRENCE AND PERSISTENCE	3
7.0 HUMAN EXPOSURE	4
8.0 REGULATORY STATUS	5
9.0 TOXICOLOGICAL DATA	7
9.1 General Toxicology	7
9.1.1 Human Data	7
9.1.2 Chemical Disposition, Metabolism, and Toxicokinetics	7
9.1.3 Acute Exposure	7
9.1.4 Short-Term and Subchronic Exposure	8
9.1.5 Chronic Exposure	9
9.1.5.1 Nitrapyrin	9
9.1.5.2 6-Chloropicolinic Acid (6-CPA)	9
9.2 Reproductive and Teratological Effects	10
9.2.1 Nitrapyrin Published Studies	10
9.2.2 Nitrapyrin Unpublished Studies	10
9.2.2.1 Nitrapyrin	11
9.2.2.2 6-CPA	15
9.3 Carcinogenicity	15
9.3.1 Nitrapyrin	15
9.3.2 6-CPA	16
9.4 Initiation/Promotion Studies	16
9.5 Anticarcinogenicity	17
9.6 Genotoxicity	17

9.7 Cogenotoxicity18

9.8 Antigenotoxicity.....18

9.9 Immunotoxicity18

10.0 STRUCTURE-ACTIVITY RELATIONSHIPS.....18

11.0 ONLINE DATABASES AND SECONDARY REFERENCES.....18

 11.1 Fee-Based Online Databases18

 11.2 Standard Secondary References.....20

12.0 REFERENCES.....20

13.0 REFERENCES CONSIDERED BUT NOT CITED.....23

ACKNOWLEDGEMENTS.....25

APPENDIX A: UNITS AND ABBREVIATIONS25

TABLES

Table 1 Regulations Relevant to Nitrapyrin6

Table 2 Acute Toxicity Values for Nitrapyrin.....7

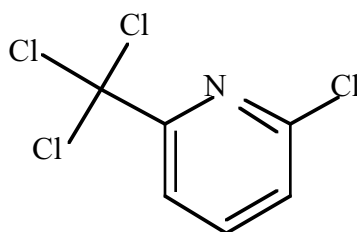
Table 3 Reproductive Toxicity of Nitrapyrin.....13

1.0 BASIS FOR NOMINATION

The nomination of 2-chloro-6-(trichloromethyl)pyridine, also called nitrapyrin, by the National Institute of Environmental Health Sciences (NIEHS) is based on its high U.S. production volume and potentially high human exposure.

2.0 INTRODUCTION

2-Chloro-6-(trichloromethyl)pyridine
[1929-82-4]



2.1 Chemical Identification

2-Chloro-6-(trichloromethyl)pyridine (C₆H₃Cl₄N; mol. wt. = 230.91) is also called:

α,α,α,6-Tetrachloro-2-picoline
Dowco-163
N-Serve[®]
N-Serve Nitrogen Stabilizer
Nitrapyrin

It will be called by its generic name, nitrapyrin, in this report.

2.2 Physical-Chemical Properties

Property	Information	Reference
Physical State	colorless or off-white crystalline solid	Radian (1991)
Odor	mild, sweet	Ludwig (1994)
Boiling Point (°C @ 11 mm Hg)	136-137.5	Budavari (1996)
Melting Point (°C)	62.5-62.9	Budavari (1996)
Density	no information available	
Vapor Pressure (mm Hg @ 23 °C)	0.0028	Radian (1991)
Solubility	practically insoluble in water (40 mg/L); soluble in anhydrous ammonia, xylene, acetone, methylene chloride, and 95% ethanol	Lide and Milne (1994)

Nitrapyrin is corrosive to aluminum and aluminum alloys (Thomson, 1995). It should not be used with hot-mix fertilizers.

2.3 Commercial Availability

Nitrapyrin is produced by Dow AgroSciences LLC located in Pittsburg, California (SRI, 1998). Four registered formulations are active: N-Serve 24 (24%), N-Serve 24E (24.3%), N-Serve TG (90.0%), and Stay-N Nitrogen Stabilizer (22.0%). The latter product is registered by Platte Chemical Company (USEPA/OPP Chemical Database, 1999). Formulations are provided as emulsifiable and nonemulsifiable concentrates.

3.0 PRODUCTION PROCESSES

A U.S. patent for nitrapyrin production was assigned to Dow Chemical Co. in 1969. Nitrapyrin is prepared by treating α -picoline with gaseous HCl to give liquid α -picoline hydrochloride followed by treating the latter with gaseous chlorine at elevated temperatures in the absence of water. Nitrapyrin is isolated by distillation (Taplin, 1969). Nitrapyrin products have been formulated in California, Arizona, Kentucky, and Louisiana (U.S. EPA, 1985).

4.0 PRODUCTION AND IMPORT VOLUMES

Nitrapyrin is listed on the U.S. Environmental Protection Agency (EPA), Office of Pollution Prevention and Toxics (OPPT) High Production Volume Chemicals list with an annual production volume of ~1.6 to 2.9 million pounds (~720 to 1300 metric tons) (U.S. EPA, 1998).

5.0 USES

Nitrapyrin is used as a fertilizer additive to control nitrification and prevent loss of soil ammonium nitrogen, by delaying nitrification by *Nitrosomonas* bacteria (Mills and McElhannon, 1980 abstr.; Budavari, 1996). It may be impregnated on dry fertilizers or applied with liquid animal waste. Nitrapyrin is selectively active against *Nitrosomonas* bacteria, the organisms responsible for nitrification of the ammonium ion to the nitrite ion in the soil (Thomson, 1995).

It has been registered for use on corn, cotton, sorghum, and wheat (Farm Chemicals, 1976; Thomson, 1995) and for strawberries in California (U.S. EPA, 1985). It is mixed with ammoniacal and urea nitrogen fertilizers and sprayed with water or impregnated on dry fertilizer for broadcast application (Farm Chemicals, 1979; Thomson, 1995). Use on cotton may be affected by the recent revocation of the tolerance for nitrapyrin and its metabolite 6-chloropicolinic acid in cottonseed. The tolerance for residues in strawberries was also revoked (U.S. EPA, 1998).

A patent was granted to Dow Chemical Co. in 1984 for (trichloromethyl)pyridine compounds useful for promoting growth and/or improving feed utilization in ruminants. In one example, growth rate and feed utilization efficiency in cattle fed a diet containing 3 to 200 ppm nitrapyrin were higher than those observed in cattle fed an equivalent diet without nitrapyrin (Phillips and Tadman, 1984).

6.0 ENVIRONMENTAL OCCURRENCE AND PERSISTENCE

Nitrapyrin may be lost from soil by hydrolysis and volatilization, with the losses increasing with increasing temperatures. Nitrapyrin degradation is not affected by changes in pH, but it is anticipated to degrade more rapidly in light than in the dark. The soil half-life, depending on soil type and ambient temperature, ranges from < 3 to 77 days (U.S. EPA, 1988; Herlihy and Quirke, 1975). 6-CPA is the principal nitrapyrin degradation product in plants and soils. In several unpublished field soil experiments with nitrapyrin or 6-CPA applied at up to 3 lb/acre, residues in the upper 6 inches were generally well below 1 ppm, with little detected below the top 6 inches of soil. Soil organic matter strongly sorbs nitrapyrin (Mullison and Norris, 1976).

Plant uptake of nitrapyrin or 6-CPA from treated soils is low. At a nitrapyrin application rate of 0.5 lb/acre, 6-CPA residues in crops ranged from an average of < 0.05 ppm in sorghum to 0.33 ppm in potatoes with no residues found in corn, wheat, and sugar beets (Mullison and Norris, 1976).

Negligible 6-CPA concentrations were found in run-off water and none was found in groundwater after nitrapyrin applications to soils. Hydrolysis in water is rapid with half-lives ranging from 0.54 day at 45 °C to 7.7 days at 25 °C (Mullison and Norris, 1976).

Nitrapyrin has been added to the Toxic Chemical Release Inventory. Dow Chemical Co. in Pittsburg, CA, reported only 1 lb released to air and none to water or soil in 1996 (TRI96, 1999).

7.0 HUMAN EXPOSURE

A 1983 National Institute for Occupational Safety and Health (NIOSH) National Occupational Exposure Survey (NOES) estimated that approximately 399 workers were exposed to nitrapyrin annually (RTECS, 1998). Occupations with possible exposure besides farm workers include manufacturing, formulating, packaging, mixing, blending, or repackaging; personal protective equipment is recommended for workers who may come into contact with nitrapyrin (NIOSH, 1978).

Loaders at commercial agricultural facilities and farmer applicators of nitrapyrin were monitored during the 1990 season for nitrapyrin exposure (Honeycutt et al., 1991 abstr.). Exposure values were consistent for the loaders and were within anticipated levels for this type of exposure, while farmers applying nitrapyrin from a closed-cab tractor had exposures that were consistently a level of magnitude lower than those of the loaders. No concentrations or study details were provided.

Nitrapyrin was reported to be soil-injected or incorporated in soil immediately following application at rates from 0.25 to 1.0 pound active ingredient per acre (U.S. EPA, 1985, 1988). Consequently, reentry intervals for farm workers were not required.

Nitrapyrin was detected at 18.0 ng/m³ in the air of a commercial pesticide storage building (product stored was an N-Serve liquid concentrate) (Yeboah and Kilgore, 1984).

Nitrapyrin degraded primarily to 2-chloro-6-(dichloromethyl)pyridine in red beets (Kallio and Sandholm, 1982). For nitrapyrin, the greatest concentration was found in the root tips and petioles, with the peel containing more than the leaf surface or other parts of the root. The

greater the nitrapyrin content, the greater the ratio of nitrapyrin to 2-chloro-6-(dichloromethyl)pyridine. There was no linear correlation between nitrapyrin content and that of its metabolite. Nitrapyrin residues were smaller in beets fertilized with $\text{Ca}(\text{NO}_3)_2$ than those fertilized with urea or NH_4NO_3 .

Residues of nitrapyrin and degradation products have been determined in strawberries and soil using gas chromatography (GC) in conjunction with a nitrogen/phosphorus detector (NPD) following solvent extraction (Iwata et al., 1981). Nitrapyrin concentrations in strawberries were below the detection limit (0.04 ppm), but the degradation product 6-chloropicolinic acid was found in concentrations up to 0.09 ppm.

Bluegill showed maximum bioconcentration factors of 33 and 60 times the concentration in water in edible tissues and viscera, respectively, but the residues depurated rapidly (U.S. EPA, 1988). 6-CPA showed no tendency to bioconcentrate in algae, daphnia, or fish (Mullison and Norris, 1976).

The theoretical maximum residue contribution (TMRC) to the human diet as a result of the existing tolerances is 0.0411 mg/day/1.5 kg of the diet (U.S. EPA, 1985). The provisional acceptable daily intake (PADI) was calculated to be 0.0015 mg/kg/day.

8.0 REGULATORY STATUS

U. S. government regulations pertaining to nitrapyrin are summarized in **Table 1**.

The American Conference of Governmental Industrial Hygienists (ACGIH) recommends a threshold limit value (TLV) of 10 mg/m^3 as an 8-hour time-weighted average (TWA) and a short-term exposure limit (STEL) of 20 mg/m^3 (ACGIH, 1996). ACGIH categorizes nitrapyrin as A4, a substance that is not classifiable as a human carcinogen. The NIOSH Recommended Exposure Limit (REL) for nitrapyrin is 10 mg/m^3 (total dust) and 5 mg/m^3 (respirable dust), both measured as 10-hour TWAs, and a STEL of 20 mg/m^3 (Ludwig, 1994).

The U.S. EPA (40 CFR 180.350) has established tolerances for nitrapyrin, 6-chloropicolinic acid, or both, measured as nitrogen, of 0.05 ppm for the meat, meat by-products, and fat of cattle, hogs, poultry, sheep, horses, and goats. A tolerance of 0.1 ppm (N) was set for

corn grain, fresh corn, wheat grain, and sorghum forage and grain. A tolerance of 0.5 ppm was established for sorghum fodder and wheat forage and straw. A tolerance of 1.0 ppm was set for cottonseed and corn fodder and forage. Nitrapyrin has regional registration for use in strawberry cultivation. The tolerance of 0.2 ppm in strawberries and 1.0 ppm in cottonseed was recently revoked (U.S. EPA, 1998).

As directed by the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), EPA is in the process of conducting a comprehensive review of older pesticides regarding their future use (OPP, 1998). EPA guidance for testing needed for nitrapyrin reregistration was published in 1985 (U.S. EPA, 1985). Nitrapyrin is in the Pre-RED (Reregistration Eligibility Decision) status, indicating that the Office of Pesticides (OPP) is currently reviewing data from producers of the chemical regarding its health and environmental effects, or OPP is determining nitrapyrin's eligibility for reregistration and developing the RED document (OPP, 1998).

Table 1. Regulations Relevant to Nitrapyrin

	Regulation	Summary of Regulation
O S H A	29 CFR 1910.1000	Table Z-1: The Occupational Safety and Health Administration (OSHA) permissible exposure limit (PEL) for nitrapyrin is 15 mg/m ³ (total dust) and 5 mg/m ³ (respirable fraction), measured as 8-hour TWAs.
	40 CFR 152	Nitrapyrin is a registered pesticide under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA).
E P A	40 CFR 180.350	Nitrapyrin; tolerances for residues: Tolerances are established for the combined residues of nitrapyrin (a soil microbiocide) and its metabolite 6-chloropicolinic acid in or on the raw agricultural commodities listed in this section.
	40 CFR 372	Toxic Chemical Release Reporting Community Right-to-Know: Information about releases of nitrapyrin must be provided to the public and surrounding communities to assist research and to aid in the development of regulations, guidelines, and standards. Suppliers must notify persons to whom they distribute mixtures or trade name products that the products contain nitrapyrin. Nitrapyrin is listed in /372.65 Chemicals and chemical categories to which Part 372 applies.
	40 CFR 455.67	Any new source subject to this subpart which introduced pollutants into a publicly owned treatment work must comply with Part 403 and achieve the pretreatment standard for existing sources. There shall be no discharge of process wastewater pollutants. Nitrapyrin is included in Table 10 to Part 455 List of Appropriate Pollution Control Technologies.

9.0 TOXICOLOGICAL DATA

9.1 General Toxicology

9.1.1 Human Data

No published human toxicity information was identified. In an unpublished study, nitrapyrin was tested for dermal sensitization/irritation (U.S. EPA, 1985).

9.1.2 Chemical Disposition, Metabolism, and Toxicokinetics

Nitrapyrin was metabolized to 6-chloropicolinic acid (6-CPA) in rats (Redemann and Clark, 1967) and a dog (Redemann et al., 1966). In the dog, at least 80% of the nitrapyrin dose was excreted as 6-CPA in the urine, primarily as *N*-(6-CPA)glycine. In the rat, less 6-CPA was conjugated with glycine. No residues (detection limit < 0.025 ppm) were found in the milk of dairy cows fed up to 100 ppm in the diet (Jensen, 1971). Beef calves and young pigs fed 6-CPA in the diet for 30 days at up to 100 ppm showed no residues in muscle, fat, and liver. At 100 ppm, 6-CPA was detected at 0.08 to 0.3 ppm in the kidneys of these animals. Laying hens fed up to 30 ppm 6-CPA for 30 days had detectable 6-CPA residues (0.06-0.08 ppm) in some liver and kidney samples but none in eggs or muscle tissue (Mullison and Norris, 1976).

9.1.3 Acute Exposure

Mammalian acute toxicity values for nitrapyrin are presented in **Table 2**. Details were not available for these studies.

Table 2. Acute Toxicity Values for Nitrapyrin

Route	Species (sex and strain)	LD ₅₀	Reference
Dermal	Rabbit (sex and strain n.p.)	LD ₅₀ = 850 mg/kg (3.68 mmol/kg)	RTECS (1998)
Oral	Mouse (sex and strain n.p.)	LD ₅₀ = 710 mg/kg (3.07 mmol/kg)	RTECS (1998)
	Rat (sex and strain n.p.)	LD ₅₀ : M = 1,070 mg/kg (4.63 mmol/kg) and F = 1,230 mg/kg (5.33 mmol/kg)	Berdasco et al. (1988)
	Rabbit (sex n.p.; New Zealand white)	LD ₅₀ = 713 mg/kg (3.09 mmol/kg)	Berdasco et al. (1988)

Abbreviations: F = female(s); LD₅₀ = dose lethal to 50% of test animals; M = male(s); n.p. = not provided

Nitrapyrin was slightly toxic to mallard ducks (oral LD₅₀ = 2708 mg/kg; 11.73 mmol/kg) and Japanese quail (oral LD₅₀ = > 820 ppm) (U.S. EPA, 1988).

Nitrapyrin was moderately toxic to *Daphnia magna* (5.8 mg/L, 48-hr acute; 0.025 mmol/L), bluegill sunfish (7.876 mg/L, 96-hr acute; 0.034 mmol/L), and rainbow trout (9.191 mg/L, 96-hr acute; 0.040 mmol/L) (U.S. EPA, 1988).

9.1.4 Short-Term and Subchronic Exposure

The California Department of Pesticide Regulation (CDPR) reviewed and summarized unpublished rat and dog subchronic studies of nitrapyrin conducted to meet pesticide re-registration requirements (CDPR, 1994). A facsimile of these summaries is presented below.

028 090540 "Nitrapyrin (N-Serve*): 13-Week Dietary Toxicity Study in Fischer-344 Rats." (J.R. Szabo, B.L. Rachunek, D.C. Mensik, and C.V. Wood; The Dow Chemical Company, Lake Jackson Research Center, Freeport, TX, 8/86). Nitrapyrin technical (LOT #: 03184-122A; purity = 94.6%) was fed to Fischer-344 rats (10/sex/group) at 0 (vehicle = diet), 10, 40 and 120 mg/kg/day for 13 weeks. **Possible adverse effect.** NOEL = 10 mg/kg/day (decreased bodyweight, packed cell volume, hemoglobin and RBC counts and an increase in serum total bilirubin in both sexes at 120 mg/kg/day; increased relative and absolute kidney and liver weights at 120 mg/kg/day in both sexes; ≥ 40 mg/kg/day showed increased relative liver weight in both sexes and an increased absolute liver weight in males; paleness of hepatic parenchyma, vacuolation consistent with fatty change was observed in both sexes at 120 mg/kg/day and ≥ 40 mg/kg/day showed centrilobular hepatocyte hypertrophy; male kidneys had acute tubular necrosis and increased severity of degenerative/regenerative tubules at ≥ 40 mg/kg/day. Female kidneys had pigment in the proximal tubule epithelial cells at ≥ 40 mg/kg/day.) M. Silva, 4/27/90.

028 090451 "Nitrapyrin (N-SERVE): Results of a 13-Week Dietary Toxicity Study in Dogs," (J.R. Szabo & B.L. Rachunek, Dow Chemical Co., Lake Jackson Research Center, Freeport, TX, 9/2/88.) Nitrapyrin technical (LOT #: WP860516-308B(T19B); purity = 92.8%) was fed in diet at 0 (vehicle = acetone and/or diet), 15, 40 and 75 mg/kg/day (changed on day 49 to 50 mg/kg/day, due to diet refusal) to Beagle dogs (4/sex/group) for 13 weeks. **No adverse effect indicated.** NOEL ≤ 15 mg/kg/day (decreased bodyweight and food consumption-->_40 mg/kg/day; brittle haircoat and muscle wasting--75 mg/kg/day; increased absolute and relative liver weights--≥ 40 mg/kg/day and adrenal weight--75 mg/kg/day; decreased ovary and testes weights--75 mg/kg/day; progressive alterations (hypertrophy & vacuolation) of hepatic lobules--≥ 15 mg/kg/day; increased basophilic staining of proximal convoluted tubules of kidney--75 mg/kg/day). Many of the effects in this study were secondary to effects of inadequate nutrition brought about by the low palatability of the diet containing nitrapyrin. These data are supplemental to 025 090169. M. Silva, 4/30/90.

Torkelson (private communication cited by ACGIH, 1986) fed dogs and rats nitrapyrin at doses of 15 mg/kg/day for 93 days and reported no adverse effects in appearance, behavior, growth, food consumption, body and organ weight, mortality, or blood chemistry. Histopathological examination revealed no organ or tissue changes.

9.1.5 Chronic Exposure

The California Department of Pesticide Regulation reviewed and summarized unpublished rat and dog chronic studies of nitrapyrin and its metabolite 6-CPA conducted to meet pesticide re-registration requirements (CDPR, 1994). A facsimile of these summaries is presented below.

9.1.5.1 Nitrapyrin

** 025 090169 "Nitrapyrin: Chronic (One-Year) Dietary Toxicity Study in Dogs" (Lake Jackson Research Centr, Dow, Project ID: TXT: K-031304-029, 12-27-89). Nitrapyrin technical (Lot #: WP 860516-308B(19B); 92.6% pure) was fed in the diet to beagle dogs at dose levels of 0, 0.5, 3 or 15 mg/kg/day, 4/sex/group. NOEL = 3 mg/kg/day (Hepatotoxicity was exhibited in high dose males and females as increased alkaline phosphatase activity and cholesterol levels. Absolute and relative liver weight was increased and diffuse hypertrophy of hepatocytes was also observed). **No adverse effects. Acceptable.** D. Shimer & M. Silva, 4/5/90.

9.1.5.2 6-Chloropicolinic acid (6-CPA)

006, 012 943515, 036148 "Results of Two-Year Dietary Feeding Studies of 6-Chloropicolinic Acid in Beagle Hounds." (2/22/67, Dow) Metabolite, 6-chloropicolinic acid, 98.5%. Three per sex per group were fed 0.02, 0.06 and 0.2% in the diet for 2 years with 1/sex/group sacrificed at 1 year. Initial review (AA, 7/24/85) found unacceptable (dose selection not justified with no overt toxicity reported at high dose, inadequate number of animals, inadequate histopath, no diet analysis.) Subsequent review (Martz, 4/7/86) found study not upgradeable and confirmed that there were positive findings for liver and kidney (degenerative changes at 0.06 and 0.2%). NOEL: 0.02% of diet.

A study of 6-CPA reported decreased body weight and renal changes in male mice fed a high dose (Dow Chemical Co., 1986; tables with data not provided). Groups of male and female B6C3F1 mice were administered diets with 0, 100, 300, or 900 mg/kg/day 6-CPA for 6, 12, or 24 months. Males fed the high dose for all three exposure durations had decreased body weight and renal changes. Treatment-related decreases in body weight were statistically significant from day 153 to day 461, and body weights were apparently decreased throughout the study. The renal

changes were characterized by total or near-total loss of normal vacuolation in proximal tubule epithelial cells. These changes were noted in some male mice given 900 mg/kg/day 6-CPA for 6, 12, or 24 months. Female mice did not show similar treatment-related effects.

9.2 Reproductive and Teratological Effects

9.2.1 Nitrapyrin Published Studies

The details of published studies described below are presented in **Table 3**.

Nitrapyrin did not cause any clinical toxicity in artificially inseminated female Fischer 344 rats dosed at 5, 15, or 50 mg/kg/day by gavage on days 6-15 of gestation, nor any teratogenic effects in the fetuses of dosed rats (Berdasco et al., 1988).

Nitrapyrin caused significant decreases in dam body weight gain at 50 or 120 mg/kg/day and significant decreases in food consumption at 120 mg/kg/day in female Sprague-Dawley rats given nitrapyrin by oral gavage at doses of 15, 50, and 120 mg/kg/day on days 6-15 of gestation. Developmental delays in the form of ossification variations in the sternbrae and ribs were noted in fetuses from dams treated with 120 mg/kg/day. The no-observed-effect-level (NOEL) was determined to be 15 mg/kg/day for maternal toxicity and 50 mg/kg/day for developmental toxicity (Carney et al., 1995 abstr.).

Nitrapyrin caused significant weight loss and significantly increased liver weights in artificially inseminated female New Zealand white rabbits dosed by gavage with 30 mg/kg/day on days 6-18 of gestation. No clinical signs of toxicity were observed in those dosed with 3 or 10 mg/kg/day, nor were teratogenic effects observed in the fetuses of any of the dose groups (Hanley et al., 1986 abstr.; Berdasco et al., 1988).

9.2.2 Nitrapyrin Unpublished Studies

The California Department of Pesticide Regulation reviewed and summarized unpublished rat and rabbit reproductive studies of nitrapyrin conducted to meet pesticide re-registration requirements (CDPR, 1994). A facsimile of these summaries is presented below.

9.2.2.1 Nitrapyrin

** 023 072241 "Nitrapyrin (N-Serve* TG): Results of a Two-Generation Reproduction Study in Fischer 344 Rats," (Health and Environmental Sciences-Texas, Dow Chem. Co., Study ID: TXT:K-031304-025, -025F1, -025FAW, -025FBW, 12-27-88). Nitrapyrin (N-Serve TG; 93.3% pure; LOT #: WP860 516-3088) was fed to Fischer 344 rats in the diet at dose levels of 0, 5, 20 and 75 mg/kg/day for a 2 generation reproduction study, 30/sex/group. NOEL (Adult) = 5 mg/kg/day (Decreased body weight and body weight gain was observed at 75 mg/kg/day in F0 (females) and F1 (both sexes); increased liver and kidney weights (absolute & relative) were observed in F0 males at ≥ 20 mg/kg/day and F0 females at 75 mg/kg/day; liver and kidney weights (absolute and relative) were significantly increased in F1 adults of both sexes at ≥ 20 mg/kg/day; histopathological effects were observed in F0 & F1 livers of both sexes at ≥ 20 mg/kg/day-- liver changes included hypertrophy of centrilobular hepatocytes and lipid vacuolation; histopathological effects were observed in kidneys of F0 & F1 males at 75 mg/kg/day which included necrosis of the intratubular epithelium). NOEL (Neonatal) = 20 mg/kg/day (at 75 mg/kg/day, F1 & F2 pup weights were significantly decreased; both sexes of F1 & F2 pups showed enlarged livers, and livers of both sexes had centrilobular vacuolation). NOEL (Reproductive) = 75 mg/kg/day (HDT). **No adverse effects. Acceptable.** M. Silva, 4/6/90.

032 130129 "A Range-finding Study to Evaluate the Developmental Toxicity of Nitrapyrin in the Rat," (Schroeder, R.E., Pharmaco LSR, Inc., East Millstone, NJ; Project ID#: 93-4049; 4/14/94). Nitrapyrin technical (92% pure) was administered by gavage to mated Sprague-Dawley CD(SD)BR female rats (10/dose) at 0 (corn oil), 50, 100 and 200 mg/kg during days 6-15 of gestation. **Maternal NOEL = 50 mg/kg** (A slight decrease in maternal body weight gain and food consumption and increased relative weights for liver and kidney were observed at 100 mg/kg. At 200 mg/kg, animals experienced significant decrease in weight, weight gain and food consumption. Clinical signs were also observed and therefore, the entire dose group was terminated early.) These data are supplemental. M. Silva, 11/7/94.

017 057213 "Nitrapyrin: Oral Teratology Probe Study in Fischer 344 Rats," (Dow Chemical, 5/12/86). Nitrapyrin technical, 91.9%, given by oral gavage to 9 - 10 per group at 0 (corn oil), 15, 50 or 100 mg/kg, days 6 - 15 of gestation with sacrifice on day 16; weight loss/decreased gain at 50 and 100 mg/kg, decreased food consumption at 100 and increased liver weights at 50 and 100 mg/kg with histopathological findings of vacuolation; includes stability and homogeneity data and dosing solution analysis for # 051088; supplemental data for 051088, dose justification, upgrading that study to acceptable status. (Gee, 5/26/88 and Parker, 6/7/88.)

** 033 130131 "A Developmental Toxicity Study in Rats with Nitrapyrin," (Schroeder, R.E., Pharmaco LSR, Inc., East Millstone, NJ; Laboratory study #: 93-4050; 4/14/94). Nitrapyrin technical (92% pure) was administered by gavage to mated female CD(SD)BR rats (28/dose) at 0 (corn oil), 15, 50 and 120 mg/kg during days 6-15 of gestation (mating confirmed = day 0 gestation). **Maternal NOEL = 15 mg/kg** (Dams showed transitory decreased body weight gain at > 50 mg/kg. Food consumption was significantly decreased at 120 mg/kg. There was an increase in emaciation, excessive salivation, alopecia, ano-genital stains and decreased fecal volume at 120 mg/kg. Alopecia in the extremities/snout was increased at \geq 50 mg/kg. Kidney and liver organ/body weights were significantly increased at 120 mg/kg.) **Developmental NOEL = 15 mg/kg** (Fetal body weights decreased in a dose-related manner--significant in females at 120 mg/kg. There was a significant increase in fetal skeletal malformations at 50 mg/kg (not at 120 mg/kg). An increase in fetal ossification variations was observed at > 50 mg/kg.) **Possible adverse effect for fetal skeletal development was observed.** Acceptable. (M. Silva, 11/14/94).

**014 051088 "Nitrapyrin: Oral Teratology Study in Fischer 344 Rats," (Dow, 9/18/86). Nitrapyrin technical, 91.9%, given by gavage on gestation days 6 - 15 at dose levels of 0, 5, 15 or 50 mg/kg/day; maternal and developmental toxicity NOEL \geq 50 mg/kg/day; initially reviewed as unacceptable based on dose selection and lack of dosing analysis (Parker, 2/10/87). With the submission of 017 057213 containing a pilot study for dose justification and also dosing analysis, the study is upgraded to acceptable status. No adverse effect. (Gee, 6/1/88 and Parker, 6/8/88.)

** 015 051513 "Nitrapyrin: Oral Teratology Study in New Zealand White Rabbits, Dow Mammalian and Environmental Toxicology Research Laboratory, 10-23-85. Nitrapyrin, 91.9% purity, administered by gavage on days 6 - 18 of gestation to groups of 25 - 27 inseminated rabbits at 0 (corn oil), 3, 10 or 30 mg/kg/day. Maternal NOEL = 10 mg/kg/day (minimal decrease in body weight gain and increase in liver and kidney weight). Developmental NOEL = 10 mg/kg/day (increased incidence of fetuses with "crooked hyoid"). **No adverse effect.** Initially reviewed as unacceptable and upgradeable (JAP 2-9-87). Submission of Probe study (#057212) and analysis of dosing solutions and individual data allow upgrade to acceptable. (Parker, 6-8-88.)

017 057212 "N- Serve: Oral Teratology Probe Study in New Zealand White Rabbits" (Dow Chemical Company, 3-27-85). Nitrapyrin, 92%, given by gavage to 6 - 7 per group inseminated rabbits at 0 (corn oil), 30, 100 or 200 mg/kg/day, days 6 - 18 of gestation with sacrifice on day 19. No dams survived at 100 or 200 mg/kg/day. At 30 mg/kg/day all dams survived and showed enlarged and pale livers and increased kidney and liver weights (absolute and relative). This was submitted as dose justification for study #051513. Analysis of dosing solution and some individual data for #051513 are included in this submission. Supplemental data. (Parker 6-3-88.)

Table 3. Reproductive Toxicity of Nitrapyrin

Species, Strain, and Age	Number and Sex of Animals	Chemical Form, Purity	Route/Dose	Exposure/Observation Period	Results/Comments	Reference
<i>Rats</i>						
Fischer 344, age n.p.	30 F	Nitrapyrin, >91.9% purity	Oral gavage; 0, 5, 15, and 50 mg/kg/day (0, 0.022, 0.065, and 0.22 mmol/kg/day) on days 6-15 of gestation	Maternal body weights recorded on days 0, 6-16, and 21 of gestation. Cesarean section performed on day 21.	No clinical signs of toxicity in dosed rats, and no evidence of teratogenicity in rat fetuses as compared with control animals.	Berdasco et al. (1988)
Sprague-Dawley, age n.p.	28 F	Nitrapyrin, purity n.p.	Oral gavage; 0, 15, 50 or 120 mg/kg/day (0, 0.065, 0.22, or 0.52 mmol/kg/day) on days 6-15 of gestation	Observation of clinical signs of toxicity, feed consumption, body weights throughout the study.	No evidence of maternal toxicity in dams given 15 mg/kg/day. Significant decreases in body weight reported days 12-16 and 6-16 in rats given 50 mg/kg/day, and on days 6-9 and 6-16 at 120 mg/kg/day. Significant decreases in feed consumption were observed on day 6-9, 12-16, and 16-20 in the 120 mg/kg/day group. Increased incidence of ossification variations were noted in the high-dose group and were thought to be related to maternal toxicity. No treatment-related effects were observed in embryos or fetuses from dams dosed with 15 or 50 mg/kg/day.	Carney et al. (1995 abstr.)

Table 3. Reproductive Toxicity of Nitrapyrin (Continued)

Species, Strain, and Age	Number and Sex of Animals	Chemical Form, Purity	Route/Dose	Exposure/Observation Period	Results/Comments	Reference
<i>Rabbits</i>						
New Zealand white, age n.p.	25-28 artificially inseminated F	Nitrapyrin in corn oil, purity n.p.	Oral gavage; 0, 3, 10, and 30 mg/kg/day (0, 0.013, 0.043, and 0.13 mmol/kg/ day) on days 6-18 of gestation.	Fetuses examined for developmental toxicity.	Dams in 30 mg/kg/day group had decreased weight gain during dosing and increased absolute and relative liver weights at C-section. Slight fetotoxicity indicated by crooked hyoid bones in the fetuses from group dosed with 30 mg/kg/day.	Hanley et al. (1986 abstr.)
New Zealand white, age n.p.	25 artificially inseminated F	Nitrapyrin, >91.9% purity	Oral gavage; 0, 3, 10, and 30 mg/kg/day (0, 0.013, 0.043, and 0.13 mmol/kg/ day) on days 6-18 of gestation	Maternal body weights recorded on days 0, 6-19, and 28 of gestation. Cesarean section performed on day 28.	Pregnant rabbits administered 30 mg/kg/day gained significantly less weight, and had significantly increased liver weights on necropsy as compared with control animals. There were no clinical signs of toxicity in dosed rabbits, and no evidence of teratogenicity in fetuses from treated groups as compared with control animals.	Berdasco et al. (1988)

Abbreviations: F = female(s); M = male(s); n.p. = not provided

9.2.2.2 6-CPA

The California Department of Pesticide Regulation reviewed and summarized unpublished reproductive studies with rats of 6-CPA, conducted to meet pesticide re-registration requirements (CDPR, 1994). A transcription of this study is presented below.

Four males and 12 females were fed 0, 0.01, 0.03, or 0.1% 6-CPA in the diet for 3 generations and 3 litters. The initial review found the report unacceptable (inadequate number of animals at risk, doses not justified with no toxicity to adults at high dose, no histopath of reproductive organs, no individual data, no diet analysis) with possible adverse reproductive effects. A subsequent review found the report to have insufficient information for evaluation. NOEL cannot be determined due to paucity of data. Unacceptable, not upgradeable.

9.3 Carcinogenicity

The California Department of Pesticide Regulation reviewed and summarized unpublished rat combined (chronic and oncogenicity) and mouse oncogenicity studies of nitrapyrin conducted to meet pesticide re-registration requirements (CDPR, 1994). A facsimile of these summaries is presented below.

9.3.1 Nitrapyrin

**** 026 090170 "Nitrapyrin (N-Serve): Two-Year Chronic Toxicity and Oncogenicity Study in Fischer 344 Rats,"** (Lake Jackson Research Center, Dow, Project ID: TXT: K-031304-023, 12-26-89). Nitrapyrin technical (93.3% pure) was fed in diet to Fischer 344 rats at 0, 5, 20 or 60 mg/kg/day for 2 years (60/sex/group with 10/sex/group selected for interim sacrifice at 1 year). NOEL (males) = 5 mg/kg/day (decrease in body weight gain; increased relative and absolute kidney weights; protein droplet accumulation in the epithelial cells of the proximal convoluted tubules; increased liver weights; hypertrophy and fatty vacuolation of hepatocytes). NOEL (females) = 20 mg/kg/day (decreased body weight gain; increased absolute and relative kidney weights; increased liver weights with hypertrophy and fatty vacuolation of hepatocytes). **Possible adverse effects include primary renal tumors in males at 60 mg/kg/day and chronic progressive glomerulonephropathy in both sexes at 60 mg/kg/day. Acceptable.** M. Silva, 4/3/90.

** 029 091273, "Nitrapyrin (N-Serve*): Two-Year Dietary Oncogenicity Study in B6C3F1 Mice", (Quast, J.F., Cosse, P.F. and Corley, R.A., The Toxicology Research Laboratory, Health and Environmental Sciences, The Dow Chemical Company, Midland, MI., Study # K-031304-027, 7/23/90), N-SERVE TG (technical grade), AGR-229141, 93.3% nitrapyrin by gas chromatography, fed in the diet for two years to B6C3F1 mice (50/sex/group) at 0 (basal diet), 5, 25, or 75 mg/kg/day. An additional 10 mice/sex/group were included as a satellite group which was sacrificed at 12 months. Chronic NOEL = 5 mg/kg/day (Males showed significantly decreased cholesterol levels at 25 mg/kg and significantly increased serum alanine aminotransferase at 75 mg/kg for the satellite--12 month group. Histopathology showed an increase in staining properties in the duodenum in both sexes at \geq 25 mg/kg/day in both satellite and oncogenicity groups. Liver showed altered cytoplasmic homogeneity in the centrilobular region at $>$ 25 mg/kg/day--males or 75 mg/kg/day--females at 12 and 24 months.) Oncogenicity NOEL \geq 75 mg/kg/day (No significant effects were observed.) **No adverse effects** are indicated. **Acceptable.** (H. Green & M. Silva, 5/13/92.)

9.3.2 6-CPA

Two-year dietary feeding studies of 6-CPA, the major metabolite of nitrapyrin (see 9.1.2), were performed with rats and dogs (unpublished; cited by Mullison and Norris, 1976). Another two-year chronic dietary study of 6-CPA with mice was submitted to the U.S. EPA (Dow Chemical Co., 1986; tables with data not provided).

Groups of male and female B6C3F₁ mice were administered diets with 0, 100, 300, or 900 mg/kg/day 6-CPA for 6, 12, or 24 months (Dow Chemical Co., 1986). Female mice given the high dose for two years showed an equivocal increase in hepatocellular carcinoma because the tumor incidence was slightly elevated (12%) when compared to the historical control range of the test laboratory (0-8%). However, the increase was not statistically significant compared to concurrent controls and controls were within the range of control values reported by other laboratories (0-15%). Treated males did not have an increased tumor incidence at any site.

Rats were given 30, 100, 300, and 1000 ppm 6-CPA in the diet for 2 years (Mullison and Norris, 1976). Significant dose-related biliary hyperplasia occurred in female rat livers, but no effects were observed in male rats or controls (U.S. EPA, 1985). Two-year feeding studies with dogs described in subsection 9.1.5.2 had inadequate numbers and other shortcomings.

9.4 Initiation/Promotion Studies

No initiation/promotion data were available.

9.5 Anticarcinogenicity

No anticarcinogenicity data were available.

9.6 Genotoxicity

Nitrapyrin (3-666 µg/plate, > 99% purity; 0.013-2.88 µg/plate) was mutagenic in a dose-dependent fashion in *Salmonella typhimurium* strain TA100 in the presence (but not the absence) of either Aroclor 1254-induced or non-induced metabolic activation, but nitrapyrin (3-333 µg/plate; 0.013-1.44 µg/plate) was not mutagenic in strain TA1535, in the presence and absence of Aroclor-1254-induced metabolic activation (Zeiger et al., 1988).

The California Department of Pesticide Regulation reviewed and summarized unpublished genotoxicity studies of nitrapyrin conducted to meet pesticide re-registration requirements (CDPR, 1994). A facsimile of these summaries is presented below.

006 943524 "Application of the Ames Test for Mutagenesis to Nitrapyrin." (4/8/76, Plant Science Res., Dow) *Salmonella* strain LT-2, TA1530. Summary. Unacceptable due to insufficient information with no increase in reversion rate reported. No data. No concentrations given. (Apostolou, 7/25/85)

** 012 036150 "Study to Determine the Ability of Nitrapyrin to Induce Mutation in Four Histidine-Requiring Strains of Salmonella Typhimurium." (1/18/85, Microtest Res. Ltd., Study no. DCE 3/S/SR/AF2.) *Salmonella* strains TA1535, TA97, TA98 and TA100 were tested at 0, 0.8, 4, 20, 100 and 500 ug/plate, based on cytotoxicity study, with and without rat liver activation, in triplicate, two trials. Test run with nitrapyrin technical, no purity stated. Acceptable with no increased reversion rate. (Gee, 3/18/86.)

** 014 051089 "Evaluation of Nitrapyrin in the Chinese Hamster Ovary Cell/Hypoxanthine-Guanine-Phosphoribosyl Transferase (CHO/HGPRT) Forward Mutation Assay." (8/22/86, Dow) Nitrapyrin, 93.4%; tested with and without rat liver activation; -S9, at 0, 20, 40, 60, 80 or 100 ug/ml, 5 plates per concentration, three trials; +S9, at 0, 120, 140, 160, 180 or 200 ug/ml, one trial. No evidence for increase in mutation frequency. Acceptable with minor variations (single trial in activation assay.) (Gee, 2/11/87.)

** 012 036152 "Nitrapyrin: Micronucleus Test in Mice." (5/30/85, Microtest) Mouse micronucleus test. Nitrapyrin, 90.64%, sample number 84-2150; given as a single oral dose at 800 mg/kg as MTD; 5/sex/group were given a single oral dose and sacrificed after 24, 48 and 72 hours. Acceptable. No adverse effect reported at 800 mg/kg based on range-finding study. Use of a single high dose (m.t.d.) is acceptable. (Gee, 3/17/86.)

** 006 943525 "N-Serve TG (Nitrapyrin: 2-chloro-6-(trichloromethyl) pyridine: Evaluation of N-Serve TG in the Rat Hepatocyte Unscheduled DNA Synthesis Assay." (1/5/82, Dow). Nitrapyrin (92% AI) was added to cultures of rat hepatocytes at 1×10^{-7} to 1×10^{-4} moles/liter, 7 concentrations. Initial review (AA, 7/25/85) found the study unacceptable, with no adverse effects. Subsequent review noted that 2 x 15 or 30 cells were actually examined from 2 slides per concentration; no S-phase blocking is required for hepatocytes and mycoplasma are not a concern in primary cultures; although desirable, few studies use more than one rat per trial and guidelines do not specify a number. No adverse effects, acceptable (Gee, 3/17/86)

9.7 Cogenotoxicity

No cogenotoxicity data were available.

9.8 Antigenotoxicity

No antigenotoxicity data were available.

9.9 Immunotoxicity

No immunotoxicity data were available.

10.0 STRUCTURE-ACTIVITY RELATIONSHIPS

No information on structure-activity relationships other than the toxicity of metabolite 6-CPA was located. Data for 6-CPA are included in appropriate subsections following data for nitrapyrin.

11.0 ONLINE DATABASES AND SECONDARY REFERENCES

11.1 Fee-based Online Databases

Chemical Information System Files

SANSS (Structure and Nomenclature Search System)
TSCATS (Toxic Substances Control Act Test Submissions)

DIALOG Files

Chemical Economics Handbook (CEH)

National Library of Medicine TOXNET Files

EMIC and EMICBACK (Environmental Mutagen Information Center)
Toxic Release Inventory (TRI)

STN International Files

BIOSIS	CHEMLIST	Registry
CANCERLIT	EMBASE	RTECS
CAPLUS	HSDB	TOXLINE
CIN	MEDLINE	

TOXLINE includes the following subfiles:

Toxicity Bibliography	TOXBIB
International Labor Office	CIS
Hazardous Materials Technical Center	HMTCC
Environmental Mutagen Information Center File	EMIC
Environmental Teratology Information Center File (continued after 1989 by DART)	ETIC
Toxicology Document and Data Depository	NTIS
Toxicological Research Projects	CRISP
NIOSH [®]	NIOSH
Pesticides Abstracts	PESTAB
Poisonous Plants Bibliography	PPBIB
Aneuploidy	ANEUPL
Epidemiology Information System	EPIDEM
Toxic Substances Control Act Test Submissions	TSCATS
Toxicological Aspects of Environmental Health	BIOSIS
International Pharmaceutical Abstracts	IPA
Developmental and Reproductive Toxicology	DART

Databases Available Free on the Internet

USEPA/OPP Chemical Database. Available at URL www.cdpr.ca.gov/cgi-bin/epa. Last accessed April 26, 1999.

In-House Databases

CPI Electronic Publishing Federal Databases on CD
Current Contents on Diskette[®]
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APPENDIX A: UNITS AND ABBREVIATIONS

°C = degrees Celsius

µg/L = microgram(s) per liter

µg/m³ = microgram(s) per cubic meter

µg/mL = microgram(s) per milliliter

µM = micromolar

ACGIH = American Conference of Governmental Industrial Hygienists

d = day(s)

DOT = U.S. Department of Transportation

EPA = U.S. Environmental Protection Agency

F = female(s)

FIFRA = Federal Insecticide, Fungicide, and Rodenticide Act

g = gram(s)

g/mL = gram(s) per milliliter

GC = gas chromatography

h = hour(s)

kg = kilogram(s)

LC₅₀ = lethal concentration for 50% of test animals

LD₅₀ = lethal dose for 50% of test animals

M = male(s)

mg/kg = milligram(s) per kilogram

mg/m³ = milligram(s) per cubic meter

mg/mL = milligram(s) per milliliter

mL/kg = milliliter(s) per kilogram

mm = millimeter(s)

mM = millimolar

mmol = millimole(s)

mmol/kg = millimole(s) per kilogram

mo = month(s)

mol. wt. = molecular weight

NIEHS = National Institute of Environmental Health Sciences

NIOSH = National Institute for Occupational Safety and Health

NOES = National Occupational Exposure Survey

n.p. = not provided

N/A = not applicable

OPPT = Office of Pollution Prevention and Toxics

OSHA = Occupational Safety and Health Administration

PEL = permissible exposure limit

ppb = part(s) per billion

ppm = part(s) per million

QSARs = quantitative structure-activity relationships

REL = recommended exposure limit

STEL = short-term exposure limit

TLV = threshold limit value

TWA = time-weighted average

wk = week(s)