6-90

NTP EXECUTIVE SUMMARY OF DATA WORKING DRAFT

ELMIRON*

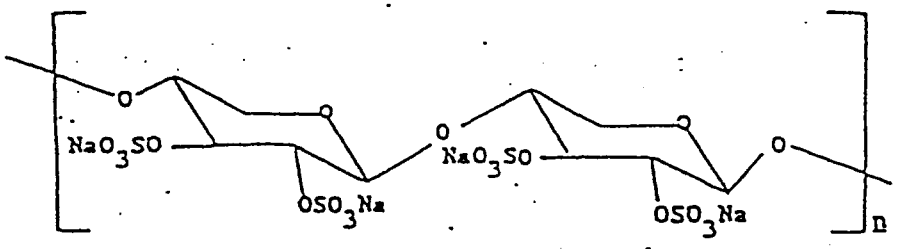
I. Chemical and Physical Information

A. Synonyms: Xylan hydrogen sulfate, sodium salt
Sodium xylan polysulfate
Sodium pentosan polysulfate
Sodium pentosane polysulfate
Thrombocid
SP54
PZ68

B. CAS Number: 37319-17-8

C. Molecular Formula: $[C_{10}H_{12}O_5(OSO_3Na)_2]n$ where n = 2-12 (Windholz, 1983; Lufkin, 1989).

D. Structural Formula:



E. Molecular Weight: Ranges from 1500 to 6000 (Windholz, 1983)

The average molecular weight of the nominated chemical is about 6000 (Lufkin, 1989).

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* The Food and Drug Administration has nominated Elmiron for chronic toxicity and carcinogenicity testing.

Submitted by SRC on January 10, 1989; revised by NTP staff, July 14, 1989; October 31, 1989; February 20, 1990; June 21, 1990.

F. Physical Properties

1. Physical State: White powder (Windholz, 1983).
2. Melting Point: No information was found.
3. Boiling Point: No information was found.
4. Flash Point: No information was found.
5. Vapor Pressure: No information was found.
6. Specific Gravity: No information was found.
7. Refractive Index: $n_D^{20} = 1.344$ (10% aqueous solution) (Windholz, 1983)
8. Solubility in Water: Soluble, 1 in 10 (Windholz, 1983; Lufkin, 1989).
9. Solubility in Organic Solvents: No information was found.
10. Log Octanol/Water Partition Coefficient: No information was found.
11. Henry's Law Constant: No information was found.
12. Other: Odorless; slightly hygroscopic; specific rotation $[\alpha]_D^{20} = -57^o$ (Windholz, 1983).

    Elmiron is the sodium salt of pentosan polysulfate, a semisynthetic sulfated polyanion composed of β-D-xylopyranose residues with properties similar to heparin (Windholz, 1983). The name for the free acid, pentosan polysulfate, is often used for the sodium salt, Elmiron, in the literature. This Executive Summary will indicate whether the data are for the free acid or the sodium salt.

II. Production/Use/Exposure/Environmental/Regulatory Data

A. Production

1. Manufacturing Process

One process for the preparation of sodium xylan polysulfates involves the reaction of xylan with chlorosulfonic acid in pyridine to give a pyridine salt, which is treated with an aqueous solution of chlorine dioxide to yield a white precipitate. An aqueous solution of this precipitate is reacted with 5N sulfuric acid and hydrogen peroxide. The reaction mixture is neutralized with 5N sodium hydroxide, bleached with chlorine dioxide, and dialyzed until a negative test for sulfate ion is obtained on the outside water. The dialyzate is then concentrated to yield the solid sodium xylan polysulfate, which is purified by crystallization from an ethanol-acetone mixture (Wander, 1953, as cited in Chemical Abstracts, 1955).

2. Volume

Neither the public portion of the Toxic Substances Control Act Chemical Substances Inventory (TSCA Inventory) nor the Chemical Economics Handbook (CEH) reported the domestic production of Elmiron (USEPA, 1988a; CEH, 1988).

The U.S. International Trade Commission (USITC) did not report domestic produciton of Elmiron for 1985, 1986, or 1987 (USITC, 1986, 1987, 1988).

Neither the public portion of the TSCA Inventory nor the Chemical Economics Handbook (CEH) reported the importation of Elmiron (USEPA, 1988a; CEH, 1988).

The U.S. Department of Commerce (USDOC) did not report the importation of Elmiron for the years 1983, 1984, and 1987 (USDOC, 1984, 1985, 1988).

3. Producers and Importers

a. Producers

No information was found.

b. Importers

The following companies have been listed as importers of Elmiron:

Pharmacia, Inc. Piscataway, NJ	FDA, 1987
Medical Marketing Specialties Boonton, NJ	SCRIP, 1986

Elmiron is imported from Bene Chemie of West Germany (FDA, 1987). It is distributed and sold exclusively in the United States by Medical Marketing Specialties, which obtained the

rights to distribute the drug from Pharmacia, Inc. (SCRIP, 1986; FDA, 1987).

4. Technical Product Composition

No information was found.

B. Use

Elmiron is a drug used for the prevention of thrombosis and hyperlipidemia in the folowing seven countries: Argentina, France, Great Britain, Italy, Mexico, Portugal, and South Africa (FDA, 1987).

Elmiron is being used for the compassionate treatment of interstitial cystitis in the United States (FDA, 1987).

C. Occupational Exposure

Elmiron is not listed in the National Occupational Exposure Survey (NOES), conducted by the National Institute for Occupational Safety and Health (NIOSH) between 1981 and 1983 (NIOSH, 1988).

Neither the American Conference of Governmental Industrial Hygienists (ACGIH, 1986, 1988) nor NIOSH (NIOSH, 1985) has recommended exposure limits for Elmiron.

D. Consumer Exposure

A small number of consumers may be exposed to Elmiron from using it for the treatment of interstitial cystitis (FDA, 1987).

E. Environmental Data

If released to water, Elmiron may be susceptible to hydrolysis (Lyman et al., 1982). Based upon its water solubility and its presumed very low vapor pressure, it will not be expected to volatilize, strongly absorb to sediment or suspended particulate matter, or bioconcentrate in aquatic organisms (Lyman et al., 1982). No information was found concerning biodegradation, photooxidation, or photolysis.

F. Regulatory Status

The Occupational Safety and Health Administration (OSHA) has not adopted a permissible exposure limit for occupational exposure to Elmiron (Bureau of National Affairs, 1988). No regulations by the U.S. Environmental Protection Agency (USEPA), the Food and Drug Administration (FDA), or OSHA were found (Bureau of National Affairs, 1988).

Elmiron has orphan drug status in the United States for the compassionate treatment of interstitial cystitis under the Investigative New Drug (IND) procedure (FDA, 1987).

Elmiron is not subject to reporting under Title III of the Superfund Amendments and Reauthorization Act (SARA) of 1986 according to the Title III List of Lists (USEPA, 1988b). The List of Lists covers SARA Section 302 Extremely Hazardous Substances, Hazardous Substances Reportable Quantity ("RQ") Chemicals of the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA), SARA Section 313 Toxic Chemicals, and Hazardous Wastes of the Resource Conservation and Recovery Act of 1976 (RCRA).

Elmiron is used only as a drug in the U.S. Therefore it is not subject to the provisions of the Toxic Substances Control Act. Hence, the Interagency Testing Committee (ITC) has not reviewed Elmiron for possible recommendation to the USEPA for industry-required testing (ITC, 1988).

III. Toxicological Effects

A. Human Data

1. Acute: Elmiron was found to have anticoagulant potential by various routes of administration. When a single dose of Elmiron was administered either orally (500 mg) or subcutaneously (50 mg) to six healthy male volunteers, a significant increase in plasminogen activator activity in plasma was observed. The effect was greatest after three

hours and disappeared by six hours (Marsh et al., 1985). The subcutaneous injection of 50 mg of Elmiron into six volunteers caused a slight increase in clotting times as measured by the activated thromboplastin time assay. Elmiron reduced thrombin generation, impaired the generation of chromogenic antifactor Xa, and increased levels of lipoprotein lipase, and euglobulin clot lysis (Fischer et al., 1982).

2. Epidemiological Evidence/Case Reports: Wound hematomas and thrombocytopenia were observed in patients who were being treated with Elmiron for prevention of deep vein thrombosis following surgery. In a pilot study, 12 patients were administered 100 mg Elmiron intramuscularly two hours preoperatively followed by 100 mg at six hours intervals. The duration of the pilot study was not specified. Seven of the twelve patients developed large wound hematomas (Joffe, 1976). In another study , 48 patients (21 males, 27 females), who had elective major surgery, were administered intramuscular doses of 50 mg Elmiron two hours preoperatively, and thereafter 50 mg every 12 hours for a minimum of seven days. A control group of 101 patients (46 male, 55 female) received no treatment. Fifteen percent of the treated patients had deep vein thrombosis compared to 51% of the control group. Two of the treated patients developed wound hematomas (Joffe, 1976).

Gouault et al. (1985) reported that a 30-year-old woman undergoing treatment by intramuscular administration of 50 mg Elmiron twice daily had thrombocytopenia with normal prothrombin and activated thromboplastin times. Elmiron treatment was stopped on the 14th day. Follea et al. (1985) reported that following perineal surgery, a 52-year-old woman was administered 25 mg Elmiron twice daily as prophylaxis for deep vein thrombosis. She developed thrombocytopenia on the ninth postoperative day.

Several side effects have been observed in the use of Elmiron for chronic non-bacterial prostatitis and interstitial cystitis (Werden, 1987; Fritjofsson et al., 1987). Ten patients with chronic non-bacterial prostatitis received oral doses of 200 mg Elmiron twice daily for three months. Two patients who were previously prone to gastrointestinal disturbances, developed diarrhea. Four other patients claimed that respiratory symptoms were more persistent than usual when they developed a common cold or influenza (Werden, 1987). Eighty seven patients with interstitial cystitis were administered oral doses of 200 mg Elmiron twice daily for six months, and were observed for an additional three months. During treatment, six patients had diarrhea, one complained of dyspepsia, and two had swollen legs. The following effects were observed in five of thirteen additional patients who did not complete Elmiron treatment for the specified period; diarrhea and

gastrointestinal distress in two patients, dysphagia in one patient, urinary infection in one patient, and anemia in one patient.

De Prost et al. (1985), and Freyburger et al. (1985) reported that pentosan polysulfate has anticoagulant activity. Maiza et al. (1985), and Bayle et al. (1986) observed thrombocytopenia as a side effect of pentosan polysulfate treatment.

3. Absorption/Distribution/Metabolism/Elimination

The use of ^{35}S- and ^{3}H- labeled Elmiron is not always suitable to study the chemical distribution of the drug in humans. The ^{35}S label is often lost during the metabolic process; the ^{3}H labeled material is hazardous, and it is consequently difficult to administer sufficient labeled material to obtain an accurate counting (Macgregor et al., 1984). Therefore, techniques involving the use of an iodine radiolabeled Elmiron or heparin as a tracer, which was shown to retain several of the biological activities associated with Elmiron, have been developed. These radiolabeled materials are administered with unlabeled Elmiron in chemical disposition studies in which a Competitive Binding Assay for sulfated polysaccharides is used to measure the concentration of Elmiron in biological fluids (Dawes et al., 1986; Macgregor et al., 1984).

Five healthy volunteers (4 male, 1 female) were injected subcutaneously with 75 mg of Elmiron. The concentration of Elmiron in the plasma was measured by a competitive binding assay (CBA) using ^{125}I-heparin as a tracer. Absorption varied from individual to individual; the area under the curve ranged from 6.7 to 12.0 ug hours/mL. Maximum plasma concentrations were achieved at 2-3 hours, and ranged from 1.30 to 3.10 ug/ml. Clearance from the plasma was almost complete at 7 hours. The recovery of Elmiron in the urine ranged from 2.9 to 4.1 %, and the correlation coefficient between excretion rate (ug/hour) and plasma concentration for the five subjects was 0.69. The CBA was used in conjunction with activated partial prothrombin time (APTT) and anti-Xa clotting assays. The results of the APTT assay were consistent with those of the CBA; however, anti-Xa clotting activity could be detected in the plasma even after the clearance of Elmiron as indicated by the CBA and APTT assay (Dawes et al., 1986).

Macgregor et al. (1985) also used a CBA to measure the clearance of Elmiron (SP54) from plasma. Elmiron was administered intravenously at doses of 0.1, 1, 10, or 100 mg, and subcutaneously at 100 mg to one female and two male volunteers at weekly intervals. In the intravenous study, the mean half-lives in plasma were 7, 21, and 55 minutes for the 1, 10, and 100 mg dose levels, respectively;

Elmiron could not be detected in the circulation after the administration of the 0.1 mg dose. Following subcutaneous administration of 100 mg Elmiron, the plasma level peaked at about 120 minutes in the three volunteers. At 480 minutes post-injection, Elmiron was almost completely cleared from the plasma.

Macgregor et al. (1984) studied the catabolism and organ distribution of Elmiron by administering unlabelled Elmiron (SP54) plus an iodinated derivative of Elmiron (^{123}I-SP54) as a tracer, to five healthy volunteers. Three subjects were injected intravenously with either 0.1, 1, or 7 mg SP54 containing 370 kBQ ^{125}I-SP54 (tracer), the fourth subject was administered intravenously tracer alone and tracer plus 50 mg SP54 at an interval of 3 weeks. The fifth subject was injected subcutaneously with 50 mg SP54 containing 370 kBQ 125I-SP54. Clearance of radioactivity was biphasic. Radioactivity was initially cleared from the blood with half-lives of 13 to 18 minutes for the intravenous doses of 0.1, 1, and 7 mg SP54 containing 370 kBq ^{125}I-SP54, and with a half-life of 45 minutes for the dose of 50 mg SP54 containing 370 kBq ^{125}I-SP54. Ninety percent of the radioactivity was removed from the blood within 80 minutes of injection for the three lower doses (0.1, 1, and 7 mg SP54 plus tracer), and within 240 minutes for the 50 mg dose plus tracer. The remainder of the radioactivity was removed in a second phase over a period of 24-96 hours. Initially

the clearance of ^{125}I-SP54 from the blood and plasma was similar; however, the radioactivity in plasma decreased more rapidly than in whole blood, due to the progressive association of the tracer with the packed cell fraction. Following subcutaneous injection of 50 mg SP54 with 370 kBq ^{125}I-SP54, radioactivity was detected in the blood at five minutes postinjection, and peaked at 80 minutes. Radioactivity was detected in the urine within one hour of intravenous injection. During the 24 hours following the intravenous and subcutaneous injections, the average recovery of radioactivity in the urine was 31%, and was not related to the dose of the unlabelled SP54.

Macgregor et al. (1984) used a combination of gel filtration and Polybrene binding techniques to study the metabolic fate of Elmiron (SP54) following the intravenous administration of Elmiron plus ^{125}I-SP54 (used as a tracer) as described above. Following intravenous injection, ^{125}I-SP54 was rapidly cleared from the circulation but was returned later in a desulfated form. However, removal was slower when the ^{125}I-SP54 was injected with 50 mg SP54 than when used with lower doses of SP54. The authors concluded that the probable sites of desulfation are the liver and spleen, which are rich sources of sulfatases. Analysis of the post-injection urine samples showed the presence of sulfated macromolecular SP54 and desulfated macromolecular and depolymerized SP54. The metabolic fate of subcutaneous

administered ^{125}I-SP54 was found to be similar to that administered intravenously.

Gamma camera images taken at 5-minute intervals from 7.5 to 47.5 minutes after the intravenous injection of 1 mg SP54 with 10.0 MBq ^{123}I-SP54 in one subject indicated progressive uptake of ^{123}I by the liver and spleen. At 50 minutes, 60% and 7.5% of the dose was associated with the liver and spleen, respectively. At 3 hours post-injection, a profile scan showed that 60% of the radioactivity was found in the liver and spleen, and 13% in the bladder. At 43 hours post-injection, 37% of the radioactivity was retained in the liver and spleen. Over the 18-hour post-injection period, urine contained 37% of the radioactivity; stools passed at 18 and 42 hours post-injection contained 0.13 and 0.07% of the radioactivity respectively (Macgregor et al., 1984).

Forestier et al. (1988) found that pentosan polysulfate (free acid) did not cross the placenta during the middle trimester of pregnancy following intravenous administration of 50 mg pentosan polysulfate to eight pregnant women who were going to have an abortion between the 18th and 23rd weeks of gestation. A control group consisted of untreated pregnant women. Comparison of the maternal results of haemostasis prior to injection and 30 minutes post-injection of the drug indicated an increase in APTT, an impairment in factor Xa generation, and a decrease in factor V level. In

contrast, there was no change in these parameters in fetal plasma, 30 minutes after the administration of pentosan polysulfate to their related mothers when compared to 16 control fetuses. For the Xa study, only 4 fetuses (out of 8) and their related mothers were used.

4. Carcinogenicity/Chronic: No information was found.

5. Teratogenicity and Reproductive Effects: No information was found.

B. Animal Data

1. Acute: No information was found on the acute lethal effects of Elmiron.

Elmiron was found to have anticoagulant properties in rats and rabbits. Hobbelen et al. (1985) used controlled subdermal damage to induce bleeding in rats (sex, strain, and number not specified in abstract of paper), and determined that the intravenous doses of Elmiron to inhibit thrombus formation by 50% and to enhance bleeding to 300% were 2.6 and 9.2 aXa (anti-factor Xa) units/kg respectively. Marsh and Gaffney (1986) observed an increase in blood fibrinolysis in groups of 4 to 8 female Sprague Dawley rats administered Elmiron at 2, 4, 6, or 10 mg/kg by subcutaneous injection, 6 mg/kg by intramuscular injection, or 10 mg/kg

by intravenous injection. In the subcutaneous studies, a dose level of 2 mg/kg caused fibrinolytic shutdown, but no dose-response relationship was observed at higher doses.

Esquivel et al. (1982) investigated the effect of Elmiron on microvascular hemostasis and platelet activity in vivo in the microcirculation of rabbit mesentery and ear chamber. Groups of six New Zealand rabbits of either sex were administered intravenous doses of 0, 0.5, 1, 2, or 5 mg/kg Elmiron, and the primary hemostatic plug formation time (PHT) and total hemostatic plug formation time (THT) were determined in venules and arterioles. A dose-related increase for both PHT and THT in venules; an increase for PHT and THT only at the highest and lowest doses in the arterioles; and a decrease in platelet activity were observed. Bjorck et al. (1984) reported that, following the intravenous injection of 0.5 mg/kg Elmiron into male and female rabbits (strain and number not specified), the occurrence of induced occluding thrombi decreased from 80% in controls to 0% in the treated animals. Fernandez et al. (1986) administered Elmiron intravenously at a dose of 12 or 24 mg/kg to rabbits (sex, strain, and number not specified), and observed a 19- and 25-fold increase in blood loss, respectively, following ear piercing.

2. Absorption/Distribution/Metabolism/Elimination: No information was found on the absorption, distribution,

metabolism, or elimination of Elmiron per se in animals. However, data are available on pentosan polysulfate. Whether it is the salt form or the free acid is not specified.

Dencker et al. (1985) showed that tritium labeled pentosan polysulfate is preferentially localized to the urinary tract in rats. Tritium labeled pentosan polysulfate (60 to 70% had molecular weight of about 2700, and 30 to 40% had molecular weight of about 1000) was administered at a dose of 5 mg/kg either orally or intravenously to Sprague-Dawley rats (sex and number not reported). In the intravenous experiment, the animals were sacrificed four hours post-injection and subjected to whole-body autoradiography. The autoradiograms showed that radioactivity was extensively distributed in the whole animal, with notable amounts in the connective tissues, and low amounts in the bone and cartilage. Radioactivity level in the brain was at the background level. The detection of radioactivity in the upper intestine suggested some hepatic excretion. The most conspicuous observation, however, was the high concentration of activity in the urine, and a preferential localization of activity corresponding to the lining of the urinary tract (pelvis, ureter, and bladder). In the oral study, the animals were killed one hour after administration. The distribution was similar to that in the intravenous study; however, the activity was lower. Other intravenous

experiments indicated that pentosan polysulfate was bound ionically with moderate strength to the bladder wall. Very high activity was detected in scattered cells in blood vessels, blood vessel walls and in connective tissues, and was judged to be indicative of specific cellular accumulation.

Eight increasing doses of unlabeled pentosan polysulfate (ranging from 6.3 to 12,656 ug/kg) plus 5 microcuries of ^{125}I-pentosan polysulfate were administered to groups of 2 - 3 New Zealand rabbits of either sex via the marginal ear. The plasma pentosan polysulfate (PPS) concentrations were determined by quantitation of covalent complexes between purified ^{125}I-human heparin cofactor II and thrombin. The disappearance of radioactivity from the plasma was triphasic. The half-lives of the α-phase (distribution phase) and γ-phase (residual radioactivity phase) ranged from 1.8 to 6.8 minutes, and 189 to 309 minutes, respectively, and were not dependent on dose. Similarly, the volume of distribution was not dose-dependent. The half-life of the β-phase (disappearance phase) was dose-dependent, and ranged from 15.1 to 18.6 minutes for doses of 6.3 to 316 ug/kg, 17.8 to 31.8 minutes for doses of 632 to 6328 ug/kg; the half-life was 41.5 minutes for the 12656 ug/kg dose. Clearance of PPS was reduced with increasing doses, and the authors suggested

a progressive saturation of the clearance mechanism (Cadroy et al., 1981).

3. Prechronic: No information was found.

4. Carcinogenicity/Chronic: No information was found.

5. Teratogenicity and Reproductive Effects: No information was found.

C. Genotoxicity: FDA (1987) reported that Elmiron was negative in two unpublished mutagenicity studies. Further details were not provided.

D. Other Relevant Information: Following the intravenous injection of 40 mg of pentosan polysulfate (PPS), the free acid, into three healthy volunteers, a significant prolongation of a modified prothrombin clotting time was observed in two of three subjects (Scully et al., 1983). Administration of PPS by intramuscular injection to four patients with ATIII congenital deficiency had a marked effect on thrombin (60% of inhibition) and F.Xa generation (50% of inhibition) (Fischer et al., 1983). The subcutaneous or intravenous administration of PPS to healthy volunteers increased fibrinolysis without increasing the release of tissue-type plasminogen activator (Sie et al., 1985). PPS demonstrated a dose-dependent anticoagulant effect following the intramuscular or subcutaneous administration of

25, 50, 75, 100, or 150 mg to eight healthy volunteers (Thebault et al., 1985).

E. Structure-Activity Relationships: No information relevant to the chronic toxicity or carcinogenicity of chemicals which are structurally related to Elmiron was found.

The National Toxicology Program (NTP) has not tested any structurally-related compound (NTP CHEMTRACK, 1988).

IV. Nomination Source

A. Source: FDA (FDA, 1987)

B. Recommendations: - Chronic toxicity
- Carcinogenicity

C. Rationale/Remarks:
- Used in compassionate treatment of interstitial cystitis under the Investigative New Drug (IND) procedure
- Potential for chronic use in the treatment of interstitial cystitis
- Used for treatment of thrombosis prophylaxis and hyperlipidemia
- Lack of toxicity data

D. Priority: None given

E. Date of Nomination: June 1987

V. Chemical Evaluation Committee Review

A. Date of Review: August 2, 1989

B. Recommendations: - Carcinogenicity

C. Priority: Moderate to high

D. NTP Chemical Selection Principle(s): 2

E. Rationale/Remarks:
- Potential as a treatment for interstitial cystitis
- FDA has granted chemical "orphan drug status"
- Lack of carcinogenicity data

VI. Board of Scientific Counselors Review

A. Date of Review: 1) November 30, 1989
2) March 14, 1990

B. Recommendations: 1) Defer
2) - Carcinogenicity
- Teratogenicity

C. Priority: 1) —
2) Moderate to high

D. Rationale/Remarks: 1) Obtain more information on efficacy and use of the drug, type of people using it, and results of animal studies and clinical trials

2) - Potential for treatment for interstitial cystitis
- FDA has granted chemical "orphan drug status"
- Lack of carcinogenicity data
- NTP should keep abreast of clinical trials
- Carcinogenicity studies pending results of clinical trials

VII. Executive Committee Review

A. Date of Review: June 14, 1990

B. Decision: Selected as NTP FY 1990 priority chemical for in-depth toxicological evaluation.

VIII. Information Sources: This report was prepared by a multidisciplinary team of scientists from SRC. The authors included Susan Coleman, William Jarvis, Philip Howard, and Michael Neal. The report was then revised by NTP staff.

The information used to prepare this review included the automated data bases listed below, journal articles, general reference materials, and agency reports.

ON-LINE DATA BASES SEARCHED

MEDLARS

CHEMLINE	
RTECS	
HSDB	
MEDLINE	1966 - Present
TOXLINE	1965 - Present
TOXLIT	1981 - Present
TOXLIT 65	1965 - 1980
CANCERLIT	1963 - Present

DIALOG

NTIS	1970 - Present
Occupational Safety and Health (NIOSH)	1972 - Present
Federal Register	1977 - Present
Chemical Industry Notes	1975 - Present
PTS Prompt	1972 - Present

CIS

SANSS
TSCA Inventory

OTHER

NOES	
NTP CHEMTRACK	
CAS ONLINE	1967 - Present

SRC

TSCATS
EFDB
CABE ARCHIVES
SRC DOCUMENTS

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