Vinyl Chloride Health Committee

Proposed 1994-1995 Budget

Budget	Activity (Explanation Attached)
$ 400,000	Epidemiology Study Update Contractor Cost - $ 350,000 ENSR Data Transfer Cost - $20,000 Dow Chemical's Monitoring Cost - $30,000
30,000	Outside Counsel for TSCA Section 4 Prop. Rule The estimated cost of the EPA recommended testing program is $850,000.
60,000	University of North Carolina Research Program Synthesis of ^{13}C-vinyl chloride - $10,000 Determination of Half-Life of Etheno-Adducts in Animals & Determination of P-450 in Human Tissues at Diff. Ages - $50,000
10,000	Vinyl Chloride Risk Assessment Consultant for Modification of the Heast Table (R. Reitz) Consultant to Demonstrate a Biological Threshold for Vinyl Chloride Induced Liver Angiosarcoma and Absence of Cause-Effect Relationship Between Vinyl Chloride and Brain Cancers (C. Tamburo) International Workshop to be Sponsored by the Vinyl Chloride Panel to Assess Available Scientific Information and Review Work in Progress or Planned to Assess Vinyl Chloride Risk
100,000	Administration Direct Time Oct.1994 - Dec.1995 - $90,000 (Based on Estimated Level of Effort of Four Days/Month) Travel and Miscellaneous - $10,000
25,000	Contingency
$ 625,000	TOTAL

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TABLE 1

COMMITMENTS NECESSARY BY COMPANY

COMPANY	1994-1995 PROJECTED COST	AMOUNT ALREADY COMMITTED, $325,172	ADDITIONAL COMMITMENT REQUESTED, $300,000		
			1994 Nameplate Capac. in MM Pounds	% 1994 Nameplate Capac.	New Commitment Requested
Borden	$ 43,756	$ 23,536	935	6.79	$ 20,370
Dow	115,570	55,630	2,773	20.13	60,390
Formosa	91,813	45,133	2,160	15.68	47,040
GEON	65,511	35,241	1,400	10.16	30,480
Georgia Gulf	58,957	31,717	1,260	9.14	27,420
OxyChem	121,637	65,447	2,500	18.15	54,450
PPG	39,295	21,145	840	6.10	18,300
Vista	41,831	22,151	910	6.60	19,800
Westlake	46,802	25,172	1,000	7.25	21,750
TOTAL	$ 625,172	$ 325,172	13,778	100.00	$ 300,000

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Detailed Explanation of 1994-1995 Proposed Activities

1) Epidemiology Study Update

Contractor Cost:

CMA conducted an epidemiology study of vinyl chloride workers from 1942-1972. The study was updated to cover the period of 1942-1982. The Vinyl Chloride Health Committee proposed to further update the study to 1992. The Committee requested proposals from potential contractors. After reviewing the proposals received, the Committee has narrowed its selection to Applied Epidemiology, Inc. (estimated cost - $350,000) and Applied Health Sciences, Inc. (estimated cost - $275,000). The Vinyl Chloride Health Committee is leaning toward Applied Epidemiology, Inc. based on an overall evaluation of the proposals.

ENSR Data Transfer Cost:

All raw data for the previous vinyl chloride epidemiology study are with ENSR Corporation. These data are extensive (100 banker's boxes) and will have to be reviewed, screened, and copied by ENSR prior to the release of the information to the selected contractor.

Dow Chemical's Monitoring Cost:

This cost will compensate Dow Chemical for its efforts in designing the study; evaluating the proposals; resolving technical issues with contractors; conducting site-visits; monitoring progress of the study; reviewing interim and draft reports; and, liaisoning with CMA and the Vinyl Chloride Health Committee.

2) Outside Counsel for TSCA Section 4 Proposed Rule

On September 30, 1994, EPA published a "Notice of Opportunity to Initiate Negotiations for TSCA Section 4 Enforceable Consent Agreements; Solicitation of Testing Proposals for ATSDR Chemicals" (Fed. Reg. 59, 49934-49938, 1994). For vinyl chloride, the notice proposes testing for reproductive, developmental, and neurotoxic effects by the inhalation route. The estimated cost of these testing is $850,000 (developmental = $150,000; reproductive = $450,000; and neurotoxicity = $250,000). In its Federal Register notice, EPA did not provide a rationale for the testing requirements and has exceeded the ATSDR requirements. The Committee recommends retaining a counsel to effectively negotiate a testing program with EPA that requires only those studies necessary to meet the ATSDR data needs.

Please note that no provision is made in the 1994-1995 proposed budget for any testing cost because of uncertainty as to what studies ultimately will be included in the Enforceable Consent Agreement or the TSCA Section 4 final rule. If an Enforceable Consent Agreement is executed with EPA, an additional testing budget may have to be developed in 1995.

3) University of North Carolina Research Program:

This research program is designed to evaluate toxicity of vinyl chloride exposure at high concentrations over a short period of time. The information developed through this program may help in establishing levels of vinyl chloride to trigger catastrophic release evacuation plans.

The program also would enable industry to develop early diagnostic tools to determine significant vinyl chloride exposures and their relevance to health risk assessment.

4) Vinyl Chloride Risk Assessment:

Modification of Heast Table

The current EPA Heast Table for carcinogenicity of vinyl chloride mentions that the consideration of metabolism pharmacokinetics will result in increased risk. According to the table, one unpublished physiologically-based pharmacokinetic model may predict a 100-fold increased risk. In the Committee's communication with EPA, we now understand that this is a speculation on the part of EPA. Documents like the Heast Table often become the basis for regulatory activities at federal, state and local levels. It is critical, therefore, to correct the Heast Table to prevent potential regulations based on misinformation. The Committee plans to work with EPA to correct the Heast Table.

Biological Threshold for Vinyl Chloride Induced Liver Angiosarcoma and Lack of Correlation Between Vinyl Chloride Exposure and Brain Cancer

Dr. Carlo Tamburo of the University of Louisville has proposed a threshold for vinyl chloride induced human liver angiosarcoma. Dr. Tamburo also suspects, based on information available to him, that there is no association between vinyl chloride exposure and incidence of brain tumors. The Committee plans to pursue these hypotheses with Dr. Tamburo. If these hypotheses are substantiated by valid and credible scientific data, the benefits to the industry will be significant.

International Workshop on Vinyl Chloride

The Committee considers an international workshop on vinyl chloride an integral part of vinyl chloride risk assessment. The workshop participants may include: regulatory agency personnel (EPA, OSHA, ATSDR); academia; other scientific research organizations; and, vinyl industry personnel.

5) Administration:

The following services are integral parts of the CMA administration:

a) General Services

1) meeting preparation, attendance, and action item follow-ups

2) coordination of Panel activities with outside counsel

3) financial management services including monthly financial statements

4) legal services (anti-trust protection; review of Records of Meetings; review of contractual agreements; guidance in cases of contractual non-compliance and/or earlier termination; guidance in protecting against restriction of trade practices; facilitating resolution of Panel/Task Force issues

5) communication services (press/news releases; responses to media/public inquiries; spokesperson for industry)

6) mail room services (copying; first class postage; local messengers)

7) management support in resolving Panel issues, if necessary

b) Advocacy Management

1) maintain awareness of pertinent regulations relating to the Panel's activities

2) communicate with government agencies on scientific and regulatory matters on behalf of the Panel

3) coordinate information flow to and from agencies, companies, other trade associations, and academic institutions

4) coordinate the development of advocacy positions with the CMA Office of General Counsel and other appropriate CMA standing committees and outside consultants

c) Research Management

1) assist in developing testing programs

2) develop budgets, assure commitments, and process invoices to participating companies

3) work with Panel to prepare protocols, identify labs, and send Request for Bids

4) assist Panel in selecting contract laboratory for testing based on bids received or prior experience

5) conduct site visits, if necessary

6) prepare and negotiate contracts

7) manage activities of contractor and outside auditor/monitor for the research program

8) legal oversight by CMA

9) manage finances of contracts, set up budget areas, verify and pay invoices

10) facilitate information exchange between contract laboratories, monitor/auditors, and Panel members and government agencies

11) facilitate Panel consensus on technical issues and communicate the consensus position with contractors

12) prepare periodic status reports for submission to Panel and regulatory agencies

13) provide regulatory compliance (TSCA, FIFRA) services at Panel's request

14) arrange for and participate in Panel meetings and in meetings with contractors and agencies

15) assist in developing the next phase of activities

1992

Table 3. ATSDR Substance-Specific Applied Research Program for Vinyl Chloride

Data Needs

	Level I	Level II	Level III
EXPOSURE			
Analytical	soil		
Physical Chemical Properties			
Exposure Levels		*EVALUATE EXISTING DATA ON LEVELS IN REM* *LEVELS IN TISS*	*POTENTIAL CANDIDATE FOR EXPOSURE REGISTRY*
Environment Fate	soil adsorp/ degradation/ transformation		
Bioavailability		food chain bioaccum (terrestrial)	
TOXICITY			
Acute	*INHALATION*, oral, dermal		
Repeated	oral, dermal		
Chronic		*INHALATION*, dermal	
Mutag			epidem studies on health effects
Repro		*2-SPECIES REPRO VIA INHALATION* (oral, dermal)	mechanistic studies
Develop		*2-SPECIES DEVELOP VIA INHALATION* (oral, dermal)	biomarkers
Immunotox	oral, dermal		*MITIGATION OF TOXICITY*
Neurotox	oral, dermal		
Carcinog			

UPPER CASE: Priority Data Needs identified for vinyl chloride.

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mechanism to cause cancer, reproductive toxicity, etc. or there exists "structural alerts" that suggest that the substance may be genotoxic. Additional studies will not be assigned priority simply to confirm or refute an equivocal database without justification.

Finding: A data need to conduct additional animal studies has not been identified.

There are substantial data on both clastogenesis and DNA alkylation in humans exposed to vinyl chloride that indicate that this chemical acts as a potent genotoxicant. Studies completed through the mid-1980s generally found a statistically significant increase in the frequency of chromosomal aberrations, usually of the chromatid type (i.e., affecting only one of the two strands formed upon deoxyribonucleic acid (DNA) replication) but also including some chromosomal-type defects such as inversions, rings, and translocations which affect the entire chromosome. Increased sister chromatid exchanges have also been reported in occupationally exposed workers (Kucerova et al. 1979; Hansteen et al. 1978; Purchase et al. 1978; Fucic et al. 1990). There are studies that indicate that the clastogenic effects of vinyl chloride exposure in humans are reversible. One study reported that the increase of chromosome aberrations observed in workers exposed to 50 ppm returned to normal within 42 months after exposure levels had been reduced to less than 5 ppm of vinyl chloride (Anderson et al. 1980).

The human findings are supported by both in vivo and in vitro animal studies that show positive genotoxicity in a variety of microbial organisms, cultured cell lines, and isolated nucleic acid assays (Laib et al. 1989; Gwinner et al. 1983; Styles 1077; Jenssen and Ramel 1980).

Priority Recommendation: A data need has not been identified.

e. Reproductive toxicity

Purpose: To determine whether populations potentially exposed to vinyl chloride are at an increased risk for developing reproductive effects for purposes of conducting meaningful follow-up exposure and health studies. The ATSDR places importance on the acquisition of reproductive toxicity data in its desire to consider the needs of susceptible populations. Additionally, it is desirable to have information on reproductive toxicity prior to the development of MRLs to ensure that target organs have been adequately evaluated.

Generally, when considering the need to assign priority, ATSDR will, in the absence of all information on this endpoint, assign priority to the conduct of 90-day studies with special emphasis on reproductive organ pathology. If (1) any indication is found in these studies that the reproductive system of either male or female animals is a target organ of substance exposure; or (2) there have been human anecdotal reports of reproductive effects following substance exposure; or (3) there are structurally similar compounds that affect reproduction, then ATSDR will consider assigning priority to multigeneration animal studies. As

before, priority will be assigned to studies conducted by the most relevant route of human exposure at Superfund sites; comparative toxicokinetic studies will be performed and evaluated prior to assigning priority to studies conducted via additional routes of exposure.

Finding: A data need to conduct additional animal reproductive studies via the inhalation, oral, and dermal routes has been identified.

A number of case reports of workers occupationally exposed to vinyl chloride provide suggestive evidence of adverse effects on male and female reproductive function. In males sexual impotence, decreased androgen levels, and loss of libido were reported in men exposed occupationally to vinyl chloride (Suciu et al. 1975; Veltman et al. 1975; Walker 1976). These studies are limited by the lack of quantification of exposure levels and possible concomitant exposures to other chemicals. In a vinyl chloride worker who died of angiosarcoma of the liver, decreased testicular size was observed. However, it is unclear whether this effect was a direct effect of the vinyl chloride exposure or due to wasting secondary to the angiosarcoma (Lee and Harry 1974). Males employed in PVC and acrylic glass industries also reported decreased testosterone levels and sexual function. However, concomitant exposure to methylmethacrylate also occurred in these workers (Makarov 1984).

In women exposed to vinyl chloride, there was an exposure-related decrease in sexual function in females between 41 and 50 years of age and in those who had been exposed to vinyl chloride for 21 or more years when compared to controls. An increase in menstrual activity followed by a hypomenstrual syndrome was reported to occur, but supporting data were not presented (Makarov et al. 1984). In another study, increased blood pressure and edema during pregnancy (preeclampsia) and decreased hemoglobin levels were found in females exposed to vinyl chloride when compared to unexposed workers (Bao et al. 1988).

No studies were located that documented the effects of vinyl chloride on reproductive performance when both parental animals were exposed. However, there were two dominant lethal studies which examined the reproductive performance of exposed males. Exposure to concentrations as high as 30,000 ppm of vinyl chloride in mice (5 days, 6 hours/day) had no effect on male fertility or pre- or post-implantation loss (Anderson et al. 1976). In contrast, exposure of male rats to concentrations as low as 250 ppm for 6 hours/day, 5 days a week, for 11 weeks caused a decrease in the ratio of pregnant to mated females, indicating a decrease in male fertility (Short et al. 1977). These results were supported by two other studies using rats in which adverse effects on the testes were observed; these effects included damage to the spermatogenic epithelium and seminiferous tubules, depletion of spermatocytes, and a decrease in testicular weight at concentrations of 100 ppm of vinyl chloride (Bi et al. 1985; Sokal et al. 1980). There were no indications of the effects on female rats in the latter two studies. There were no studies regarding reproductive effects in huma or animals following oral or dermal exposure to vinyl chloride. There

were no data on reproductive toxicity following dermal exposure.

Due to the suggestive evidence in humans that vinyl chloride causes reproductive effects this endpoint should be evaluated in future epidemiology studies.

Priority Recommendation: The identified data need to conduct additional animal reproductive studies via the inhalation route is considered priority. Reproductive toxicity assessment (i.e., 2 species multigenerational studies) using currently accepted protocols is necessary since there is suggestive human data and animal studies (dominant lethal) which indicates that exposure to vinyl chloride causes adverse reproductive effects. These studies should be conducted via the primary route of exposure at hazardous waste sites, inhalation.

Reproductive studies following the oral or dermal routes are not considered priority at this time because they are not the major routes of exposure for populations living in the vicinity of hazardous waste sites.

f. Developmental toxicity

Purpose: To determine whether populations potentially exposed to vinyl chloride are at an increased risk for developing developmental effects for purposes of conducting meaningful follow-up exposure and health studies. Similar to reproductive toxicity assessment, the Agency places importance on the assessment of developmental toxicity data, and does not consider an MRL to be of high confidence if this data is lacking.

In the absence of any reproductive or teratologic information, ATSDR will consider proposals to simultaneously acquire reproductive and teratological information. Additionally, ATSDR acknowledges that there will be some circumstances that require that separate conduct of classical teratology studies; these studies are generally assigned priority after the conduct of 90-day studies that assess reproductive organ pathology, the consideration of data generated on structurally similar compounds, or evidence from human anecdotal reports. As for reproductive toxicity, priority will be assigned to studies conducted by the most relevant route of human exposure at Superfund sites; comparative toxicokinetic studies will be performed and evaluated before assigning priority to the conduct of studies via additional routes of exposure.

Finding: A data need to conduct additional animal developmental studies via the inhalation, oral and dermal routes has been identified.

Epidemiology studies suggest that exposure to vinyl chloride may cause developmental effects. Although a statistically significant increase in congenital abnormalities has been observed in members of some communities located near a vinyl chloride processing facility, reports have failed to establish a statistically significant association between developmental toxicity and either parental occupation or proximity to

the facility (Edmonds et al. 1978; Infante et al. 1976a, 1976b; Rosenman et al. 1989; Theriault et al. 1983; Waxweiler et al. 1977). In another similar study, pregnancy outcomes of mothers occupationally exposed to vinyl chloride were compared to those of pregnant workers not exposed to vinyl chloride. The authors concluded that exposure to vinyl chloride did not correlate with involuntary infertility, pregnancy outcome, or the incidence of congenital abnormalities (Bao et al. 1988). Epidemiologic studies designed to examine this endpoint would be helpful due to the inconclusive human data.

In contrast, a number of inhalation studies using pregnant animals have shown developmental toxicity consisting of resorptions, decreased litter size and fetal weight, delayed ossification, and dilated ureters. These effects occurred when animals were exposed during the first trimester of pregnancy and at moderately high levels of vinyl chloride (500-2,500 ppm) (John et al. 1977, 1981; Ungvary et al. 1978). However, these levels also produced maternal toxicity characterized by increased liver weight, decreased body weight and food consumption, and increased mortality. Adverse postnatal effects have been observed in rats following in utero exposure to low levels of vinyl chloride. Pregnant rats were exposed to 0, 1.9, or 13.9 ppm vinyl chloride for 4 hours/day, and offspring examined 6 months postnatally. Rats at 6 months were found to have decreased hemoglobin and leukocytes and decreased organ weights (males: liver, kidney, spleen; females: lung, liver). In addition, exposure to 13.9 ppm in utero resulted in a decreased ability of the rats to orient themselves (Sal'nikova and Kotsovskaya 1980). In a similar study, pregnant rats were exposed continously throughout gestation to 2.4 ppm of vinyl chloride. This study reported decreased fetal weight and increased early post-implantation loss, hematomas, and hydrocephaly with intracerebral hematoma. Weanling rats had hepatotoxic effects and increased hexobarbital sleep time. No histological data on the livers of the pups or information regarding maternal health, or statistical analyses of the data were presented (Mirkova et al. 1978). Also, both this study and the report by Sal'nikova and Kotsovskaya (1980), failed to provide information on the number of animals in each test group. There were no studies located regarding developmental effects in humans or animals following oral or dermal exposure to vinyl chloride.

Priority Recommendation: The identified data need to conduct additional animal developmental studies via the inhalation route is considered priority. In view of the inadequate animal data and the suggestive human data, developmental toxicity should be assessed in future reproductive toxicology testing (i.e., two species developmental study). Th se studies should be conducted via the primary route of exposure at hazardous waste sites, inhalation. Data for oral and dermal routes of exposure are not considered priority at this time because these are not the major routes of exposure for populations living in the vicinity of hazardous waste sites.

g. Immunotoxicity

Purpose: To evaluate the mechanism of vinyl chloride-induced toxicity for purposes of defining target organs and future mitigation activities. There is increasing evidence to suggest that the immune system may be a susceptible target organ for many environmental contaminants. In the absence of any information on the immune system as a target organ, priority will be assigned evaluation of the immune system (lymphoid tissue, blood components) as an endpoint in 90-day studies (Level I) before assigning priority to an immunotoxicology battery as recently defined by the NTP. For those substances that either (1) show evidence of immune system effects in 90-day studies, (2) have human anecdotal data to suggest that the immune system may be affected, or (3) are structurally similar to known immunotoxicants, an immunotoxicology battery of tests will be assigned priority.

Finding: A data need to conduct animal immunotoxicty studies following oral and dermal exposure to vinyl chloride has been identified.

A number of studies have examined the immunologic profile of workers occupationally exposed to vinyl chloride. A statistically significant increase in circulating immune complexes and immunoglobulins were found in workers exposed to vinyl chloride when compared to levels in unexposed workers (Bodganikowa and Zawilska 1984; Wagnerova et al. 1986, 1988). The most frequent immunologic finding in workers with "vinyl chloride disease," was an increase in circulating immune complexes or cryoglobulinemia. As the severity of the clinical signs of vinyl chloride disease increased, there was an increase in B-cell proliferation, hyperimmunoglobulinemia, and complement activation (Grainer et al. 1980; Langauer-Lewowicka et al. 1976; Ward 1976).

Animal data following inhalation exposure to vinyl chloride support the findings seen in humans. A stimulation of the immune response has been observed in mice exposed to low to moderate levels of vinyl chloride via inhalation for 4 weeks: lymphocytes had increased spontaneous and lectin-stimulated transformation. This increase was not observed when lymphocytes from unexposed mice were cultured in the presence of vinyl chloride (Sharma and Gehring 1979).

There were no studies located regarding immunological effects in humans or animals after oral or dermal exposure to vinyl chloride.

Priority Recommendation: The identified data needs to conduct animal immunotoxicity studies following oral and dermal exposure to vinyl chloride are not considered priority because they are not the major routes of exposure for populations living in the vicinity of hazardous waste sites.

h. Neurotoxicity

Purpose: To evaluate the mechanism of vinyl chloride-induced toxicity for purposes of defining target organs and future mitigation activities.

Similar to immunotoxicity, there is a growing body of data to suggest that the nervous system is a very sensitive target organ for many environmental chemicals. In the absence of any information on the nervous system as a target organ, priority will be assigned evaluation of the nervous system as an endpoint in 90-day studies (Level I) before assigning priority to a neurotoxicology battery. Additionally, it may be possible to assign priority to evaluation of demeanor in 90-day studies along with neuropathology. For those substances that either (1) show evidence of nervous system effects in 90-day studies, (2) have human anecdotal data to suggest that the nervous system may be affected, or (3) are structurally similar to known neurotoxicants, a neurotoxicology battery of tests will be assigned priority.

Finding: A data need to conduct animal neurotoxicity studies following oral and dermal exposure to vinyl chloride has been identified.

The central nervous system is one of the major targets of vinyl chloride toxicity. Neurotoxicity in humans and animals have been well documented. Concentrations as low as 8,000 ppm may cause dizziness in humans exposed by inhalation (Lester et al. 1963). Workers exposed to vinyl chloride, before occupational standards were made more rigorous, complained of dizziness, drowsiness, euphoria, nausea, headach , and occasional loss of consciousness (Juhe et al. 1974; Langauer-Lewowicka et al. 1976; Lilis et al. 1975; Marsteller et al. 1975; Spirtas et al. 1975; Suciu et al. 1963, 1975; Veltman et al. 1975; Walker 1976). Similar neurological effects have been observed in animals as w ll as damage to nervous tissue. Histopathological examination revealed diffuse degeneration of gray and white matter, cerebellar degeneration in the purkinje cell layer, and peripheral nerve endings were surrounded and infiltrated with fibrous tissue (Viola 1970; Viola et al. 1971; Hehir et al. 1981; Jaeger et al. 1974; Mastromatteo et al. 1960).

No studies were located regarding neurological effects in humans or animals after oral or dermal exposure to vinyl chloride.

Priority Recommendation: The identified data need to conduct additional animal neurotoxicity studies following oral and dermal exposure to vinyl chloride is not considered priority because they are not the major routes of exposure for populations living in the vicinity of hazardous waste sites.

i. Toxicokinetics

Purpose: To evaluate the disposition of vinyl chloride across species and routes of exposure for purposes of elucidating target organs and mechanisms of toxicity, and to assess the need to conduct studies by other than the primary route of exposure.

Finding: A data need has not been identified. There are few data on humans for all toxicokinetic parameters across all exposure routes, and limited information is available regarding interspecies differences kinetics. However, human and animal data indicate that similar targ

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assessments by ASTDR. In addition, because of the involvement by other Federal Agencies and EPA offices in reviewing the testing needs identified for these chemicals, this testing program will supply test data which will also meet the needs of other Federal Agencies and EPA programs.

Table 1.--Data Needs and Testing Guidelines

Chemical and CAS No.	Proposed Testing	Guideline (40 CFR)
Vinyl chloride (75-01-4)	Reproductive inhalation	R
	Developmental inhalation	D
	Neurotoxicity inhalation	N
Benzene (71-43-2)	Subchronic oral	798.2650
	Subchronic inhalation	798.2450
	Neurotoxicity inhalation	N
	Functional observational battery	
	Motor activity	
	Neuropathology	
	Reproductive inhalation	R
Trichloroethylene (79-01-6)	Acute oral	798.1175
	Subchronic oral	798.2650
	Immunotoxicity oral	I
Tetrachloroethylene (127-18-4)	Acute inhalation	A
	Reproductive inhalation	R
	Neurotoxicity subchronic inhalation	N
	Functional observational battery	
	Motor activity	
	Neuropathology	
	Developmental inhalation	D
	Immunotoxicity inhalation	I
Hydrogen cyanide (74-90-8)	Acute inhalation	A
	Subchronic inhalation	798.2450

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	Developmental inhalation	D
	Neurotoxicity subchronic inhalation	N
	Functional observational battery	
	Motor activity	
	Neuropathology	
Sodium cyanide (143-33-9)	Developmental oral	D
Toluene (108-88-3)	Comparative pharmacokinetic	PK
	Immunotoxicity oral	I
Methylene chloride (75-09-2)	Subchronic oral	798.2650
	Developmental oral	D
	Neurotoxicity subchronic oral	N
	Functional observational battery	
	Motor activity	
	Neuropathology	
	Immunotoxicity oral	I
Chloroethane* (Ethyl chloride) (75-00-3)	Comparative pharmacokinetic	PK
Mercury**(TBD)		
Chromium**(TBD)		
Beryllium**(TBD)		

Notes:

*Note that a soon-to-be-published proposed test rule on hazardous air pollutants (HAPs) will cover chloroethane.

**A workgroup set up by TASARC is in the process of identifying the specific forms of these metals.

TBD -- The Chemical Abstract Service Registry Number(s) for the chemical(s) to be tested is yet to be determined.

R -- Proposed revised EPA guidelines for reproductive toxicity testing are under development and are anticipated to be finalized in the near future. Copies of the latest draft to date are available in the docket established for this action.

D -- Proposed revised EPA guidelines for developmental toxicity testing are under development and are anticipated to be finalized in the near future. Copies of the latest draft to date are available in the docket established for this action.

N -- EPA intends for parties subject to neurotoxicity testing requirements under this rule to follow the 1991 Neurotoxicology Testing Guidelines which