
**ENVIRONMENTAL PROTECTION
AGENCY**
40 CFR Part 799
[OPTS-42134; FRL 3774-7]
**Multi-substance Rule for the Testing of
Neurotoxicity**
AGENCY: Environmental Protection
Agency (EPA).

ACTION: Proposed rule.

SUMMARY: EPA is proposing a test rule, under section 4 of the Toxic Substances Control Act (TSCA), that would require manufacturers and processors of 10 substances to conduct testing for neurotoxicity. The 10 substances are related in that all are volatile solvents with high production volumes, occupational exposure, consumer exposure, and presence in and/or release to the environment. This rule proposes cognitive function and screening level tests for neurotoxicity where such data are not available for that substance. This proposed rule supports EPA's effort to require the testing of many substances for a single effect or endpoint, in this case neurotoxicity.

DATES: Submit written comments on or before May 3, 1991. If persons request an opportunity to submit oral comments by April 18, 1991, EPA will hold a public meeting on this rule in Washington, DC. For further information on arranging to speak at the meeting, see Unit VIII. of this preamble.

ADDRESSES: Submit written comments, identified by the docket number (OPTS-42134), in triplicate to: TSCA Public Docket Office (TS-793), Office of

Pesticides and Toxic Substances, Environmental Protection Agency, Rm. G004, NE Mall, 401 M St., SW., Washington, DC 20460. A public version of the administrative record supporting this action (with any confidential business information deleted) is available for inspection at the above address from 8 am to noon, and 1 pm to 4 pm, Monday through Friday, except legal holidays.

FOR FURTHER INFORMATION CONTACT: Michael M. Stahl, Director, Environmental Assistance Division (TS-799), Office of Toxic Substances, Rm. E-543B, 401 M St., SW., Washington, DC 20460, (202) 554-1404, TDD (202) 554-0551.

SUPPLEMENTARY INFORMATION: EPA is proposing a test rule under section 4(a) of TSCA to obtain neurotoxicity data for 10 volatile substances that have substantial production, for which there is or may be substantial human exposure, and for which data on neurotoxicity are insufficient.

I. Introduction
A. Background

EPA has developed this multi-substance test rule to test a number of substances for a single toxicological endpoint, neurotoxicity. EPA believes that available data on the neurotoxic effects of many chemicals in commerce, to which millions of Americans are exposed, are insufficient to evaluate human health risk and has initiated this program to test them. This approach is supported by a recent study by the Office of Technology Assessment (OTA) on the health threat from neurotoxic chemicals (Ref. 1). The OTA study stated that little is known about the potentially adverse effects of thousands of chemicals on the nervous system because of inadequate research and testing. EPA intends this proposed rule to be the first in a series of rules to obtain data on neurotoxicity.

Organic solvents were targeted for the first neurotoxicity endpoint rule because as a group they are thought to be associated with neurological effects and because they contain some high exposure chemicals (Ref. 4). Each solvent in this rule has a high vapor pressure, and their widespread use in the workplace and by consumers assures that many people will have acute and/or chronic exposure. Although some neurotoxicity data is available on most of these solvents, animal testing using methods equivalent to the TSCA neurotoxicity guidelines is rare. It is anticipated that data derived from testing according to these guidelines will not only screen for

certain neurotoxic effects of each solvent, but will also indicate the relative safety of the tested solvents for this endpoint.

During the development of this proposed test rule EPA considered two basic approaches to chemical selection. The first approach was to identify those chemicals that are believed to cause health effects in man or laboratory animals, based on toxicity studies and/or structural activity relationships (SAR), and to then select those with the highest exposure potential. This is the approach EPA followed in construction of the developmental and reproductive toxicity endpoint rule published elsewhere in this issue of the *Federal Register*. The second approach was to select chemicals solely on exposure potential. EPA determined that the second approach was more appropriate for selecting chemicals for the neurotoxicity test rule. For some types of test rules the first approach of basing chemical selection on available toxicity studies or SAR is preferable. In the case of an endpoint like neurotoxicity, however, EPA does not believe that reliance on available toxicity studies and SAR is the best approach for the following reasons. The existing literature and knowledge of SAR are fairly sparse on the neurotoxic effects of organic solvents. In addition, the few studies that have been identified are typically short-term or high-dose studies which, although they might support concern for more testing (as is the case for 6 of the 10 chemicals in this proposed rule), do not necessarily reflect higher potency or hazard potential than non-tested chemicals. Because of this EPA chose the second approach, i.e., selection based on exposure. By selecting those organic solvents with high exposure the limited resources available for testing would be focused on the few chemicals with widespread use and human exposure, instead of requiring EPA to consider the whole universe of organic solvents for testing.

The initial selection of specific organic solvents by EPA as candidates for testing was based on five criteria: production level greater than 10 million pounds, occupational exposure greater than 10,000 workers, consumer exposure, vapor pressure greater than 5 mmHg, and presence in or release to the environment (Ref. 2). Production data from 1986 to 1988 were considered in prioritizing the substances by production volume. Occupational exposure data were obtained from the National Occupational Exposure Survey (NOES) conducted by the National Institute for Occupational Safety and

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Health (NIOSH) in 1981-1983. Consumer exposure was estimated by EPA based on a usage survey of products containing the substances in this rule (Refs. 5, 6, and 9). Vapor pressure values were obtained from the CHEMFATE database (Ref. 2). Environmental release data were obtained from the 1987 Toxic Release Inventory (TRI) (Ref. 8) and data on presence in the environment were obtained from the Hazardous Substance Databank (Ref. 28). Production and occupational exposure data were considered simultaneously in prioritizing chemicals for testing. The resulting list was modified by eliminating chemicals with a vapor pressure less than 5mm Hg, because those chemicals have less tendency to volatilize and cause exposure by inhalation. Consumer exposure and environmental release data were the last criteria used in the selection of chemical candidates for this rule.

By this process, 14 substances were selected as candidates for the neurotoxicity test rule: acetone (CAS No. 67-64-1), *n*-amyl acetate (CAS No. 628-63-7), 1-butanol (CAS No. 71-36-3), *n*-butyl acetate (CAS No. 123-86-4), diethyl ether (CAS No. 60-29-7), ethanol (CAS No. 64-17-5), 2-ethoxyethanol (CAS No. 110-80-5), ethyl acetate (CAS No. 141-78-6), isobutyl alcohol (CAS No. 78-83-1), methyl ethyl ketone (CAS No. 78-93-3), methyl isobutyl ketone (CAS No. 108-10-1), tetrahydrofuran (CAS No. 109-99-9), toluene (CAS No. 108-88-3), and xylenes (CAS No. 1330-20-7). Of these 14 chemicals, 6 are among the top 25 chemicals emitted into the air in 1987 according to the Toxic Release Inventory (Ref. 1). After the collection and review of available neurotoxicity data on these 14 substances, 4 of them, ethanol, methyl ethyl ketone, toluene, and xylenes were found to have sufficient neurotoxicity data to justify exclusion from this proposed test rule (Ref. 3 and 34). This finding for methyl ethyl ketone, toluene, and xylenes confirms decisions in previous TSCA section 4 actions which did not require neurotoxicity testing for these four substances (47 FR 56325, December 29, 1982; 47 FR 56391, December 16, 1982; 47 FR 56392, December 16, 1982). The remaining 10 substances were found to have insufficient neurotoxicity data. This rule proposes neurotoxicity testing for these 10 substances:

Chemical name/CAS No.	Docket No.
acetone (CAS No. 67-64-1)	42134/42138
<i>n</i> -amyl acetate (CAS No. 628-63-7)	42134/42139

Chemical name/CAS No.	Docket No.
1-butanol (CAS No. 71-36-3)	42134/42137
<i>n</i> -butyl acetate (CAS No. 123-86-4)	42134/42138
diethyl ether (CAS No. 60-29-7)	42134/42139
2-ethoxyethanol (CAS No. 110-80-5)	42134/42140
ethyl acetate (CAS No. 141-78-6)	42134/42141
isobutyl alcohol (CAS No. 78-83-1)	42134/42142
methyl isobutyl ketone (CAS No. 108-10-1)	42134/42017B
tetrahydrofuran (CAS No. 109-99-9)	42134/42143

B. Test Rule Development Under TSCA

Under section 4(a) of TSCA, EPA shall, by rule, require testing of a substance to develop appropriate test data if the Administrator makes certain findings as described in TSCA section 4(a)(1)(A) or (B). Discussions of the statutory section 4 findings are provided in EPA's first and second proposed test rules which were published in the Federal Register of July 18, 1980 (45 FR 48510) and June 5, 1981 (46 FR 30309).

In evaluating the testing needs for these 10 substances, EPA considered the available published and unpublished information on the production volume, human exposure, environmental release, and neurotoxicity to animals and humans. From its evaluation of these data, EPA is proposing specific neurotoxicity testing for these substances under TSCA section 4(a)(1)(B). In addition, EPA considered available information on whether these substances may present an unreasonable risk of injury to health and as a consequence EPA is proposing neurotoxicity testing for six of the substances also under TSCA section 4(a)(1)(A).

EPA will continue to evaluate the need for this type of testing of additional substances and will amend this rule as necessary to require such testing. EPA intends to identify future candidates for this rule from its chemical screening program, TSCA section 6(e) data, Premanufacture Notices, Structure Activity Relationship data, nominations from other EPA programs, Interagency Testing Committee recommendations, and other relevant sources.

In addition, elsewhere in this issue of the Federal Register, EPA is proposing another TSCA section 4 multi-substance test rule. The other rule requires developmental and/or reproductive effects testing of 12 substances (none of which are the same as those included in

this notice). The codified portion of the proposed rule for neurotoxicity testing is written as an amendment to the codified portion of the proposed rule for developmental and reproductive toxic testing. For future multi-substance rules, EPA plans to prepare amendments to the combined proposed section of the CFR (i.e., § 799.5050). By so doing, these and subsequent multi-substance endpoint rules would be listed in a single table, and their test requirements (health, environmental, chemical fate, etc.) for a substance would be in a single location. EPA believes that listing the test requirements for all the multi-substance endpoint rules in one table will be advantageous for those subject to TSCA section 4 test rules and will simplify and aid in their monitoring and compliance.

II. Review of Available Data

A. Use

Organic solvents are used as solubilizers, dispersants, or diluents, and because of this have many industrial and consumer applications (Ref. 4). They can be incorporated in a variety of products, including paints, varnishes, lacquers, adhesives, plastics, inks, waxes, polishes, smokeless powder, perfume, and medicine. They can also be used in extraction processes, chemical synthesis, and cleaning, degreasing, and drying operations. The following Table 1 lists some of the uses of the 10 organic solvents which are the subjects of this proposed rule.

TABLE 1.—USES OF ORGANIC SOLVENTS

Name/CAS No.	Uses ¹
acetone (67-64-1)	37% — Production of methacrylic acid and ester; 10% — production of methyl isobutyl ketone; 14% — production of bisphenol A; solvent for industrial coatings.
<i>n</i> -amyl acetate (628-63-7)	>50% — solvent for nitrocellulose lacquers and paints; extraction solvent in penicillin manufacture and electrostatic spray coatings for automobile and misc. uses.
1-butanol (71-36-3)	15% — direct solvent use; 7% — plasticizers; 35% — production of butyl acrylate/methacrylates; 25% in production of glycol ethers.
<i>n</i> -butyl acetate (123-86-4)	81% — solvent for coatings; 9% — process solvent; 10% — misc. solvent use.

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TABLE 1.—USES OF ORGANIC SOLVENTS—Continued

Name/CAS No.	Uses ¹
diethyl ether (60-29-7).	50% — smokeless powder manufacture; 20% — as an engine starting fluid; 10% — extraction solvent for fats and oils; 10% — pharmaceutical and medical uses; 10% — perfume.
2-ethoxyethanol (110-80-5).	26% — Preparation of ethylene glycol monoethyl ether acetate; 7% — general solvent uses for coatings and inks; 65% — exported.
ethyl acetate (141-78-5).	64% — solvent for lacquers and enamel coatings; 15% — solvent for inks; 13% — plastics solvent; 3% — chemical synthesis.
isobutyl alcohol (78-83-1).	28% — direct solvent uses; 11% — preparation of isobutylamines; 21% — as a lube oil additive; 19% — preparation of isobutyl acetate; 6% — preparation of amino resins.
methyl isobutyl ketone (108-10-1).	75% — solvent for protective coatings; 15% — solvent extraction; 5% — solvent for adhesives and ink.

TABLE 1.—USES OF ORGANIC SOLVENTS—Continued

Name/CAS No.	Uses ¹
tetrahydrofuran (109-99-9).	77% — production of polytetrahydrofuran; 23% — solvent use (PVC cements, magnetic tape, reaction solvent).

¹Source: "Economic Impact Evaluation of Proposed Multi-Chemical Rule for the Testing of Neurotoxicity". July 25, 1990. (Ref. 32).

B. Exposure, Production, Vapor Pressure

Organic solvents such as those included in this proposed rule have a higher potential for human exposure than many other chemicals because they are often highly volatile and are able to penetrate the skin due to their nonpolar structure. Because of their high volatility, a major route of exposure is inhalation. Once organic solvent vapors enter the lungs, they diffuse across respiratory membranes, due to their relatively small molecular weight and lipid solubility, and enter the bloodstream. These properties also permit a second major route of exposure

via skin penetration. For example, two *in vitro* studies which looked at absorption through human epidermis found rates of 0.65 $\mu\text{mol}/\text{cm}^2/\text{hr}$ for pure 1-butanol (Ref. 36) and 0.79 $\text{mg}/\text{cm}^2/\text{hr}$ for pure 2-ethoxyethanol (Ref. 37). This demonstrated absorption plus the ubiquity of solvents and the casual approach to their use almost assure exposure by inhalation and skin contact (Ref. 4).

The potential for consumers to be exposed to solvents is high because solvents comprise a large fraction of many consumer products and are used for purposes such as cleaning and paint removal where a person is in close contact with the solvent. To estimate the potential for consumer exposure to these ten substances, EPA determined their presence in consumer products and, with a usage survey (Ref. 35), estimated the number of consumers potentially exposed to each solvent by consumer product. As shown in the following Table 2, EPA found that all 10 substances were present in consumer products.

TABLE 2.—CONSUMER EXPOSURE

Chemical/CAS No.	Presence in Consumer products(number)	Consumer usage per product(millions of consumers) ¹
acetone (67-64-1).....	51.....	3.7 to 112
n-amyl acetate (628-63-7).....	1.....	79.2
1-butanol (71-36-3).....	2.....	79.2
n-butyl acetate (123-96-4).....	2.....	64 to 112
diethyl ether (60-29-7).....	1.....	87.8
2-ethoxyethanol (110-80-5).....	14.....	52 to 112
ethyl acetate (141-78-5).....	3.....	64 to 112
isobutyl alcohol (78-83-1).....	4.....	55 to 112
methyl isobutyl ketone (108-10-1).....	17.....	7.2 to 112
tetrahydrofuran (109-99-9).....	11.....	4.5 to 112

¹ Source: USEPA "Household Solvent Products: A National Usage Survey." EPA-OTS 560/5-87-005. 1987. (Ref. 35).
² Source: Versar, Inc., Springfield, VA. (Ref. 10).

The number of products in which each chemical was present ranged from 1 to 51. Based on the reported usage, the potential number of consumers exposed to a single product ranged from 3.7 to 112 million (Refs. 5, 6, 9, and 10).

Many solvents also have a high potential for acute and chronic exposure in the workplace due to their high production volumes and widespread use, as well as the high volatility and ability to penetrate the skin mentioned

above. Table 3 presents data on occupational exposure taken from the National Occupational Exposure Survey (NOES), conducted by NIOSH from 1981-1983, and based on field surveys of 4490 facilities.

TABLE 3.—OCCUPATIONAL EXPOSURE, PRODUCTION, VAPOR PRESSURE

Name/CAS No.	NOES ¹	Annual production ² (pounds)	Vapor pressure ³
acetone (67-64-1).....	1,510,107	2,458,000,000	231.5
n-amyl acetate (628-63-7).....	172,440	12,029,600	9.7
1-butanol (71-36-3).....	794,284	1,854,126,000	6.7
n-butyl acetate (123-96-4).....	720,612	194,845,000	150.0
diethyl ether (60-29-7).....	175,489	55,000,000	442.0
2-ethoxyethanol (110-80-5).....	233,416	121,908,000	5.6
ethyl acetate (141-78-5).....	375,906	257,348,000	93.6
isobutyl alcohol (78-83-1).....	192,949	165,459,000	10.4
methyl isobutyl ketone (108-10-1).....	467,763	225,312,000	19.8

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TABLE 3.—OCCUPATIONAL EXPOSURE, PRODUCTION, VAPOR PRESSURE—Continued

Name/CAS No.	NOES ¹	Annual production ² (pounds)	Vapor pressure ³
tetrahydrofuran (109-99-9)	303,049	154,000,000	132

¹ National Occupational Exposure Survey, Number of occupationally exposed employees (Ref. 7).
² Source: Ref. 32.
³ Vapor pressure in mmHg per CHEMFATE (Ref. 2).

Using the NOES data, the number of workers potentially exposed to each of these solvents ranges from 172,440 to 1,510,107 (Ref. 2). The annual production of the 10 solvents, as shown in Table 3, is very high, ranging from 12 million to 2.4 billion pounds (Ref. 32). Also in Table 3 are vapor pressure values ranging from 5.6 to 442. Vapor pressure

values indicate volatility and the potential for exposure by inhalation.

C. Presence in and Release to the Environment

Presence in and release to the environment also contribute to the potential for chronic exposure to solvents. Nine of the solvents have been

found to be present in various environmental media (ground water, surface water, drinking water, air, effluent) at survey sites throughout the United States. The following Table 4 presents the measured concentration ranges of contaminants found at some of these sites.

TABLE 4.—PRESENCE IN AND RELEASE TO THE ENVIRONMENT

Name/ CAS No.	Environmental Media ¹	Concentration Range ² (in environmental media)	Annual Release ³
acetone (67-64-1)	A DW E SW	0.3 to 6.5 ppb NQ 6 to 2501 ppb 1 to 4 ppb	195
n-amyl acetate (628-63-7)	E	26 to 31 ppm	
1-butanol (71-36-3)	A E E(DS) SW	34 to 445 ppb 16 ppm 210 ppm NQ	36
n-butyl acetate (123-86-4)	A E	3 µg/m ³ 10 ppb	
diethyl ether (60-29-7)	A DW E GW SW	NQ NQ 10 to 100 ppb 2.5 ppb 1 to 10 ppb	
2-ethoxyethanol (110-80-5)			2.9
ethyl acetate (141-78-6)	DW E SW	NQ NQ 1 ppb	
isobutyl alcohol (78-83-1)	A DW	2.5 mg/m ³ NQ	
methyl isobutyl ketone (106-10-1)	A A(DS) E GW(DS) SW	270 ppt 0.5 - 13 ppm 0.2 to 105 ppm 172 to 263 ppb NQ	29
tetrahydrofuran (109-99-9)	E SW	0 to 450 ppm 1 to 318 ppb	

¹ A=Air, DW=Drinking Water, DS=Disposal Site, E=Effluent, GW=Ground Water, SW=Surface Water.
² Concentration data is from Hazardous Substances Databank printout (Ref. 28). NQ=Not Quantified, but detected.
³ 1987 Environmental Release in millions of pounds per year per the Toxics Release Inventory (Ref. 8).

A few of the survey sites are near disposal sites, but most are sites with even a greater potential for exposure to the general public.

The annual release to the environment of 4 of these solvents, as reported to EPA, ranges from 2.9 to 195 million

pounds (Ref. 8). Table 4 lists release levels of these 4 solvents. It is also worthy of note that 3 of these solvents are among the Toxics Release Inventory's (TRI) top 25 chemicals emitted into the air in 1987 (Ref. 1).

D. Neurotoxicity

In general, acute exposure to organic solvents affects the central nervous system by causing the anesthetic effects of drowsiness, lack of coordination, and narcosis, which although they may have

no discernable permanent effects on health, may increase the risk of accidents (Ref. 4). With longer exposure solvents may have neurotoxic effects on memory, learning, and performance which can be permanent. These effects are less well understood as is the effect of chronic, low-level exposure (Ref. 4).

Given the general neurotoxicity effects of organic solvents, EPA considers that the appropriate TSCA guidelines to screen for all aspects of neurotoxicity are the Functional Observational Battery (FOB; 40 CFR 798.8050), Motor Activity (MA; 40 CFR 798.8200), Neuropathology (NP; 40 CFR 798.8400), and the Schedule-Controlled Operant Behavior test (SCOB; 40 CFR 798.8500). EPA reviewed the available literature to determine if adequate and reliable data exist on these 10 substances for these types of neurotoxicity and neurobehavioral endpoints. EPA also reviewed existing data on these substances for other neurotoxic endpoints. A discussion of the results of this review follows:

No studies were located in the available literature regarding neurotoxicological effects in either humans or animals for three solvents: *n*-amyl-acetate, isobutyl alcohol, and tetrahydrofuran (Ref. 3).

Studies were identified for the other 7 solvents, including acetone, 1-butanol, *n*-butyl acetate, diethyl ether, 2-ethoxyethanol, ethyl acetate, and methyl isobutyl ketone but these studies did not provide adequate data to assess neurotoxic effects which could be obtained by requiring testing under the four TSCA guidelines for neurotoxicity mentioned above (Ref. 3).

1. Acetone. Only acute human and animal studies were identified for acetone. The study in human volunteers by Dick et al. (Ref. 11) indicated that a 4-hour exposure to 250 ppm acetone produced a small decrease in the auditory tone discrimination in both sexes and a significant change in the profile of mood states in men.

Bruckner and Peterson (Ref. 12) examined unconditioned performance and reflexes in male rats exposed to 4 doses of acetone from 12,600 to 58,600 ppm for 3 hours. A concentration-related decrease was observed in the mean score of the test battery consisting of wire maneuver, visual placing, grip strength, tail pinch, and righting reflex. Although this study evaluated the animals for the endpoints considered by the functional observational battery, only male mice were studied and only for an acute dose.

Glowa and Dews (Ref. 13) assessed the effects of 4 doses of acetone from 1,000 to 58,000 ppm which were

sequentially administered at 30-minute intervals to male mice. The authors found a dose-related decrease in schedule-controlled response. This study is inadequate because it exposed the same animals to more than one substance. Also, this study does not satisfy the neurotoxicity data needs because it is an acute study and only male mice were tested (Ref. 3).

2. 1-butanol. Only acute animal studies were identified that examined the neurotoxic properties of 1-butanol. Wallgren (Ref. 14) assessed motor coordination in rats by testing their ability to balance in a sliding plane before and after the oral administration of 4.5 g/kg of 1-butanol. Wallgren's results suggest that 1-butanol affects motor control because of the animals' significantly impaired ability to maintain their balance. Maickel and Nash (Ref. 15) examined the motor performance of male mice in a rotarod system after administration of 1-butanol at 3 dose levels from 0.5 to 2.0 g/kg. 1-Butanol was found to induce a dose-related impairment in motor performance which was suggested by the authors as due to a generalized central nervous system (CNS) depression. This study does not satisfy the information needs for motor activity because only male mice were tested and the test was not comparable to that required by the TSCA guideline (Ref. 3).

DeCeaurriz et al. (Ref. 16) exposed male mice to 4 air concentrations of 1-butanol from 470 to 965 ppm for 4 hours and evaluated them in the behavioral despair swimming test. The authors found that 1-butanol prolongs the escape-directed activity in a dose-related manner. Schulze (Ref. 17) treated rats with 1 daily injection of 36 mg/kg 1-butanol for 4 consecutive days and found a significant increase in the mean landing foot splay scores (an index of ataxia). These studies do not satisfy the neurotoxicity data needs because they are acute studies and only male mice were tested.

3. *n*-butyl acetate. Only one review by Toy (Ref. 18) was found regarding the health effects in animals of *n*-butyl acetate. No neurotoxic effects attributed to *n*-butyl acetate were evaluated in this review.

4. Diethyl ether. Both human and animal studies were found on the neurotoxic effects of diethyl ether. Two acute human studies looked at the sensory evoked response induced by stimulation of the ulnar nerve in 17 male volunteers. In the first study by Hosick et al. (Ref. 19), subanesthetic concentrations (1.0 to 1.5 percent, v/v in air) of diethyl ether suppressed in a dose-related manner, the late activity of

sensory potentials recorded in the contralateral postRolandic area (C2P) and at a midline position 6 cm anterior to the vertex (M8A). In the second study by Clark et al. (Ref. 20), a concentration that induced anesthesia (4 percent diethyl ether) completely abolished the sensory evoked responses in C2P and M8A. Both studies were aimed at determining possible central nervous system mechanisms involved in anesthesia. While these tests provide information on the anesthetic effects on sensory systems, they do not provide a broader picture of neurotoxicity.

Essman and Jarvik (Ref. 21) studied the effect of diethyl ether on the acquisition of an avoidance response in male mice. The results showed that ether anesthesia, induced immediately after an electric shock, effectively interfered with the acquisition of an avoidance response, but if the mice were anesthetized 1 hour after the shock was given, the avoidance response was retained. A similar acute study by Wimer and Huston (Ref. 22) showed that exposure to diethyl ether at concentrations not resulting in loss of the righting reflex, significantly enhanced the performance of a previously learned task. Both studies point out the importance of the duration of the exposure (level of anesthesia achieved) in the assessment of schedule-controlled operant behavior tests. However, both studies are inadequate to provide the information on subchronic schedule-controlled operant behavior (SCOB) because the tests were not comparable to the TSCA guideline for SCOB, the exposure duration was not subchronic, and only male mice were tested.

Several studies, designed to examine the central nervous system effects of anesthetic levels of diethyl ether in animals, were identified. Concentrations of diethyl ether that produced a very deep stage of anesthesia in cats also induced epileptiform activity (Ref. 23). In rats, diethyl ether decreased spontaneous electroencephalograph (EEG) spikes recorded from the dorsal area of the hippocampus, and at anesthetic doses completely abolished this activity (Ref. 24). In rats and cats, a concentration of 8 percent (v/v in air) diethyl ether suppressed excitatory responses in the midbrain reticular formation (Ref. 25). These studies do not satisfy the neurotoxicity data needs because only anesthetic doses were used.

5. 2-ethoxyethanol. A developmental neurotoxicity study was located which evaluated the neurotoxic effects of prenatal exposure to 2-ethoxyethanol.

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B.K. Nelson et al (Ref. 30) exposed rats to 100 ppm 2-ethoxyethanol and found statistically significant changes in the offspring in the rotorod test, the activity wheel test, and avoidance conditioning. At 200 ppm, a maternally toxic dose, even greater alterations were seen in these tests (Ref. 31). These studies do not satisfy the data needs for neurotoxicity because they only evaluate the effects of prenatal exposure to 2-ethoxyethanol.

6. *Ethyl acetate*. Only animal studies were located regarding the acute neurotoxic effects of ethyl acetate. Glowa and Dews (Ref. 13) assessed the effects of ethyl acetate on a schedule-controlled response test (the interruption of a photocell beam located behind a nose-poke hole) in male mice. The study showed that at 5 concentrations from 300 to 3,000 ppm, ethyl acetate decreased the schedule-controlled response in a dose-related manner. This study is inadequate because it exposed the same animals to more than one substance. Also, only male mice were studied and the test is not equivalent to the TSCA guideline for SCOB.

Tham et al. (Ref. 26) examined the neurological effects of intravenous injection of ethyl acetate in rats and found that it depressed the vestibulo-ocular reflex (VOR) and thereby the equilibrium system of the animals. It was suggested by the authors that the depression of the VOR was caused by an interaction of the solvent with central pathways in the reticular formation and the cerebellum. This study is not comparable to those which would be done according to the TSCA guidelines for neurotoxicity testing because the route of administration was by injection instead of the expected route of human exposure.

7. *Methyl isobutyl ketone*. A developmental toxicity study was located which reported a neurotoxic effect after exposure to methyl isobutyl ketone. In rats and mice exposed to 3,000 ppm methyl isobutyl ketone, neurotoxicity was demonstrated in the dams by partial hindlimb paralysis (Ref. 29). This study does not satisfy the neurotoxicity data needs because it did not evaluate the range of endpoints which are normally required by the TSCA guidelines.

In summary, neurotoxicity data were not identified for three solvents. The other seven solvents had no subchronic neurotoxicity data and the acute and developmental data, although adequate to raise concern for neurotoxicity, were not adequate to evaluate the effects of acute or subchronic exposure to the extent that would have been achieved if

the TSCA or equivalent state-of-the-art guidelines had been followed.

III. TSCA Section 4(a) Findings

The proposed neurotoxicity testing is based on the authority of section 4(a)(1)(A) and (B) of TSCA. EPA finds that: available data indicate that 6 of the substances may present an unreasonable risk of injury to human health; all 10 substances are produced in substantial quantities; there is or may be significant or substantial human exposure to all 10 substances; there is or may be substantial environmental release of 4 of these substances; there are insufficient data and experience to determine or predict the neurotoxic effects from manufacturing, processing, use, and disposal of these substances; and testing is necessary to develop these data.

EPA is currently in the process of developing a general policy under TSCA section 4(a)(1)(B) (the "B" policy) in which it will articulate its criteria for making findings under this provision. The "B" policy is being developed in response to the April 12, 1990 decision in *CMA v. EPA* (Ref. 38) in which the Court of Appeals for the Fifth Circuit remanded the TSCA section 4 rule for cumene to EPA to "articulate the standards or criteria on the basis of which it found the quantities of cumene entering the environment from the facilities in question to be 'substantial' and human exposure potentially resulting to be 'substantial'." Although not mandated by the cumene decision, EPA also will be addressing the criteria for "substantial production" and "significant human exposure." EPA intends to publish the criteria for public comment, but has not yet developed such a Federal Register notice.

To avoid delay, EPA has decided to propose this neurotoxicity test rule under TSCA section 4(a)(1)(B) without waiting for the "B" policy to be completed and published in the Federal Register. The Court in *CMA v. EPA* (Ref. 38) made it clear that EPA need not adopt a definition applicable to all cases, but may choose to proceed on a case-by-case basis, if it rationally explains its exercise of discretion. Thus, because this proposal articulates the criteria used in making findings under TSCA section 4(a)(1)(B) for these substances, it is not necessary to wait for publication of a generic policy before proposing this test rule.

TSCA does not provide EPA with much guidance on what criteria and standards should be used in making "B" findings. The statute does not define the terms "significant" or "substantial." The policy section of TSCA, however, makes

it clear that Congress considered testing of chemical substances to be an important aspect of the Act. This section provides:

adequate data should be developed with respect to the effect of chemical substances and mixtures on health and the environment and that the development of such data should be the responsibility of those who manufacture and those who process such chemical substances and mixtures.

The legislative history of TSCA also provides some guidance on what criteria are to be used in making "B" findings. The legislative history states that "[t]he conditions specified in [TSCA] section 4(a)(1)(B) reflect the Committee's recognition that there are certain situations in which testing is desirable even though there is an absence of information indicating that the substance or mixture may be harmful" (Ref. 39) and "there are certain situations in which testing should be conducted even though there is an absence of information indicating that the substance or mixture per se may be hazardous" (Ref. 40). The legislative history also provides that EPA "is not limited to consideration of sheer volume of production or exposure at a specific point in time. The duration of exposure, the level of or intensity of exposure at various periods of time, the number of people exposed, or the extent of environmental exposure are among the considerations which may be relevant in particular circumstances" (Ref. 39). EPA believes that it is reasonable to interpret the duration of exposure and level of, or intensity of exposure as relating to "significant" human exposure, the number of people exposed as relating to "substantial" human exposure, and the extent of environmental exposure as relating to "substantial" quantities of environmental release.

All 10 of the substances in this proposal are produced in quantities exceeding 12 million pounds per year. EPA is reserving discussion on what it considers to be the minimum production volume that can be considered "substantial" until it publishes its "B" policy. Nevertheless, EPA finds that 12 million pounds per year clearly is above the minimum level that can be considered "substantial." EPA believes it is reasonable to interpret substantial production to mean large production, and that 12 million pounds is a large amount of production. Moreover, production information reported in connection with the TSCA section 8(b) inventory of the substances in commerce shows that only 4.8 percent of the listed substances have production volumes over 10 million pounds,

together accounting for over 95 percent of the total production of all substances produced in the United States (Ref. 41). EPA believes that it is reasonable to conclude that this small group of substances (i.e., the top 4.8 percent according to production volume), which account for the vast majority of all production, clearly are substances with substantial production.

EPA believes that the term "substantial" used in connection with environmental release is intended to capture substances with extensive release to the environment, which in itself would be sufficient reason to require testing in the absence of any information that the substance may be hazardous to human health or the environment. In other words, as with substantial production, release of substantial quantities means large release. The four substances for which substantial release findings are made are all released in quantities exceeding 1 million pounds per year. EPA finds that 1 million pounds of release to the environment is a sufficiently large amount of release that EPA should require testing even in the absence of any hazard information. Moreover, the Toxics Release Inventory (TRI), compiled under section 313 of the Emergency Planning and Community Right-to-Know Act (Ref. 42), shows that only 37 percent of the listed substances have releases over 1 million pounds, but account for over 99 percent of the total reported releases on the TRI by volume released. Because the TRI does not include all substances, less than 37 percent of all substances would have releases above 1 million pounds. EPA believes that it is reasonable to conclude that this small group of substances (i.e., less than 37 percent), which accounts for over 99 percent of all releases, clearly are substances with substantial releases.

EPA believes that it is reasonable to interpret the term "substantial human exposure" to mean widespread human exposure, or in other words, exposure to a large number of people. Available consumer data indicate that at least 3.7 million consumers are exposed to each of the subject substances. EPA believes that exposure to 3.7 million people is substantial exposure because where millions of people are exposed to a chemical substance, it is reasonable that EPA should have data on the potential hazards associated with the substance so that EPA can implement appropriate risk management efforts where necessary to protect the public against unreasonable risk.

Moreover, at least 172,000 workers are believed to be exposed to each of the 10 subject substances. EPA believes that exposure to 172,000 workers is substantial exposure. As a general matter EPA has found that workers tend to be subject to routine or episodic exposure over a long period of time. The Court in *CMA v. EPA* recognized that there could be some overlap between substantial and significant human exposure: "it is not necessarily clear that 'significant' and 'substantial' as used in clause (II) must be understood in a way that prevents any overlap in their respective meanings or requires that any factor relevant to one be necessarily irrelevant to the other" (Ref. 38, n. 17). Thus, exposure, to be considered substantial, does not have to be as widespread for workers as for consumers or the general population. EPA believes that exposure to 172,000 workers is widespread enough to necessitate testing to determine the potential hazards of the substances to evaluate whether worker protection, or other risk management efforts are necessary.

1. *The 10 substances are or will be produced in substantial quantities.* All of the substances subject to this proposed test rule are listed on the TSCA Section 8(b) Inventory. Other sources of more recent production data have been evaluated to update the TSCA inventory data (Ref. 32). EPA has reviewed these data and has found that the reported production volume of each substance (12 million to 2.4 billion pounds per year) is substantial.

2. *There is or may be substantial human exposure to each of the substances.* EPA believes there is substantial occupational exposure to each of these substances. The NOES data indicate that over 172,000 workers are exposed to each of these substances. Exposure also may be enhanced given the propensity of these substances to penetrate the skin and to have high volatility, which facilitates inhalation. Available data on skin absorption and the vapor pressures of these substances support this position. EPA also believes there is potential for substantial consumer exposure to these substances from their widespread presence in consumer products. EPA has determined that each of these substances is present in 1 to 51 consumer products and has estimated that at least 3.7 million consumers are exposed to each product. EPA finds that exposure to over 172,000 workers and 3.7 million consumers is "substantial" as that term is used in TSCA section 4(a)(1)(B).

3. *There is or may be substantial quantities of four substances released to the environment.* Four of the substances (acetone, 1-butanol, 2-ethoxyethanol, and methyl isobutyl ketone) are listed on EPA's Toxics-Release Inventory and have been reported to be released to the environment in quantities exceeding 1 million pounds per year. EPA finds that this amount of release is "substantial" as that term is used in TSCA section 4(a)(1)(B).

4. *Activities involving 6 of the substances may present an unreasonable risk of injury to human health.* In addition to the findings made under section 4(a)(1)(B)(i), for all the subject chemicals, EPA also finds under section 4(a)(1)(A)(i) that the neurotoxicity studies discussed in Unit II for acetone, 1-butanol, diethyl ether, 2-ethoxyethanol, ethyl acetate, and methyl isobutyl ketone and the worker and consumer exposure to these substances indicate that the manufacturing, processing, use, and disposal of these substances may present an unreasonable risk of injury to human health from neurotoxicity. The finding that acetone may present a risk is based on the human study which showed a decrease in auditory tone discrimination after a 4-hour exposure to 250 ppm acetone (Ref. 11) and the dose-related functional decrements observed in rats and mice after exposure to 1,000 to 56,000 ppm acetone (Refs. 12 and 13). The finding that 1-butanol may present a risk is based on its observed impairment of motor control in rats (Refs. 14 and 17) and motor performance in mice (Refs. 15 and 16). The finding that diethyl ether may present a risk is based on its interference with the acquisition of an avoidance response in mice (Ref. 21). The finding that 2-ethoxyethanol may present a risk is based on the alteration of motor performance and avoidance conditioning in the offspring of rats exposed to 100 and 200 ppm (Refs. 30 and 31). The finding that ethyl acetate may present a risk is based on the dose-related decrease in a schedule-controlled response in mice after exposure to 300 to 3,000 ppm (Ref. 13). Also, intravenous injection of ethyl acetate depressed the vestibulo-ocular reflex in rats (Ref. 26). The finding that methyl isobutyl ketone may present a risk is based on the hindlimb paralysis seen in rats and mice exposed to 3,000 ppm (Ref. 29).

5. *Insufficient data and experience.* Under section 4(a)(1)(A)(ii) and (B)(ii), EPA finds that there are insufficient data and experience to reasonably determine or predict the potential neurotoxic effects from acute and

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subchronic exposures from manufacturing, processing, use, and disposal.

EPA believes that the guidelines found at 40 CFR part 792 represent state-of-the-art methodology and form the basis for a valid and scientifically acceptable test standard for evaluating the neurotoxicity of these substances. The available studies are not acceptable to EPA because they do not conform with the guidelines as detailed in the following Table 5.

TABLE 5.—DATA INSUFFICIENCY FINDINGS UNDER TSCA 4(A)(1)(A)(ii) AND (B)(ii)

Name/CAS No.	Data Insufficiency (Notes)	Reference
acetone (67-64-1)	(a)	12
	(b,c,d)	13
n-amy acetate (528-83-7)	(a)	
1-butanol (71-36-3)	(c)	15
n-butyl acetate (123-86-4)	(a)	
diethyl ether (60-29-7)	(a,c,d)	21
	(c,c,d)	22
	(a)	26
2-ethoxyethanol (110-80-6)	(a)	27
	(a,b,c,d)	13
ethyl acetate (141-78-6)	(a)	
isobutyl alcohol (78-83-1)	(a)	
methyl isobutyl ketone (108-10-1)	(a)	20
tetrahydrofuran (108-99-8)	(a)	

Notes:

- Only male mice were tested; no females were tested.
- Animals were exposed to more than one chemical.
- Test was not equivalent to the TSCA guideline.
- Not a subchronic test.
- Provided data on effects to offspring only.
- This is primarily a developmental toxicity test.
- No study addressing neurotoxicity was found.

6. **Necessity of testing.** Under section 4(a)(1)(A)(iii) and (B)(iii), EPA finds that testing each of these substances is necessary to develop such data for neurotoxicity. EPA believes the data resulting from the proposed testing will be relevant to a determination as to whether manufacturing, processing, use, and disposal of these substances does or does not present an unreasonable risk of injury to human health.

IV. Proposed Rule

A. Proposed Testing and Test Standards

Given the section 4(a)(1) findings for the 10 substances, EPA has the authority

to require other health effects testing for which there is an insufficiency of data and for which testing is necessary.

However, as a matter of policy, EPA is proposing only neurotoxicity testing for the substances included in this proposed rule at this time to focus on the deficiency in neurotoxicity data. EPA may, in the future, find other data deficiencies for these substances and propose other tests.

Functional observational battery, motor activity, neuropathology, and schedule-controlled operant behavior studies are proposed for the 10 substances. Although the schedule-controlled operant behavior test has in the past typically been required under EPA's testing policy as a second-tier test, it is proposed as a first-tier test in this rule because of EPA's desire to obtain data on the effects of solvents on learning, memory, and performance. The studies are proposed to be conducted in accordance with EPA's TSCA Good Laboratory Practice (GLP) Standards in 40 CFR part 792 and the specific TSCA test guidelines as enumerated in 40 CFR part 792, as amended in this proposed rule.

EPA is proposing that these 10 substances undergo acute and subchronic testing according to the TSCA test guidelines at 40 CFR 792.0200 and 792.0200. EPA is also proposing that these 10 substances undergo subchronic testing using the TSCA test guidelines at 40 CFR 792.0400 and 792.0500. The studies should be performed in rats with inhalation as the route of administration. The duration of exposure for acute testing would be 6 hours per day for 1 day; duration of exposure for subchronic testing would be 6 hours per day for 5 days per week for 13 weeks (90 days).

EPA is proposing that the above-referenced neurotoxicity test guidelines, and any modifications to these guidelines, be the test standards for testing these substances.

B. Test Substances

EPA is proposing that the purity of the test substances be 99 percent or greater. EPA believes that the percent purities listed in Table 6 are readily available.

TABLE 6.—AVAILABLE PURITY OF TEST SUBSTANCE

Substance/CAS No.	Available percent purity
acetone (67-64-1)	99.9
n-amy acetate (528-83-7)	99.9
1-butanol (71-36-3)	99.9
n-butyl acetate (123-86-4)	99.9

TABLE 6.—AVAILABLE PURITY OF TEST SUBSTANCE—Continued

Substance/CAS No.	Available percent purity
diethyl ether (60-29-7)	99.9
2-ethoxyethanol (110-80-6)	98.0
ethyl acetate (141-78-6)	99.9
isobutyl alcohol (78-83-1)	99.9
methyl isobutyl ketone (108-10-1)	99.9
tetrahydrofuran (108-99-8)	99.5

EPA has specified relatively pure substances for testing because it is interested in evaluating the effects attributable to the substances themselves. This requirement lessens the likelihood that any effects seen are due to impurities or additives.

C. Persons Required to Test

Because of the findings in Unit III, EPA is proposing that persons who manufacture (including import) and/or process, or who intend to manufacture and/or process one or more of the named test substances, other than as an impurity, at any time from the effective date of the final test rule to the end of the reimbursement period be subject to the testing requirements in this proposed rule. This period is defined in 40 CFR 791.3(h). Byproduct manufacturers and importers of one or more of these substances would be considered manufacturers under this rule. As explained in 40 CFR part 790, initially, manufacturers but not processors of one or more of these substances would be required to submit letters of intent or exemption applications. Pursuant to a recent amendment to part 790, small quantity research and development manufacturers are not required to submit letters of intent or exemption applications initially. Such manufacturers should consult the Federal Register of May 7, 1990 (55 FR 18881) for further details.

EPA is not proposing to require the submission of equivalence data as a condition for exemption from the proposed testing for these substances. EPA is interested in evaluating the effects attributable to the substances themselves and has specified relatively pure substances for testing.

D. Reporting Requirements

As required in 40 CFR 792.10, all data developed under the final rule would be conducted and reported in accordance with the TSCA GLP Standards, which appear in 40 CFR part 792.

As required by TSCA section 4(b)(3)(C), EPA is proposing specific reporting requirements for each of the

proposed test standards as follows. Final reports of acute testing under 40 CFR 798.6050 and 798.6200 would be due 9 months from the effective date of the final rule; interim progress reports would be due 6 months from the effective date of the final rule.

Final reports for subchronic testing under 40 CFR 798.6050, 798.6200, 798.6400, and 798.6500 would be due 21 months from the effective date of the final rule; interim progress reports would be due at 6-month intervals beginning 6 months from the effective date of the final rule.

The effective date of the final rule will be 44 days after the date of publication of the final rule in the **Federal Register**.

According to a recent EPA report entitled "EPA Census of the Toxicological Testing Industry", laboratory availability for neurotoxicity testing should be adequate to accommodate the testing proposed in this rule (Ref. 33). If potential test sponsors can document that the neurotoxicity testing proposed in this rule needs to be staggered due to insufficient laboratory availability, thereby necessitating extending the reporting deadlines, EPA proposes the following. The substances with a section 4(a)(1)(A) finding would be tested first and ranked according to production volume as reported in this rule. Those substances with the largest production volumes would be required to be tested first, followed by those substances with the next largest volumes. The substances with only a section 4(a)(1)(B) exposure finding would be tested next and likewise ranked according to production volume as reported in this rule.

V. Issues for Comment

1. The following issues concern the criteria used to select chemicals for testing for this particular rule:

(a) Some have questioned whether, as a matter of policy, it is appropriate to use exposure alone as a testing criterion without specific indication of the potential hazard or potency of these substances. EPA solicits comment on this issue.

(b) They have also questioned the reasonableness of the burden/cost of testing for substances with only exposure evidence but no hazard information and suggested that there should be some minimum likelihood that a neurotoxic hazard exists before testing is required. EPA solicits comment on this issue.

(c) Questions have also been raised on the chemical selection criteria and numerical cutoffs EPA used to increase the likelihood of selecting chemicals for

this rule with widespread human exposure. These criteria are: (1) production level of 10 million pounds, (2) occupational exposure of 100,000 workers, (3) environmental release of 1 million pounds, (4) vapor pressure of 5 mmHg or greater, and (5) presence in consumer products. EPA solicits comment on this issue.

(d) Some have questioned the appropriateness of having different selection criteria for different testing endpoints. For example, the developmental/reproductive toxicity rule published today elsewhere in this issue of the **Federal Register** uses selection criteria different from those used under this rule. EPA solicits comment on this issue.

2. EPA solicits additional information on the neurotoxicity of the substances listed in this rule. Such information may cause EPA to alter its decision on the need for testing of one or more of these substances.

3. This rule would require that as many as 40 neurotoxicity tests be run concurrently. EPA believes that adequate laboratory capacity exists for conducting this testing within the reporting deadlines. Further, EPA believes that if it were to amend the rule periodically by requiring testing of an additional 15 to 20 substances per year, laboratory facilities would still be able to meet this testing demand. EPA requests comment on laboratory availability and the reporting requirements.

4. In the schedule-controlled operant behavior test, a multiple fixed ratio/differential reinforcement of low rate (DRL) schedule is specified. Although EPA believes that a multiple schedule would be useful to insure that potential effects aren't missed, an alternative schedule may provide comparable information. For example, the fixed-interval (FI) schedule may be a reasonable substitute for the DRL and would not foster compensatory mechanisms that would mask effects as might happen with the DRL. EPA requests comments on the DRL, FI, and other multiple schedules.

5. Butyl acetate should readily hydrolyze to 1-butanol (and acetic acid) once inhaled or absorbed through the skin. As such, testing either butyl acetate or 1-butanol should provide similar toxicological results. EPA solicits comment on whether or not it should require only one of these two substances to be tested. EPA solicits comment on whether data should be required on the hydrolysis rate to determine if a separate effect from butyl acetate may occur before being hydrolyzed to 1-butanol. Comments also

should be submitted on whether, if testing of only one were to be required, it should be 1-butanol which is produced at 10 times greater volume (1.8 billion vs. 194 million pounds per year) and to which an estimated 74,000 more workers are exposed, or butyl acetate, which has a greater vapor pressure and would, therefore, be more likely to provide higher exposure on an equal volume of use basis, and to which EPA estimates more consumers are exposed (64 to 176 million vs. 79 million). If only one of these substances is tested should the manufacturers of the other also be subject to the rule and share in the cost of testing since the data obtained would be used to assess the risk of both substances?

6. Ethyl acetate may readily hydrolyze to ethanol for which there exists sufficient neurotoxicity data. EPA solicits comment on whether it should accept the data on ethanol as predictive of the effects of ethyl acetate and whether data should be required on the hydrolysis rate (using a pharmacokinetics guideline comparable to those previously proposed by EPA) to determine if a separate effect from ethyl acetate may occur before being hydrolyzed to ethanol.

VI. Economic Analysis of Proposed Rule

EPA has prepared an economic analysis that evaluates the potential for significant economic impacts on test sponsors as a result of the proposed testing (Ref. 32). The economic analysis estimates the costs of conducting the proposed testing for each of the 10 substances, including both laboratory and administrative costs, and evaluates the potential for adverse economic impacts as a result of these test costs, using a comparison between a substance's annualized test costs and its annual revenues.

The estimated total costs of testing for each of the substances are \$494,188 to \$875,100, including \$395,350 to \$700,080 in laboratory costs and \$98,838 to \$175,020 in administrative costs. This is based on the cost range for each test given in the following Table 7.

TABLE 7.—COST RANGE OF TSCA NEUROTOXICITY TESTS

Test	Cost Range in Dollars
Functional observational battery.....	16,500 to 23,325
Acute, 40 CFR 798.6050.....	
Subchronic, 40 CFR 798.6050.....	92,013 to 170,625
Motor Activity.....	18,625 to 26,388
Acute, 40 CFR 798.6200.....	

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TABLE 7.—COST RANGE OF TSCA NEUROTOXICITY TESTS—Continued

Test	Cost Range in Dollars
Subchronic, 40 CFR 798.6200	86,275 to 162,368
Neuropathology: Subchronic, 40 CFR 798.6400	112,638 to 200,125
Schedule-controlled operant behavior: Subchronic, 40 CFR 798.6500	166,138 to 292,250

Actual test costs per substance should be lower since EPA assumed that each test would be done independently of one another and the sponsors might choose to combine the subchronic tests for a given substance which would conserve both animals and resources.

To evaluate potential economic impacts of the proposed testing, test costs are annualized and compared with annual revenues. The annualized test costs, using a 7 percent cost of capital over a period of 15 years, are \$54,259 to \$96,061 for each of the ten substances.

Dividing these annualized costs by the appropriate production volumes in Table 3 for each substance, and then dividing these amounts by the appropriate price per pound in the following Table 8, the percent price increase per pound due to testing was estimated.

TABLE 8.—ECONOMIC ANALYSIS

Chemical/CAS No.	Chemical Price/Pound (Dollars)	Percent Chemical Price Increase/pound
acetone (67-64-1)	0.318	0.0071 to 0.0126
n-amyl acetate (628-63-7)	0.680	0.0834 to 1.2161
1-butanol (71-36-3)	0.360	0.0077 to 0.0136
n-butyl acetate (123-86-4)	0.430	0.0646 to 0.1147
diethyl ether (60-29-7)	0.515	0.1916 to 0.3382
2-ethoxyethanol (110-80-5)	0.750	0.0584 to 0.1062
ethyl acetate (141-78-6)	0.410	0.0514 to 0.0911
isobutyl alcohol (78-83-1)	0.380	0.0663 to 0.1528
methyl isobutyl ketone (108-10-1)	0.450	0.0535 to 0.0648
tetrahydrofuran (109-99-8)	1.220	0.0289 to 0.0511

Table 8 shows that for 9 of the 10 substances, unit test costs are substantially lower than one percent of price. For these 9 substances, it appears

that the costs of testing will have little significant adverse economic impact. In the case of n-amyl acetate, costs range from 0.68 to 1.21 percent of price, which is substantially higher than that of the other 9 substances (due to its lower production volume). In only the upper bound case, these costs may pose some potential for adverse impacts. If comments are received which indicate that the impacts are greater, a more comprehensive and detailed analysis will be conducted which more precisely predicts the magnitude and distribution of the expected impacts.

For a complete discussion of test cost estimation and potential for economic impact resulting from these costs, refer to the economic analysis which is contained in the public record for this rulemaking.

VII. Availability of Test Facilities and Personnel

EPA has determined that test facilities and personnel are available to perform the testing specified in this proposed rule (Refs. 27 and 33).

This rule would require concurrent neurotoxicity testing of 10 substances. EPA believes that space within the laboratories is available to adequately accommodate the 10 substances proposed for neurotoxicity testing. EPA also anticipates that laboratory capacity would increase to accommodate the demand created by future amendments to this rule.

VIII. Public Meeting

If requested, EPA will hold a public meeting in Washington, DC after the close of the public comment period. Persons who wish to attend or to present comments at the meeting should call Mary Louise Hewlett, Chemical Testing Branch (202) 475-8162 by April 18, 1991. The meeting is open to the public, but active participation will be limited to EPA representatives and those who requested to comment. Participants are requested to submit copies of their statements by the meeting date. These statements and a transcript of the meeting will become part of EPA's rulemaking record.

IX. Comments Containing Confidential Business Information

All comments will be placed in the public file unless they are clearly labeled as Confidential Business Information (CBI) when they are submitted. While a part of the record, CBI comments will be treated in accordance with 40 CFR part 2. A sanitized version of all CBI comments should be submitted to EPA for the public file.

It is the responsibility of the commenter to comply with 40 CFR part 2 in order that all materials claimed as confidential may be properly protected. This includes, but is not limited to, clearly indicating on the face of the comment (as well as on any associated correspondence) that CBI is included, and marking "CONFIDENTIAL", "TSCA CBI" or similar designation on the face of each document or attachment in the comment which contains CBI. Should information be put into the public file because of failure to clearly designate its confidential status on the face of the comment, EPA will presume any such information which has been in the public file for more than 30 days to be in the public domain.

X. Rulemaking Record

EPA has established a record for this rulemaking (docket number OPTS-42134). In addition, each substance in the rule has a separate docket number. This record contains the basic information considered by EPA in developing this proposal and appropriate Federal Register notices. EPA will supplement this record as necessary.

A public version of the record, from which all CBI has been deleted, is available for inspection in the TSCA Public Docket Office, Room G-004, NE Mall, 401 M St., SW., Washington, DC 20460, from 8 am to noon, and 1 pm to 5 pm, Monday through Friday, except legal holidays.

The record includes the following information:

A. Supporting Documentation

- (1) Federal Register notices pertaining to this rule consisting of:
 - (a) Notice of final rule on EPA's TSCA Good Laboratory Practice Standards (54 FR 34034; August 17, 1989).
 - (b) Notice of final rule on data reimbursement policy and procedures (46 FR 31786; July 11, 1983).
 - (c) Notice responding to the Interagency Testing Committee's (ITC's) recommendation on methyl ethyl ketone. (47 FR 58025, December 29, 1982).
 - (d) Notice responding to the ITC's recommendation on toluene. (47 FR 56391, December 16, 1982).
 - (e) Notice responding to the ITC's recommendation on xylenes. (47 FR 56392, December 16, 1982).
- (2) TSCA test guidelines cited as test standards for this rule.
- (3) Communications before proposal consisting of:
 - (a) Contact reports of telephone conversations.

(b) Meeting summaries including RM1 meeting (July 12, 1990).

(4) Support documents consisting of:

(a) Economic impact analysis of NPRM for the substances contained in this proposed rule.

(5) Reports - published and unpublished factual materials including "Evaluation of TSCA guidelines for neurotoxicity testing." (April 14, 1987).

B. References

- (1) U.S. Congress, Office of Technology Assessment. Neurotoxicity: Identifying and Controlling Poisons of the Nervous System. Chapter 1. "Summary, Policy Issues, and Options for Congressional Action". OTA-BA-438. Washington, DC. US Government Printing Office. (April 1990).
- (2) Syracuse Research Corporation. Syracuse, NY. "Technical Support for Selection of Solvents for a Neurotoxicity Test Rule." Contract No. 68-D8-0117, Task 103. TR 89-218. (January 11, 1990).
- (3) Syracuse Research Corporation. Syracuse, NY. "Neurotoxicity Profile of Solvents." Contract No. 68-D8-0117, Task: 07. (July 31, 1990).
- (4) Casarett and Doull's Toxicology. Editors: Klaassen, C.D., Amdur, M.O. and Doull, J. Chapter 20: Toxic Effects of Solvents and Vapors. pp. 636-638. 3rd edition. (1988).
- (5) United States Environmental Protection Agency (USEPA). "Consumer exposure assessment." Memorandum from Conrad Flessner, Exposure Assessment Branch, to Catherine Roman, Chemical Testing Branch, Office of Toxic Substances (OTS), USEPA, Washington, DC. (July 18, 1990).
- (6) USEPA. "Consumer exposure assessment." Memorandum from Sidney Abel, Exposure Assessment Branch, to Catherine Roman, Chemical Testing Branch, OTS, USEPA, Washington, DC. (July 17, 1990).
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- (8) USEPA. Toxics-Release Inventory. EPA 560/4-89-006. Office of Pesticides and Toxic Substances, Washington, DC. (June 1989).
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- (10) Versar, Inc., Springfield, VA. "Estimates of consumer exposure to ethyl ether." Memorandum from Carl D'Ruiz, Versar, Inc., to Conrad Flessner, Exposure Assessment Branch, OTS, USEPA, Washington, DC. (September 20, 1990).
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- (13) Glowa, J.R. and Dewa, P.B. "Behavioral toxicology of volatile organic solvents. IV. Comparison of the rate-decreasing effects of acetone, ethyl acetate, methyl ethyl ketone, toluene, and carbon disulfide on schedule-controlled behavior of mice". *Journal of the American College of Toxicology*. 6:461-469. (1987).
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- (17) Schulze, G.E. "2,4-n-Butyl ester (2,4-D ester) induced ataxia in rats: Role for n-butanol formation". *Neurotoxicology and Teratology*. 10:81-84. (1988).
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- (19) Hosick, E.C., Clark, D.L., Adam, N., and Rosner, B.S. "Neurophysiological effects of different anesthetics in conscious man". *Journal of Applied Physiology*. 31: 892-899. (1971).
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- (39) H. Rept. 1341, 94th Cong. 2d Sess. (1976), at 18 reprinted in, A Legislative History of the Toxic Substances Control Act (Comm. Print 1976) ("Leg. Hist.") at 425.
- (40) H. Conf. Rept. 1679, 94th Cong. 2d Sess. (1976), reprinted in, Leg. Hist. at 874.
- (41) USEPA. Information Management Division, Confidential Data Branch. 1977 Chemical Commerce Information Search.
- (42) Toxics Release Inventory under the Emergency Planning and Community Right-to-Know Act, 42 U.S.C. section 11023.

XI. Other Regulatory Requirements

A. Executive Order 12291

Under Executive Order 12291, EPA must judge whether a rule is "major" and therefore subject to the requirement of a Regulatory Impact Analysis. EPA has determined that this proposed test rule would not be major because it does not meet any of the criteria set forth in section 1(b) of the Order; i.e., it would

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not have an annual effect on the economy of at least \$100 million, would not cause a major increase in prices, and would not have a significant adverse effect on competition or the ability of U.S. enterprises to compete with foreign enterprises.

This proposed rule was submitted to the Office of Management and Budget (OMB) for review as required by Executive Order 12291. Any written comments from OMB to EPA, and any EPA response to those comments, are included in the rulemaking record.

B. Regulatory Flexibility Act

Under the Regulatory Flexibility Act (5 U.S.C. 601 et seq., Pub. L. 96-354, September 19, 1980), EPA is certifying that this test rule, if promulgated, would not have a significant impact on a substantial number of small businesses because: (1) They would not be expected to perform testing themselves or to participate in the organization of the testing effort; (2) they would experience only very minor costs, if any, in securing exemption from testing requirements; and (3) they are unlikely

to be affected by reimbursement requirements.

C. Paperwork Reduction Act

OMB has approved the information collection requirements contained in this proposed rule under the provisions of the Paperwork Reduction Act of 1980, 44 U.S.C. 3501 et seq., and has assigned OMB control number 2070-0033.

Public reporting burden for this collection of information is estimated to range from 499 to 6,984 hours per response (average of 2,400 hours per response). The estimates include time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information.

Send comments regarding the burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to Chief, Information Policy Branch, PM-223, U.S. Environmental Protection Agency, 401 M St., SW., Washington, DC 20460; and to the Office of Management and Budget, Paperwork Reduction Project (2070-0033), Washington, DC

20503. The final rule will respond to any OMB or public comments on the information collection requirements contained in this proposal.

List of Subjects in 40 CFR Part 799

Chemicals, Chemical export, Environmental protection, Hazardous substances, Testing laboratories, Reporting and recordkeeping requirements, Testing.

Dated: February 25, 1991.

Victor J. Kimm,
Acting Assistant Administrator for Pesticides and Toxic Substances.

Therefore, it is proposed that 40 CFR, chapter I, Subchapter R, part 799 be amended as follows:

PART 799—[AMENDED]

1. The authority citation for part 799 continues to read as follows:

Authority: 15 U.S.C. 2603, 2611, and 2625.

2. By amending § 799.5050 by adding in CAS No. order, 10 designated substances and their appropriate testing requirements to read as follows:

TABLE 1.—CHEMICAL SUBSTANCES SUBJECT TO TESTING UNDER THIS SECTION

CAS No.	Chemical name/types of testing	Basic testing requirements	(b) Additional testing requirements	Limitations and restrictions	Effective dates	
60-29-7	diethyl ether					
	Health effects testing:					
	Acute neurotoxicity:					
	Functional observational battery	§ 798.6050, except (d)(1)(i), (5) and (6)	paragraphs	(1)(ii), (2)(i), (3)(i)	Reports: 9 mo.	(-/-/-)
	Motor activity	§ 798.6200, except (d)(1)(i), (5) and (6)	paragraphs	(1)(ii), (2)(i), (3)(i)	Reports: 9 mo.	(-/-/-)
	Subchronic neurotoxicity:					
	Functional observational battery	§ 798.6050, except (d)(1)(i), (5) and (6)	paragraphs	(1)(ii), (2)(ii), (3)(i)	Reports: 21 mo.	(-/-/-)
Motor activity	§ 798.6200, except (d)(1)(i), (5) and (6)	paragraphs	(1)(ii), (2)(ii), (3)(i)	Reports: 21 mo.	(-/-/-)	
	Neuropathology	§ 798.6400, except (d)(1)(i), (5) and (6)	paragraphs	(1)(ii), (2)(ii), (3)(i)	Reports: 21 mo.	(-/-/-)
	Schedule-controlled operant behavior	§ 798.6500, except (d)(2)(i)(A), (6), (7) and (8)(v)	paragraphs	(1)(ii), (2)(ii), (3)(i)	Reports: 21 mo.	(-/-/-)
	67-64-1	acetone				
		Health effects testing:				
Acute neurotoxicity:						
Functional observational battery		§ 798.6050, except (d)(1)(i), (5) and (6)	paragraphs	(1)(ii), (2)(i), (3)(i)	Reports: 9 mo.	(-/-/-)
Motor activity	§ 798.6200, except (d)(1)(i), (5) and (6)	paragraphs	(1)(ii), (2)(i), (3)(i)	Reports: 9 mo.	(-/-/-)	
Subchronic neurotoxicity:						
Functional observational battery	§ 798.6050, except (d)(1)(i), (5) and (6)	paragraphs	(1)(ii), (2)(ii), (3)(i)	Reports: 21 mo.	(-/-/-)	
Motor activity	§ 798.6200, except (d)(1)(i), (5) and (6)	paragraphs	(1)(ii), (2)(ii), (3)(i)	Reports: 21 mo.	(-/-/-)	

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TABLE 1.—CHEMICAL SUBSTANCES SUBJECT TO TESTING UNDER THIS SECTION—Continued

CAS No.	Chemical name/types of testing	Basic testing requirements	(b) Additional testing requirements	Limitations and restrictions	Effective dates	
	Neuropathology	§ 798.6400, except (d)(1)(i), (5) and (6)	paragraphs	(1)(ii), (2)(ii), (3)(i)	Reports: 21 mo.	(-/-/-)
	Schedule-controlled operant behavior	§ 798.6500, except (d)(2)(i)(A), (6), (7) and (8)(v)	paragraphs	(1)(ii), (2)(ii), (3)(i)	Reports: 21 mo.	(-/-/-)
71-36-3	1-butanol					
	Health effects testing:					
	Acute neurotoxicity:					
	Functional observational battery	§ 798.6050, except (d)(1)(i), (5) and (6)	paragraphs	(1)(ii), (2)(ii), (3)(i)	Reports: 9 mo.	(-/-/-)
	Motor activity	§ 798.6200, except (d)(1)(i), (5) and (6)	paragraphs	(1)(ii), (2)(ii), (3)(i)	Reports: 9 mo.	(-/-/-)
	Subchronic neurotoxicity:					
	Functional observational battery	§ 798.6050, except (d)(1)(i), (5) and (6)	paragraphs	(1)(ii), (2)(ii), (3)(i)	Reports: 21 mo.	(-/-/-)
	Motor activity	§ 798.6200, except (d)(1)(i), (5) and (6)	paragraphs	(1)(ii), (2)(ii), (3)(i)	Reports: 21 mo.	(-/-/-)
	Neuropathology	§ 798.6400, except (d)(1)(i), (5) and (6)	paragraphs	(1)(ii), (2)(ii), (3)(i)	Reports: 21 mo.	(-/-/-)
	Schedule-controlled operant behavior	§ 798.6500, except (d)(2)(i)(A), (6), (7) and (8)(v)	paragraphs	(1)(ii), (2)(ii), (3)(i)	Reports: 21 mo.	(-/-/-)
78-83-1	isobutyl alcohol					
	Health effects testing:					
	Acute neurotoxicity:					
	Functional observational battery	§ 798.6050, except (d)(1)(i), (5) and (6)	paragraphs	(1)(ii), (2)(ii), (3)(i)	Reports: 9 mo.	(-/-/-)
	Motor activity	§ 798.6200, except (d)(1)(i), (5) and (6)	paragraphs	(1)(ii), (2)(ii), (3)(i)	Reports: 9 mo.	(-/-/-)
	Subchronic neurotoxicity:					
	Functional observational battery	§ 798.6050, except (d)(1)(i), (5) and (6)	paragraphs	(1)(ii), (2)(ii), (3)(i)	Reports: 21 mo.	(-/-/-)
	Motor activity	§ 798.6200, except (d)(1)(i), (5) and (6)	paragraphs	(1)(ii), (2)(ii), (3)(i)	Reports: 21 mo.	(-/-/-)
	Neuropathology	§ 798.6400, except (d)(1)(i), (5) and (6)	paragraphs	(1)(ii), (2)(ii), (3)(i)	Reports: 21 mo.	(-/-/-)
	Schedule-controlled operant behavior	§ 798.6500, except (d)(2)(i)(A), (6), (7) and (8)(v)	paragraphs	(1)(ii), (2)(ii), (3)(i)	Reports: 21 mo.	(-/-/-)
108-10-1	methyl isobutyl ketone					
	Health effects testing:					
	Acute neurotoxicity:					
	Functional observational battery	§ 798.6050, except (d)(1)(i), (5) and (6)	paragraphs	(1)(ii), (2)(ii), (3)(i)	Reports: 9 mo.	(-/-/-)
	Motor activity	§ 798.6200, except (d)(1)(i), (5) and (6)	paragraphs	(1)(ii), (2)(ii), (3)(i)	Reports: 9 mo.	(-/-/-)
	Subchronic neurotoxicity:					
	Functional observational battery	§ 798.6050, except (d)(1)(i), (5) and (6)	paragraphs	(1)(ii), (2)(ii), (3)(i)	Reports: 21 mo.	(-/-/-)
	Motor activity	§ 798.6200, except (d)(1)(i), (5) and (6)	paragraphs	(1)(ii), (2)(ii), (3)(i)	Reports: 21 mo.	(-/-/-)
	Neuropathology	§ 798.6400, except (d)(1)(i), (5) and (6)	paragraphs	(1)(ii), (2)(ii), (3)(i)	Reports: 21 mo.	(-/-/-)
	Schedule-controlled operant behavior	§ 798.6500, except (d)(2)(i)(A), (6), (7) and (8)(v)	paragraphs	(1)(ii), (2)(ii), (3)(i)	Reports: 21 mo.	(-/-/-)
109-99-9	tetrahydrofuran					
	Health effects testing:					

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TABLE 1.—CHEMICAL SUBSTANCES SUBJECT TO TESTING UNDER THIS SECTION—Continued

CAS No.	Chemical name/types of testing	Basic testing requirements	(b) Additional testing requirements	Limitations and restrictions	Effective dates
	Acute neurotoxicity:				
	Functional observational battery	§ 798.6050, except (d)(1)(i), (5) and (6)	paragraphs	(1)(ii), (2)(i), (3)(i) Reports: 9 mo.	(-/-/-)
	Motor activity	§ 798.6200, except (d)(1)(i), (5) and (6)	paragraphs	(1)(ii), (2)(i), (3)(i) Reports: 9 mo.	(-/-/-)
	Subchronic neurotoxicity:				
	Functional observational battery	§ 798.6050, except (d)(1)(i), (5) and (6)	paragraphs	(1)(ii), (2)(ii), (3)(i) Reports: 21 mo.	(-/-/-)
	Motor activity	§ 798.6200, except (d)(1)(i), (5) and (6)	paragraphs	(1)(ii), (2)(ii), (3)(i) Reports: 21 mo.	(-/-/-)
	Neuropathology	§ 798.6400, except (d)(1)(i), (5) and (6)	paragraphs	(1)(ii), (2)(ii), (3)(i) Reports: 21 mo.	(-/-/-)
	Schedule-controlled operant behavior	§ 798.6500, except (d)(2)(i)(A), (6), (7) and (8)(v)	paragraphs	(1)(ii), (2)(ii), (xx), (3)(i) Reports: 21 mo.	(-/-/-)
110-80-5	2-ethoxyethanol				
	Health effects testing:				
	Acute neurotoxicity:				
	Functional observational battery	§ 798.6050, except (d)(1)(i), (5) and (6)	paragraphs	(1)(ii), (2)(i), (3)(i) Reports: 9 mo.	(-/-/-)
	Motor activity	§ 798.6200, except (d)(1)(i), (5) and (6)	paragraphs	(1)(ii), (2)(i), (3)(i) Reports: 9 mo.	(-/-/-)
	Subchronic neurotoxicity:				
	Functional observational battery	§ 798.6050, except (d)(1)(i), (5) and (6)	paragraphs	(1)(ii), (2)(ii), (3)(i) Reports: 21 mo.	(-/-/-)
	Motor activity	§ 798.6200, except (d)(1)(i), (5) and (6)	paragraphs	(1)(ii), (2)(ii), (3)(i) Reports: 21 mo.	(-/-/-)
	Neuropathology	§ 798.6400, except (d)(1)(i), (5) and (6)	paragraphs	(1)(ii), (2)(ii), (3)(i) Reports: 21 mo.	(-/-/-)
	Schedule-controlled operant behavior	§ 798.6500, except (d)(2)(i)(A), (6), (7) and (8)(v)	paragraphs	(1)(ii), (2)(ii), (xx), (3)(i) Reports: 21 mo.	(-/-/-)
123-86-4	<i>n</i> -butyl acetate				
	Health effects testing:				
	Acute neurotoxicity:				
	Functional observational battery	§ 798.6050, except (d)(1)(i), (5) and (6)	paragraphs	(1)(ii), (2)(i), (3)(i) Reports: 9 mo.	(-/-/-)
	Motor activity	§ 798.6200, except (d)(1)(i), (5) and (6)	paragraphs	(1)(ii), (2)(i), (3)(i) Reports: 9 mo.	(-/-/-)
	Subchronic neurotoxicity:				
	Functional observational battery	§ 798.6050, except (d)(1)(i), (5) and (6)	paragraphs	(1)(ii), (2)(ii), (3)(i) Reports: 21 mo.	(-/-/-)
	Motor activity	§ 798.6200, except (d)(1)(i), (5) and (6)	paragraphs	(1)(ii), (2)(ii), (3)(i) Reports: 21 mo.	(-/-/-)
	Neuropathology	§ 798.6400, except (d)(1)(i), (5) and (6)	paragraphs	(1)(ii), (2)(ii), (3)(i) Reports: 21 mo.	(-/-/-)
	Schedule-controlled operant behavior	§ 798.6500, except (d)(2)(i)(A), (6), (7) and (8)(v)	paragraphs	(1)(ii), (2)(ii), (xx), (3)(i) Reports: 21 mo.	(-/-/-)
141-78-6	ethyl acetate				
	Health effects testing:				
	Acute neurotoxicity:				
	Functional observational battery	§ 798.6050, except (d)(1)(i), (5) and (6)	paragraphs	(1)(ii), (2)(i), (3)(i) Reports: 9 mo.	(-/-/-)
	Motor activity	§ 798.6200, except (d)(1)(i), (5) and (6)	paragraphs	(1)(ii), (2)(i), (3)(i) Reports: 9 mo.	(-/-/-)
	Subchronic neurotoxicity:				

TABLE 1.—CHEMICAL SUBSTANCES SUBJECT TO TESTING UNDER THIS SECTION—Continued

CAS No.	Chemical name/types of testing	Basic testing requirements	(b) Additional testing requirements	Limitations and restrictions	Effective dates
	Functional observational battery	§ 798.6050, except (d)(1)(i), (5) and (6)	paragraphs	(1)(ii), (2)(ii), (3)(i)	Reports: 21 mo. (---/---)
	Motor activity	§ 798.6200, except (d)(1)(i), (5) and (6)	paragraphs	(1)(ii), (2)(ii), (3)(i)	Reports: 21 mo. (---/---)
	Neuropathology	§ 798.6400, except (d)(1)(i), (5) and (6)	paragraphs	(1)(ii), (2)(ii), (3)(i)	Reports: 21 mo. (---/---)
	Schedule-controlled operant behavior	§ 798.6500, except (d)(2)(i)(A), (6), (7) and (8)(v)	paragraphs	(1)(ii), (2)(ii), (xx), (3)(i)	Reports: 21 mo. (---/---)
628-63-7	<i>n</i> -amyl acetate				
	Health effects testing:				
	Acute neurotoxicity:				
	Functional observational battery	§ 798.6050, except (d)(1)(i), (5) and (6)	paragraphs	(1)(ii), (2)(i), (3)(i)	Reports: 9 mo. (---/---)
	Motor activity	§ 798.6200, except (d)(1)(i), (5) and (6)	paragraphs	(1)(ii), (2)(i), (3)(i)	Reports: 9 mo. (---/---)
	Subchronic neurotoxicity:				
	Functional observational battery	§ 798.6050, except (d)(1)(i), (5) and (6)	paragraphs	(1)(ii), (2)(ii), (3)(i)	Reports: 21 mo. (---/---)
	Motor activity	§ 798.6200, except (d)(1)(i), (5) and (6)	paragraphs	(1)(ii), (2)(ii), (3)(i)	Reports: 21 mo. (---/---)
	Neuropathology	§ 798.6400, except (d)(1)(i), (5) and (6)	paragraphs	(1)(ii), (2)(ii), (3)(i)	Reports: 21 mo. (---/---)
	Schedule-controlled operant behavior	§ 798.6500, except (d)(2)(i)(A), (6), (7) and (8)(v)	paragraphs	(1)(ii), (2)(ii), (xx), (3)(i)	Reports: 21 mo. (---/---)

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