**ENVIRONMENTAL PROTECTION AGENCY**

**40 CFR Part 799**

**[OPPTS-42134B; FRL 4050-9]**

**RIN 2070-AC27**

## Multi-Substance Rule for the Testing of Neurotoxicity

**AGENCY:** Environmental Protection Agency (EPA).

**ACTION:** Final rule.

**SUMMARY:** EPA is issuing a final rule, under section 4 of the Toxic Substances Control Act (TSCA), requiring manufacturers and processors of 10 substances to conduct testing for neurotoxicity. The 10 substances are acetone (CAS No. 67-64-1), technical grade *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), 2-ethoxyethanol (CAS No. 110-80-5), ethyl acetate (CAS No. 141-78-6), isobutyl alcohol (CAS No. 78-83-1), methyl isobutyl ketone (CAS No. 108-10-1), and tetrahydrofuran (CAS No. 109-99-9). These substances are related in that all are volatile solvents with high production volumes, occupational exposure, presence in and/or release to the environment, and, with the exception of 2-ethoxyethanol, consumer exposure. This rule requires cognitive function and screening level tests for neurotoxicity.

**DATES:** This rule shall become effective on September 9, 1993. In accordance with 40 CFR 23.5, this rule shall be promulgated for purposes of judicial review at 1 p.m. eastern daylight time on August 10, 1993.

**FOR FURTHER INFORMATION CONTACT:** Susan B. Hazen, Director, Environmental Assistance Division (TS-799), Office of Pollution Prevention and Toxics, Rm. E-543B, 401 M St., SW., Washington, DC 20460, (202) 554-1404, TDD (202) 554-0551.

**SUPPLEMENTARY INFORMATION:**

**Electronic Availability:** This document is available as an electronic file on *The Federal Bulletin Board* at 9 a.m. on the date of publication in the **Federal Register**. By modem dial 202-512-1387 or call 202-512-1530 for disks or paper copies. This file is available in Postscript, Wordperfect 5.1 and ASCII.

EPA is issuing a final test rule under section 4(a) of TSCA to obtain neurotoxicity data for ten 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. Test Rule Development Under TSCA*

This final rule is part of the overall implementation of section 4 of TSCA, 15 U.S.C. 2603, which contains authority for EPA to require the development of data relevant to assessing the risk to health and the environment posed by exposure to particular chemical substances or mixtures (hereafter "substances").

Under section 4(a) of TSCA, EPA must require testing of a chemical substance to develop health or environmental data if the Administrator makes certain findings as described in TSCA under section 4(a)(1)(A) or (B). Detailed 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 30300). Additional discussion of the TSCA section 4(a)(1)(B) finding can be found in the **Federal Register** notice which articulates the criteria EPA uses for making that finding (58 FR 28736, May 14, 1993).

#### *B. Background*

On March 4, 1991 (56 FR 9105), EPA proposed a multi-substance test rule to test 10 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 is initiating this program to test some of them. This approach is supported by a recent study by the Office of Technology Assessment (OTA) on the health threat from neurotoxic chemicals (Ref. 46). 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. Although EPA has previously required neurotoxicity testing as part of comprehensive test programs of individual substances, EPA intends this rule to be the first in a series of actions to obtain data solely on neurotoxicity.

Organic solvents were targeted for the first neurotoxicity endpoint rule because, as a group, they are associated with neurological effects. There is wide concern about a range of potentially adverse neurological consequences of short-term and long-term exposure to organic solvents. The human syndrome may include fatigue, difficulty in concentration, personality and mood changes, performance deficits, neurological signs, and neurological damage.

Organic solvents were also targeted for the first neurotoxicity endpoint rule because they include many high exposure substances (Ref. 47). By selecting those organic solvents with high exposure, the limited resources available for testing will be focused on a few substances with widespread use and human exposure, instead of requiring EPA to consider the whole universe of organic solvents for testing. Each solvent in this rule was selected for testing consideration because it has a high production volume, high vapor pressure, widespread use in the workplace, and, with the exception of 2-ethoxyethanol, widespread use by consumers. EPA believes these characteristics assure that many people are likely to have acute and/or chronic exposure to these substances. A more detailed description of how exposure criteria were used to select the 10 candidate solvents for testing can be found in the preamble to the proposed test rule (56 FR 9105-9108, March 4, 1991). The 10 solvents for which testing was proposed are acetone, n-amyl acetate, 1-butanol, *n*-butyl acetate, diethyl ether, 2-ethoxyethanol, ethyl acetate, isobutyl alcohol, methyl isobutyl ketone, and tetrahydrofuran.

EPA proposed that four neurotoxicity tests be conducted with each solvent. These tests are the functional observational battery, motor activity, neuropathology, and schedule-controlled operant behavior. These tests will examine neurobehavioral function in animals exposed by inhalation and 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. EPA does not consider this test program to be the most comprehensive program possible, but rather to be a start in addressing a complex and long-neglected issue. The testing in this rule, therefore, should not be viewed as a rigid universal template for all future test rules of solvents. Other test programs have been suggested in the past to examine solvent effects. A 1985 workshop co-sponsored by representatives from industry, academia, and government (Ref. 55) recommended batteries of neurobehavioral, electrophysiological, and neuropathological tests in rodents and primates exposed to solvents for up to several years.

EPA's efforts to obtain data to address its concern for the neurotoxicity of specific solvents dates back over 10

years to a proposed test rule (45 FR 48524, July 18, 1980) which discussed EPA's concerns for the neurotoxic effects of chloromethane in adults after chronic exposure and on offspring exposed *in utero*, and concerns related to abuse liability. All of these concerns are considered to be generally relevant to solvents as a class. This rule addresses only the first of these three concerns, and in a limited way. It will utilize relatively short-term (90-day) exposures as a surrogate for chronic exposures. It requires testing in adult rodents only. Further, it requires only a single test of complex neurobehavioral function, schedule-controlled operant behavior (SCOB). The SCOB evaluates the effect on performance of a complex task, which is dependent on memory and learning. By way of contrast, a much more extensive battery was proposed at the solvent workshop (Ref. 55), which included: sensory and motor electrophysiology; delayed matching-to-sample (a test of short term memory); repeated acquisition (a test of learning); cued reaction time, including a correlative electrophysiological monitor; a vigilance and tracking task; and psychomotor tests. Thus, EPA is requiring a very modest testing program in this area in comparison to the scientifically acknowledged diversity of the potential neurotoxic effects of concern.

In evaluating the testing needs for these substances, EPA considered the available published and unpublished information on the use, production volume, vapor pressure, occupational and consumer exposure, presence in and release to the environment, and neurotoxicity to animals and humans (56 FR 9106–9110, March 4, 1991). From its evaluation of these data, EPA proposed 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 also proposed neurotoxicity testing for six of the substances under TSCA section 4(a)(1)(A).

After reviewing the public comments submitted in response to the proposed rule, EPA is requiring neurotoxicity testing for the following 10 substances:

| Chemical name | CAS No. | Docket No. |
|---|---|---|
| acetone | 67–64–1 | 42134B/42135A |
| *n*-amyl acetate, technical grade | 628–63–7 | 42134B/42136A |
| 1-butanol | 71–36–3 | 42134B/42137A |
| *n*-butyl acetate | 123–86–4 | 42134B/42138A |
| diethyl ether | 60–29–7 | 42134B/42139A |
| 2-ethoxyethanol | 110–80–5 | 42134B/42140A |
| ethyl acetate | 141–78–6 | 42134B/42141A |
| isobutyl alcohol | 78–83–1 | 42134B/42142A |
| methyl isobutyl ketone | 108–10–1 | 42134B/42017C |
| tetrahydrofuran | 109–99–9 | 42134B/42143A |

EPA will continue to evaluate the need for this type of testing of additional substances and may pursue rulemaking on additional substances as necessary to require such testing. EPA intends to identify future candidates for addition to this rule from its chemical screening program, TSCA section 8(e) data, Premanufacture Notices, Structure-Activity Relationship data, nominations from other EPA programs, Interagency Testing Committee (ITC) recommendations, and other relevant sources.

The regulatory text of this rule is in tabular form under 40 CFR 799.5050. For future multi-substance rules, EPA is considering amending § 799.5050. Hence, this and subsequent multi-substance endpoint rules would be listed in a single table, and all the test requirements (health, environmental, chemical fate, etc.) for a substance will be in a single location. EPA believes that listing the test requirements for all the multi-substance endpoint rules in one table would be advantageous for persons subject to TSCA section 4 test rules and will simplify and aid in their monitoring and compliance.

## II. Public Comments

EPA received comments on the proposed "Multi-substance Rule for the Testing of Neurotoxicity" (56 FR 9105, March 4, 1991) from the Chemical Manufacturers Association (CMA) (Ref. 3), CMA's Acetone Panel (Refs. 4, 5 and 68), CMA's Glycol Ethers Panel (Ref. 6), CMA's Ketones Panel (Refs. 7 and 8), CMA's Oxo Process Panel (Refs. 9 through 12), the American Industrial Health Council (AIHC) (Ref. 1), the Diethyl Ether Manufacturers Task Group (DEMTG) (Ref. 13), BASF Corporation (BASF) (Ref. 2), The Dow Chemical Company (Dow) (Ref. 14), DuPont (Ref. 15), Kodak (Ref. 16), Monsanto (Ref. 17), Rohm and Haas (Ref. 18), Union Carbide (Ref. 19), the Interagency Testing Committee (ITC) (Ref. 21), Dr. J. Glowa of the U.S. Department of Health and Human Services (Ref. 20), Dr. D. McMillan of the University of Arkansas (Ref. 22), Dr. R. Neal of Vanderbilt University (Ref. 25), and Drs. D. Cory-Slechta (Ref. 23) and B. Weiss (Ref. 24) of the University of Rochester. These submissions contained both comments regarding the proposed rule and additional studies for EPA to consider before promulgating the final rule. These comments are addressed in detail below.

### *A. General Testing Policy Issues*

CMA (Ref. 3) submitted comments which addressed several general testing policy issues, specifically, comments regarding the use of endpoint versus comprehensive test rules, the selection criteria for determining candidates for testing consideration, the pre-rulemaking information gathering process, and the use of a screening battery. EPA believes that these comments address general policy issues that extend beyond the scope of this rulemaking. Although resolution of such general policy issues is largely within EPA's discretion, they are addressed briefly below.

The ITC (Ref. 21) indicated its support for the concept of a multi-substance endpoint rule in general and particularly when such a rule targets "substantially produced chemicals" as with the proposed neurotoxicity test rule. CMA (Ref. 3) commented that the multi-substance endpoint test rule

proposal was an important new initiative in the TSCA testing program noting that, in the past, EPA traditionally required in-depth testing of multiple endpoints on a single substance that was time and resource intensive for both EPA and industry. CMA and Monsanto (Ref. 17) further stated that the value of focused endpoint rules will be lost if, at a later date, EPA requires comprehensive testing on a substance that was subject to an endpoint rule.

EPA does not believe that multi-substance endpoint rules should be the exclusive means for testing chemical substances, nor that endpoint rules should always focus solely on the "endpoint of greatest concern." Multi-substance endpoint rules are only one means by which EPA can require testing to develop data on chemical substances for which there are insufficient data or experience upon which the effects of manufacture, distribution in commerce, processing, use, or disposal of such substance on health or the environment can reasonably be determined or predicted. EPA's testing efforts are intended to develop information on any endpoints of concern. Without any, or with only limited knowledge about a specific endpoint, it cannot be determined whether this endpoint is the "endpoint of greatest concern." Therefore, as scientific advances and developments may indicate a cause for concern in the future, EPA cannot, consistent with its statutory mandate, state that testing of a substance will be limited to a particular endpoint.

Furthermore, EPA does not believe that future comprehensive tests of a substance would lessen the value of the endpoint rule concept. "Endpoint" and "comprehensive" test rules are two valuable, but different, approaches to developing data on chemical substances that will not necessarily lead to duplicative testing requirements. If data generated under an endpoint rule adequately addresses the concerns underlying the testing requirements, there would be no justification for further testing on the same endpoint — even if additional "comprehensive" testing of the same chemical substance were later required. Under TSCA, additional testing can be required only where an appropriate rationale for such testing (including a "data insufficiency" finding) can be provided. In addition, data from endpoint testing may allow EPA to focus and tailor subsequent testing so as to obtain more useful data or, as indicated above, to decide that no additional data are necessary. For these reasons, EPA continues to believe that both types of rulemaking activities have their place in the TSCA section 4 process.

CMA (Ref. 3) commented that supportable criteria are needed in selecting substances for an endpoint rule to assure that the endpoint is a priority concern for the substance and not merely a data gap. CMA was also concerned that, as future substances are added to the endpoint rule, EPA provide a clear justification for and an opportunity to comment on the selection of substances for testing consideration.

EPA agrees that supportable criteria are needed for selection of substances as candidates for testing consideration, and that once EPA has determined it will require testing of certain substances — including any additions to this rule — the public must have the opportunity to comment on EPA's proposed findings in support of its testing decision. However, in the context of this rulemaking, CMA's concerns regarding the chemical selection process are addressed below.

In this rule, EPA has identified a class of substances (organic solvents) that demonstrate a high potential to be neurotoxic agents, as well as a high potential for exposure. EPA noted in the proposed rule that there are scientific data indicating that neurotoxicity is a concern for organic solvents as a class, including substances which have already been tested under TSCA section 4. While some of these scientific data may not specifically relate to the substances in this rule, taken as a whole, the data form the basis for evaluating the neurotoxicity of these solvents. This issue is outlined in the OTA report (Ref. 46). In addition, EPA believes that high production volume, substantial human exposure, substantial environmental release, and high volatility as outlined in the proposed rule are supportable criteria for selecting the group of solvents in this final rule. Therefore, EPA believes that there is adequate support for the selection of these substances for consideration for neurotoxicity endpoint testing.

CMA (Ref. 3) expressed concern that EPA relied too heavily on gross indicators of exposure in its chemical selection process for the proposed rule. These indicators included size of worker population, presence in consumer products, and total amount released into the environment. CMA believes that more relevant indicators include frequency and duration of workplace exposure, the use of protective equipment and process controls, concentrations at which exposure occurs, the levels at which the subject chemicals are present in consumer products, the likelihood of release during use of these products, and the frequency with which they are used. According to CMA, these exposure factors are important in the chemical selection process because studies indicate that neurotoxic effects are a function of dose levels and duration of exposure.

EPA believes that section 4 of TSCA does not require EPA to use CMA's approach in selecting, from the entire universe of substances currently in production, those substances which it wishes to consider for testing under section 4 of TSCA. In short, this level of exposure information is more appropriate in a determination to regulate the substances rather than a decision to require testing. In addition, the types of data suggested by CMA to evaluate exposure are not always available to EPA, nor is it always feasible for EPA to acquire them independently. A complete assessment of all exposure scenarios as suggested by CMA would be very resource intensive, and such costs are unjustified at this stage in the process. This type of exposure assessment is resource intensive since specific industries, processes, and work functions must be identified and analyzed for exposure potential; then monitoring studies must be designed, performed, and analyzed for each exposure scenario. Monitoring studies, additionally, must be conducted over a period of time that will allow some assessment of the variability in exposure concentrations and worker activities (e.g., maintenance activities, repair work), further adding to the cost of the assessment. Similarly, consumer exposure estimates require that many consumer products containing the substance in question be identified and the use patterns and frequency be identified, and expected exposure concentrations and routes estimated.

Although EPA agrees that more detailed exposure information is desirable and that neurotoxicity as well as most other toxic responses are dose/duration dependent, EPA believes that the strategy it used in selecting these substances for testing consideration is valid. Whenever there is a large number of workers involved in the manufacture and use of substances, it can readily be assumed that some exposure is likely and that smaller groups of the large population will have exposures higher than the average as a result of specific job functions, accidents, or poor work practices.

CMA also commented that EPA relied exclusively on exposure indicators, and did not take into account existing data on neurotoxicity in its chemical

selection process. EPA disagrees. EPA's chemical selection process for this endpoint rule had two stages. The first stage assessed potential exposure and release, while the second stage evaluated available neurotoxicity data. Clearly, EPA took into account existing health effects studies, since the original exposure and release assessment identified 14 substances for consideration in the proposed rule. Following evaluation of neurotoxicity data for the 14 substances, EPA determined that four of these substances were adequately tested for the types of tests required by this rule and these were removed from consideration.

CMA noted that existing 28- and 90-day tests may provide indicators of neurotoxicity or the absence of neurotoxic potential even if these studies do not follow current TSCA neurotoxicity guidelines. EPA agrees with CMA that data from subchronic studies can provide suggestive evidence that a substance is a neurotoxicant; however, the absence of an indication of neurotoxicity in a study not designed specifically to examine neurotoxicity provides at best only minimal indication of the neurotoxic potential of a compound. EPA does not believe that this level of information is sufficient to obviate the need to consider these substances for testing under TSCA section 4.

CMA noted that in the proposed rule EPA indicated that it was not going to rely on structure-activity relationships (SAR) in selecting candidates since existing information in this area is sparse for solvents. CMA concurred with a cautious use of SAR, but indicated that judicious use of SAR with exposure data and existing studies provide useful tools for prioritizing substances for neurotoxicity testing. Because of unique aspects of the nervous system, EPA believes that test design is critical in evaluating substances for neurotoxic potential. EPA fully understands the use of SAR as one of the tools available for prioritizing substances for testing. EPA chose not to use SAR data for selecting substances for testing consideration for this rule because the information on organic solvents was insufficient for a valid SAR analysis.

CMA (Ref. 3) expressed concern with how the endpoint rule will relate to other testing schemes such as the Organization for Economic Cooperation and Development (OECD) Screening Information Data Set (SIDS) battery, and to previous evaluations of testing needs under TSCA. CMA believes that when exposure and production are the main reasons for requiring testing of a substance or class of substances, the first step in testing should be the conduct of a SIDS battery which would allow determination of the most appropriate test in a more focused endpoint rule.

EPA believes that there are a number of approaches to selecting and testing substances. However, discussion of these options is more appropriately addressed in the context of EPA's ongoing review of the role screening level testing and endpoint testing should play in the section 4 test program as part of its development of an overall testing strategy. One possible approach is use of the SIDS battery or other screening studies as a first examination of a substance followed by use of the data generated to select additional testing. The first SIDS data which became available in late 1992 will be important in this evaluation. It should be noted, however, that the SIDS battery does not explicitly address neurotoxicity and thus may not be useful to determine the need for such studies.

CMA (Ref. 3) and Monsanto (Ref. 17) noted that some of the substances in the proposed rule have had previous TSCA testing activity; in particular, the evaluation of methyl isobutyl ketone (MIBK) was reported to Congress as complete under section 4. CMA and Monsanto requested that EPA provide a rationale for reopening rulemaking on MIBK in the absence of additional scientific data. EPA notes that MIBK testing was complete only in regards to the previously agreed upon testing program. EPA, however, had not evaluated the need for neurotoxicity testing at the time industry proposed its testing program in 1982. This evaluation was not done because EPA did not have guidelines for neurotoxicity testing should it have determined that neurotoxicity testing was necessary. More importantly, as noted under Unit II.J of this preamble, EPA believes that evaluation of testing needs for a chemical is a progressive process which can be influenced by emerging scientific and social concerns, therefore, it is unlikely that EPA could say that complete data are available on any substance.

CMA (Ref. 3) noted that because the endpoint rule was not initiated by designation from the ITC, EPA did not have the advantage of the exposure and health effects studies that would have been submitted under TSCA sections 8(a) and 8(d). CMA suggested that EPA should publish lists of substances to be included in endpoint rules prior to committing resources to rulemaking in order to obtain any unpublished data. Similarly, Rohm and Haas (Ref. 18) stated that a section 8(d) rule is the most effective means of obtaining unpublished data, particularly from sources that may not be aware of the need for data because they are not manufacturers or importers of the substance. Furthermore, Rohm and Haas believes a modified section 8(d) rule, which requires only submission of data related to the endpoint and does not have a 10-year reporting requirement, would be effective in providing EPA with the data necessary to assure that duplicative testing is not required.

EPA agrees with the manufacturers that review of all reasonably available information, including unpublished studies, is necessary prior to promulgating a final rule. Although publishing a section 8(d) rule would result in submission of unpublished studies, publication of a proposed test rule requesting comments also results in the submission of unpublished studies and other relevant information. As indicated during the public meeting and by the submission of studies during the public comment period, publication of the proposed multi-substance neurotoxicity testing rule was effective in obtaining unpublished studies. EPA has the opportunity to review these studies and make any appropriate changes in the final rule. EPA also believes that the individuals who have data which would be submitted under section 8(d) are likely to be the same as those impacted by the rule, and thus they would submit any data that would meet the data needs of the rule during the comment period. In addition, since a section 8(d) rule was not promulgated, the need to submit data disappears after the final rule is promulgated, which addresses the concerns expressed by Rohm and Haas regarding the 10-year reporting requirement (Ref. 18).

*B. Section 4(a)(1)(B) Finding*

In addition to comments on general testing policy issues, EPA received comments regarding its proposed findings in support of the neurotoxicity testing required by this rule. These comments are addressed below.

CMA (Ref. 3) commented that EPA should reexamine its proposed section 4(a)(1)(B) finding ("B" finding) for the 10 substances for which findings were made in the proposed rule. It believes that EPA should first finalize its policy for exposure-based findings ("B" findings) proposed in response to the Fifth Circuit Court of Appeals remand in the cumene case before taking final action in this rulemaking; second, avoid the use of gross indicators of human exposure to solvents, namely the

National Occupational Exposure Survey (NOES), to estimate worker exposure, and consumer usage and product surveys to estimate consumer exposure, in support of its findings for requiring testing of these solvents; and finally, avoid the use of chemical release data as contained in the Toxics Release Inventory (TRI) because, CMA contends, it is not sufficient to justify entry of a compound into the environment. CMA's Panels (Refs. 4, 6, 7 and 9), Dow (Ref. 14), Du Pont (Ref. 15), DEMTG (Ref. 13), BASF (Ref. 2), Kodak (Ref. 16), and Monsanto (Ref. 17) also commented that a "B" finding for either individual organic solvents or the group as a whole is not justified. Public comments which are specific to the individual members of this group will be addressed below on a substance by substance basis, while comments and responses appropriate to all members of this group follow.

1. *Policy for exposure-based findings.* CMA (Ref. 3), CMA's Oxo Process Panel (Ref. 9), and Monsanto (Ref. 17) commented that EPA should first finalize its policy for exposure-based findings ("B" findings) before taking final action in this rulemaking. (The "B" policy was proposed in the **Federal Register** of July 15, 1991 (56 FR 32294)). They maintain that formalization of this policy is required by the Fifth Circuit Court of Appeals in the cumene case and will aid in future rules enacted under TSCA.

The final "B" policy was issued on May 14, 1993 (58 FR 28736). However, EPA does not agree that issuance of this policy was mandated before final action could be taken in this rule. The Fifth Circuit Court of Appeals in *CMA vs. EPA* (Ref. 26 at p. 359) 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. EPA has fully articulated its decision-making rationale in this rule and in the proposed multi-substance rule for the testing of 10 organic solvents for neurotoxicity (56 FR 9105, March 4, 1991). EPA believes that this rule and the proposed rule clearly articulate the criteria it used in making a finding under TSCA section 4(a)(1)(B)(i). Because EPA considers this rule to be legally sufficient, EPA did not reopen the comment period for this rule when the "B" policy was proposed on July 15, 1991 (56 FR 32294). Despite the independence of this rule from the "B" policy, the 4(a)(1)(B) findings in this rule meet the criteria of the "B" policy.

2. *Purposes of TSCA section 4(a)(1)(B).* In addressing EPA's findings under section 4(a)(1)(B), CMA and other commenters state that EPA has inadequately considered all of the factors relevant to testing decisions under section 4(a)(1)(B). CMA (Ref. 3, pp. 18–19) contends that:

> EPA's basic inquiry should be whether, taking into account known toxicity data for other chemicals, exposure is sufficiently great to present a significant and widespread risk if testing is positive for the endpoint in question.

Furthermore, if EPA cannot make such a determination:

> * * * testing would not be required to determine whether the substance presents an "unreasonable risk of injury" under TSCA section 6 because there would be no need to control its manufacture or use even if test results are positive.

EPA believes that CMA's comments reflect an inaccurate understanding of the role of chemical testing conducted under the authority of section 4 within TSCA's statutory framework and purposes. TSCA was enacted to ensure that, given the exposure of humans and the environment to a large number of chemical substances and mixtures with potentially harmful effects, there would be effective regulation of commerce in such substances (TSCA section 2(a), 15 U.S.C. 2601(a)). Since the potential effects of many chemical substances in commerce are not known, the policy provisions of TSCA reflect Congress' intent that:

> * * * 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 [substances]. (TSCA section 2(b)(1), 15 U.S.C. 2601(b)(1))

Section 4 of TSCA provides EPA the authority to require such testing. In contrast, section 6 of TSCA provides EPA the authority to regulate these chemical substances once their effects are more adequately characterized, i.e., once the Administrator makes a finding that a chemical substance "presents or will present an unreasonable risk of injury to health or the environment." 15 U.S.C. 2605.

In effect, CMA argues that EPA must make a finding that a chemical substance would pose an unreasonable risk of injury at some hypothetical level of toxicity in order to require testing under section 4(a)(1)(B) of TSCA. To do this, CMA envisions EPA doing a formal exposure assessment. This approach was explicitly rejected by the court in *CMA v. EPA* (Ref. 26 at 354–355), which stated:

> If the EPA properly concludes [under sections 4(a)(1)(B)(ii) and (iii)] that the existing data and experience do not suffice as a basis for it to reasonably predict that there will be no health or environmental injury from the manufacturing (or processing, etc.) of the chemical, then affirmative evidence and findings of risk of injury to health or the environment at hypothetical toxicity levels under section 4(a)(1)(B)(i) are not necessary to provide a nexus between requiring testing under section 4(a)(1)(B) and congressional concern for health and the environment.

Furthermore, CMA's approach would essentially have EPA making the same finding for a section 4 rule as for a section 6 rule — a requirement that the courts have repeatedly rejected. "[T]he level of certainty of risk warranting a section 4 test rule is lower than that warranting a section 6 regulatory rule" under TSCA. *CMA v. U.S. EPA* (Ref. 58 at 979). See also *Ausimont U.S.A. Inc. v. EPA* (Ref. 66 at 95–98), (EPA's burden is to demonstrate not fact, but doubt and uncertainty, in order to require testing under section 4); and *CMA v. U.S. EPA* (Ref. 58 at 984–988) (EPA need not gather information to make a reasonable prediction or determination of risk before issuing a test rule).

EPA now turns to addressing comments regarding the individual components of its findings under section 4(a)(1)(B) of TSCA in support of the testing requirements.

3. *Substantial production.* EPA indicated in the proposed rule that all 10 of the substances in the proposal are produced in quantities exceeding 12 million pounds annually (56 FR 9107, March 4, 1991). Production data reported for substances listed in the TSCA inventory (presently over 70,000 entries) indicate that only 4.8 percent of the listed substances have production volumes over 10 million pounds. Clearly, if the 10 members of this group of solvents are produced in quantities greater than 95 percent of the other compounds listed in the TSCA inventory, EPA believes it is reasonably and unambiguously justified in making a section 4(a)(1)(B)(i) finding based on substantial production. It should be noted that the "B" policy specifies that 1 million pounds be established as the substantial production threshold. The production volumes of all 10 substances in this rule are consistent with, and indeed, well above the threshold.

4. *Substantial human exposure.* CMA and its Panels (Refs. 3, 4, 6, 7, and 9), DEMTG (Ref.13), Dupont (Ref. 15), and Monsanto (Ref. 17) questioned the use of gross indicators of worker exposure to solvents, namely the size of the affected workplace population and the presence of these solvents in consumer products, as EPA's basis for making its TSCA section 4(a)(1)(B)(i) findings in support of the testing requirements. The

commenters maintained that the findings should place a greater emphasis on intensity, duration, and frequency of exposure in determining neurotoxic potential. CMA and the manufacturers maintained that a large number of exposed workers in itself does not constitute substantial exposure to support a section 4(a)(1)(B) finding.

EPA believes that the exposure parameters of intensity, duration and frequency are more relevant to a finding of "significant" exposure, than to a finding of "substantial" exposure. Although EPA did not make a finding of "significant" exposure, it, nevertheless, considered chemical/physical properties which would contribute to significant exposure. EPA articulated in the proposed rule that available data on the vapor pressure of these substances was of major concern to EPA in making its findings because inhalation is a major route of exposure for volatile organic solvents (56 FR 9111, March 4, 1991). The rule also stated that volatile organic solvents are typically small (low molecular weight) molecules which may permit a second major route of exposure, skin penetration. Therefore, EPA believes that it has explained, albeit generally, that the physical and chemical properties and uses of these solvents contribute to human exposure.

EPA also believes that it clearly articulated in the proposed rule its rationale for interpreting the term "substantial human exposure" to refer to "widespread human exposure" or "exposure to a large number of people" within the meaning of TSCA section 4(a)(1)(B)(i)(II). (56 FR 9110–9111, March 4, 1991). In the proposed rule, EPA found, using low-range estimates, that 172,000 workers and 3.7 million consumers are potentially exposed to each of the organic solvents subject to this test rule. High-range estimates indicate that as many as 1.5 million workers and 112 million consumers may be exposed to these substances (56 FR 9107, March 4, 1991). For these reasons, EPA believes that it has met its burden under TSCA section 4(a)(1)(B)(i)(II) to demonstrate that there is or may be substantial human exposure to each of the organic solvents subject to this rule.

CMA contends that both the National Occupational Exposure Survey (NOES) and EPA's own consumer product survey, on which a finding of substantial human exposure was based, are flawed. This position was shared by CMA's Panels (Refs. 4, 6, 7 and 9), Dow (Ref. 14), DuPont (Ref. 15), DEMTG (Ref. 13), AIHC (Ref. 1), BASF (Ref. 2), Kodak (Ref. 16), and Monsanto (Ref. 17). CMA's Acetone Panel (Ref. 4) commented that EPA's consumer usage and product surveys greatly overestimate both the number of products which contain acetone and human exposure to it. This position was also held by CMA's Ketones Panel (Ref. 7) for methyl isobutyl ketone, and by CMA (Ref. 3) for all 10 substances discussed in the proposed rule.

EPA does not agree that its reliance on the NOES and consumer usage and product surveys for its analysis of human exposure to the organic solvents was unreasonable. The NOES, conducted in 1981 to 1983, was based on field surveys of 4,490 facilities that served as a statistical sample of virtually all workplace environments, except mining and agriculture, in the United States where 8 or more persons are employed. Based on these samples, the numbers of persons nationwide who are potentially exposed to different substances were estimated. Substances in trade name products were also included. No information was obtained on actual or potential concentrations of substances at potential worker exposure sites (Ref. 61). Therefore, the NOES data is not intended to be an exact determination of worker exposure to a chemical compound in a quantitative sense; rather, it is intended as an estimate of potential human exposure to the test substances in the workplace. This information is a valid basis for, and is relevant to a determination that testing of these substances under TSCA section 4 is warranted. While EPA has acknowledged that there may be sampling errors in the NOES survey, EPA disagrees with the implication that the survey is of little value in determining occupational exposure relative to other substances used in commerce for purposes of TSCA section 4(a)(1)(B)(i). According to the NOES survey, at least 172,000 and as many as 1,510,107 workers are exposed to each of the organic solvents (56 FR 9107, March 4, 1991) subject to this rule. Although the exact numerical value of NOES estimates may be questioned, EPA believes that the range of potential exposures is a sufficient basis for concern under TSCA section 4(a)(1)(B)(i). In addition, the potential for occupational exposure to these solvents is consistent with EPA's "B" policy which specifies that the threshold criterion for substantial worker exposure be 1,000 workers (58 FR 28736, May 14, 1993). In fact, this substantial worker exposure threshold is clearly exceeded by all of the solvents subject to this test rule. Therefore, EPA concludes that there is, or may be, substantial worker exposure to these compounds.

In the proposed rule, EPA indicated that each of the solvents was present in from 1 to 51 consumer products, and that their formulations had widespread use in industry (56 FR 9107, March 4, 1991). EPA also notes that human exposure estimates from its consumer product survey, which incorporated a degree of uncertainty as to the range of values reported in the estimates, indicated that 3.7 to 112 million consumers were potentially exposed to each of the individual solvents (Id.). These estimates also clearly exceed EPA's threshold of 10,000 consumers as its criterion for a substantial human exposure finding (58 FR 28736, May 14, 1993). From data contained in their own submissions, manufacturers (Refs. 9c, 9h and 10b) and CMA (Refs. 7f, 7i and 7j) have indicated that the solvents contained in the proposed rule are widely present in commercial products. Also, based on the solvents' presence in numerous chemical formulations, CMA (Ref. 3) commented that compliance with the export notification requirement under section 12(b) of TSCA would be burdensome for thousands of formulators. This comment by CMA indicates that the solvents are present in products produced by thousands of formulators and that EPA's estimates of consumer exposure have a sound basis.

EPA concludes that both worker and consumer exposure, as described by NOES data and the consumer product usage survey respectively, are consistent with a section 4(a)(1)(B)(i)(II) finding by indicating that there is, or may be, substantial human exposure. Both worker and consumer exposure estimates far exceed the "B" finding threshold criteria. EPA believes that potential exposure to as many as 1.5 million workers and 112 million consumers (56 FR 9107, March 4, 1991), which, as indicated by the manufacturers own comments, may be underestimated, fulfills the spirit and intent of TSCA section 4(a)(1)(B).

5. *Substantial environmental release.* The CMA Panels (Refs. 4, 6, 7 and 9) commented that Toxics Release Inventory (TRI) release data are not sufficient to establish if a compound "enters the environment" within the meaning of TSCA section 4. While they agreed with the quantities of solvents cited as released to the atmosphere, they argued that atmospheric release of a substance does not in itself constitute "entry" into the environment as required by section 4(a)(1)(B). They supported this argument with atmospheric modeling results which indicated that fenceline concentrations

of the solvents are below occupational exposure guidelines (Refs. 4 and 7). CMA also commented that EPA should look at other factors, such as environmental fate and persistence, rather than release and monitoring data alone (Ref. 9).

The TRI was mandated by the Emergency Planning and Community Right-to-Know Act (EPCRA) enacted by Congress in October 1986 and requires certain manufacturers, processors, and users to report to EPA and the States the amounts of approximately 300 chemicals and categories of chemical compounds that they release directly to air, water, or land, or that they transfer to off-site facilities. These data must be compiled into an annual inventory available to the public in a computerized database. While not all industrial producers, importers, processors, and users are required to report (e.g., minimum volume production/use requirements), the inventory is a valuable resource in assessing releases (Ref. 65).

In the proposed rule, EPA made substantial release findings for four of the solvents, acetone, 1-butanol, 2-ethoxyethanol, and methyl isobutyl ketone, each of which were found to have been released into the environment in quantities exceeding 1 million pounds per year (56 FR 9108 and 9111, March 4, 1991). The proposed rule also indicated that 9 of the solvents have been detected in air, drinking water, disposal sites, effluent, ground water, and surface water samples, and points out that 3 of the 4 solvents for which a substantial release finding was made were in the top 25 TRI chemicals emitted into the air in 1987 (56 FR 9108, March 4, 1991).

EPA does not agree with the CMA Panels that use of TRI environmental release information to support a finding under TSCA section 4 is not appropriate, or that large releases of a compound do not necessarily constitute entry into the environment under section 4(a)(1)(B)(i)(I). Under TSCA section 4(a)(1)(B)(i), a finding can be made if, given substantial production, a substance enters, or may reasonably be anticipated to enter, the environment in substantial quantities (Ref. 27). EPA believes that it is reasonable to interpret the phrase "enters the environment in substantial quantities" to refer to large quantities of releases of a chemical into the environment. CMA's arguments notwithstanding, EPA believes that the statutory language and legislative history, which are silent as to consideration of quantities released versus the concentrations which result from these releases in making the determination that a chemical "enters the environment", do not compel EPA to adopt a different (i.e., CMA's) interpretation of TSCA section 4(a)(1)(B)(i)(I):

> In these circumstances, Congress is deemed to have implicitly delegated to the EPA the power to define or interpret "substantial," and we will sustain the agency's interpretation as long as it is rational and consistent with the statutory scheme and the legislative history.

*CMA v. EPA* (Ref. 26 at 354). The Court also stated that EPA "has considerable latitude in defining and interpreting 'substantial' as it is used in clauses (I) and (II) of section 4(a)(1)(B)(i)" and that EPA is "not obliged to adopt or take into account a specific criterion (such as, for example only, persistence after entry)" when interpreting and making a finding under section 4 (Ref. 26 at 359 and 360). As explained in the proposed rule (56 FR 9110–9111, March 4, 1991), EPA believes that substances that are released into the environment in millions of pounds annually must be considered to "enter the environment in substantial quantities" within the meaning of TSCA section 4(a)(1)(B)(i)(I). Furthermore, this is consistent with the recently published "B" policy which specifies an environmental release threshold of 1 million pounds aggregate annual release (58 FR 28736, May 14, 1993). In fact, the release data and exposure estimates found in this rule far exceed the thresholds for making "B" findings that EPA articulated in the proposed rule and specified in the "B" policy. By reasonable interpretation of TSCA section 4(a)(1)(B)(i), EPA believes these substances meet the definition of potential substantial release and/or exposure.

One CMA Panel (Ref. 9) commented that EPA should consider environmental fate and persistence when determining the extent to which a substance enters the environment, while other CMA Panels challenged "entry into the environment" by providing fenceline concentrations of solvents predicted by air dispersion modeling studies at several industrial sites (Refs. 4 and 7). While EPA agrees that many of the factors CMA has urged the Agency to consider when making its section 4(a)(1)(B)(i)(I) finding are useful in exposure assessment, EPA does not believe that it is required to consider them in each and every case. However, it should be noted that where sufficient fate and toxicity data are available, EPA analyzes the data to determine whether the data are adequate to reasonably determine or predict the effects of the substance and whether further testing is necessary. Consequently, EPA always welcomes exposure information of the type CMA urges it to consider.

EPA did consider air dispersion modeling studies submitted by CMA which confirmed that millions of pounds of solvents were released annually. CMA contended, however, that these studies demonstrate that the solvents do not "enter the environment in substantial quantities" because predicted short-term and annual average concentrations of the solvents would be at less than the allowable occupational exposure limits. While EPA believes there is merit in utilizing data on environmental persistence and atmospheric modeling to estimate human exposure, EPA disagrees with the contention that, under section 4(a)(1)(B), a solvent will not "enter the environment" when there are over a million pounds of aggregate annual releases of the substance based solely on modeling studies which point only to a low average fenceline concentration. These fenceline concentrations are typically modeled for ground level and they give no indication of what levels may exist at higher altitudes. Moreover, TSCA section 4(a)(1)(B) considers quantities released and not the concentration which results from these releases.

EPA also notes that consistency with the occupational exposure guidelines does not guarantee that all issues related to exposure to the substance have been resolved. These guidelines were developed to protect healthy workers exposed for 8 hours/day, 5 days/week, and are not necessarily protective of the general population, which contains both the very young and very old as well as individuals with varying health problems and sensitivities, exposed continually for 24 hours per day. Therefore, EPA believes the modeling studies submitted by the manufacturers do not negate a substantial release finding.

Other studies submitted during the comment period documented that some of the solvents are used in coatings, adhesives, nail polish, and printing inks (Refs. 7f, 7i, 8c and 9a). For products of this type which dry or cure over time, EPA believes that volatilization of the solvent to the atmosphere is often an intended outcome of its use. For solvents such as *n*-butyl acetate, of which 157,824,450 pounds are used in coatings (56 FR 9106, March 4, 1991), these types of releases, although unreportable under EPCRA, may make a considerable contribution to total environmental releases. In the case of *n*-butyl acetate, EPA believes it may have underestimated environmental release.

In conclusion, EPA does not agree that a TSCA section 4(a)(1)(B)(i)(I) finding is unjustified, or that release data does not qualify for a finding of entry into the environment. EPA does not believe that the arguments provided through public comment refute the data or rationale provided in this rule or the proposed rule in support of its "B" finding. In addition, EPA believes that it has rationally explained its decision in promulgating this rule, and therefore, has adhered to the directives of the Fifth Circuit Court of Appeals in its cumene decision.

*C. TSCA Section 4(a)(1)(A) Finding*

CMA (Ref. 3) commented that EPA failed to conduct an adequate exposure analysis to support a section 4(a)(1)(A) finding under TSCA. According to CMA, this analysis needs to relate exposure scenarios to toxicologic concerns by identifying the duration, level, and scope of human exposure, and determining whether an unreasonable risk would occur under these exposure conditions. CMA contends this analysis is needed to meet the mandates of a D.C. Circuit Court of Appeals decision in *CMA v. EPA* (Ref. 58)("EHA case") that the Agency needs to have a more-than-theoretical basis for determining that [the substance] may present an unreasonable risk before it can require testing under TSCA section 4(a)(1)(A). CMA's Panels (Refs. 4, 7 and 9) and Du Pont (Ref. 15) provided similar comments to those of CMA along with substance- specific comments on the section 4(a)(1)(A) findings which will be addressed later in this response.

EPA believes that it has clearly demonstrated in this rule that it has a more-than-theoretical basis for determining that exposure to these solvents may present an unreasonable risk. The high release to the environment, large production, presence in consumer products, and relatively high vapor pressure, taken together, provide the basis for a finding of potential human exposure in support of the testing required by this rule. Furthermore, EPA believes the type of data and analysis that the commenters would like EPA to perform before requiring testing is not generally available and very resource intensive to generate, and is far more justified when EPA is considering regulation of a substance under section 6 of TSCA rather than testing under section 4. In addition, EPA provided monitoring data from various media for nine of the solvents; four of the solvents, acetone, diethyl ether, ethyl acetate, and isobutyl alcohol, were detected in drinking water (56 FR 9108, March 4, 1991). EPA further contends that for the substances for which section 4(a)(1)(A) findings were made, although the (primarily acute) data discussed in the proposed rule show that these solvents are potential neurotoxins, these studies are inadequate to estimate the risk from long- term, low-level exposure. Such data that are suggestive of an adverse effect are adequate to support a TSCA section 4(a)(1)(A) "may present an unreasonable risk" finding.

According to the D.C. Circuit in the EHA case, EPA need not demonstrate fact, but rather "doubt and uncertainty," in order to support a "may present an unreasonable risk" finding under TSCA section 4(a)(1)(A) (Ref. 58 at 992). In light of the exposure and hazard information it has presented and considered, EPA believes that it has rationally articulated its basis for making a section 4(a)(1)(A) finding in support of the testing required by this rule.

In Units II.E through K of this preamble, which discuss specific substance issues, additional studies submitted during the comment period are reviewed to determine if there now are adequate data to define the potential risk from exposure.

*D. EPA's Data Analysis*

CMA (Ref. 3) commented that testing should not be required because risk assessment and risk management decisions can be made with existing data. CMA contended that it is unreasonable for EPA to rely on the current TSCA neurotoxicity test guidelines, which are of recent vintage and have not yet been validated as a standard for determining the quality of existing studies, as the basis for finding existing studies insufficient. CMA further maintained that although EPA used the TSCA neurotoxicity guidelines to determine if a study is inadequate to assess a substance's neurotoxic effects, EPA used existing studies that did not follow the guidelines to support concerns for the neurotoxic effects of chemicals in making a section 4(a)(1)(A) finding. CMA commented that if EPA is going to use the TSCA guidelines as a measure of adequacy, EPA should use the guidelines in all aspects of its testing decisions and not use studies that do not meet the guidelines to support 4(a)(1)(A) findings. AIHC (Ref. 1) and Dow (Ref. 14) submitted similar comments. CMA's Ketone Panel (Ref. 7) endorsed AIHC's comments.

EPA disagrees with CMA. Preliminary data which indicate concerns for hazards posed by a substance (or a class of substances) are exactly the type of information EPA should use to make its section 4(a)(1)(A) "may present an unreasonable risk" finding under TSCA. CMA's comment suggests that EPA should never use such data (and consequently, be unable to require testing), or alternatively, that EPA use such "insufficient data" as the basis for evaluating neurotoxic potential and making regulatory decisions. Neither is a reasonable interpretation of TSCA. TSCA section 4 was intended, and should be used to develop data through testing. These data may then be used to make regulatory decisions under TSCA section 6.

EPA agrees that if there are adequate neurotoxicity data for risk assessment and risk management, then additional testing should not be required. It is essential, however, that the data are adequate for the intended purpose. Some risk assessments have been performed using less than fully adequate data; however, even though a risk assessment is then available, this does not preclude the potential need for additional testing if the uncertainty in the risk assessment is unacceptably large for risk management decisions. EPA used scientific judgement in addition to the TSCA guidelines in evaluating existing data, utilizing a weight-of-evidence approach in addition to an individual study evaluation. Thus, it is sometimes possible that a group of studies, each of which would individually be judged inadequate, would, when considered together, yield enough information to characterize the toxicity of a substance. Existing data were reviewed and considered adequate for 4 of the 14 substances considered in developing the proposed rule and a decision was made not to require testing of these 4 (ethanol, methyl ethyl ketone, toluene, and xylenes).

Comments on existing data related to specific substances are discussed in Units II.E, II.F, and II.H through II.K of this preamble.

*E. Tetrahydrofuran*

BASF (Ref. 2) commented that tetrahydrofuran (THF) exposure needs to be more accurately evaluated for workers and consumers in terms of level and duration of exposure. BASF maintained that there is some evidence that occupational exposure is much less than applicable exposure guidelines and that consumer exposure will be limited by both the frequency of use of consumer products containing THF and the concentration of the solvent therein. BASF also noted that the exposure to the general public through environmental releases via effluent and

surface waters will not be significant as monitoring data indicate that current THF concentrations are much less than the Maximum Allowable Concentration (M.A.C.) of water class I used in the production of drinking water.

While EPA agrees with BASF that there are some uncertainties in the estimates of consumer exposure to this and other solvents, these uncertainties were allowed for by providing a range of consumer exposure, as noted in Unit II.B.4 of this preamble. EPA also believes the level of uncertainty does not eliminate the basis for the Agency's finding of potential substantial human exposure to THF. Furthermore, EPA believes that NOES data are a valid indication of potential substantial worker exposure to a substance. EPA notes that NOES data for THF exceed the 1,000 worker threshold specified in the "B" policy (58 FR 28736, May 14, 1993).

BASF contends that the environmental fate and persistence of THF should be considered when estimating human exposure for TSCA section 4(a)(1)(B) purposes. In essence, BASF would require EPA to undertake a risk assessment before making its finding under TSCA section 4(a)(1)(B). However, as was recognized by both the court in *CMA v. EPA* (Ref. 26 at 347) and by CMA (Ref. 3 at 17), section 4(a)(1)(B) authorizes EPA to require testing even without a finding that a substance may present an unreasonable risk of health or environmental injury. Furthermore, the environmental fate and persistence analysis urged by BASF is not relevant for determining occupational exposure where exposure will occur due to a definable release source, typically in close proximity to the worker such that degradative processes will not be operative and significant. For these reasons, EPA believes that potential substantial occupational and consumer exposure to THF evidenced by the NOES and consumer usage data is sufficient to support a TSCA section 4(a)(1)(B)(i)(II) finding for THF.

Concerning the relationship between potential human exposure and the existing regulatory standards for THF, EPA notes that the standards for THF have been established in the absence of any neurotoxicity data for this substance and may not be protective if neurotoxicity proves to be a sensitive toxicologic endpoint for THF. As BASF noted, there are no neurotoxicity test data available on THF; therefore EPA believes testing is necessary to develop such data.

BASF cited one acute study by Katahira (Ref. 2a), two subchronic studies by Katahira (Ref. 2b) and Chhabra et al. (Ref. 2c), and one developmental toxicity study by Mast et al. (Ref. 2d), which BASF believed provided some indication of the neurotoxic potential of THF. In addition, BASF noted that there is currently a 2-year study in mice and rats in progress under the National Toxicology Program (NTP) which may provide a good indication of neurotoxic potential.

EPA obtained and reviewed the cited studies (Ref. 50). Although the subchronic study by Katahira et al. (Ref. 2b) made no mention of central nervous system (CNS) effects, the other studies (Refs. 2a, 2c and 2d) reported some CNS effects despite the design of these studies which could detect only gross signs of neurotoxicity. The 2-year study underway in mice and rats by NTP is also not designed to permit sensitive measures of neurotoxicity and would not satisfy EPA's neurotoxicity data needs for THF. EPA believes that the detection of some CNS effects by these studies supports the need for the additional neurotoxicity testing specified in this rule; however, EPA does not believe that the available studies, taken as a whole, are sufficient for risk assessment purposes.

*F. Acetone*

CMA's Acetone Panel (Ref. 4) commented that EPA has not justified its finding that releases to the environment of acetone or human exposure to acetone are substantial within the meaning of TSCA section 4(a)(1)(B). The Panel asserted that a finding of substantial environmental release based on TRI data alone is not sufficient. They noted that EPA has not analyzed the likely level of human exposure from expected airborne concentrations of acetone beyond sites' boundaries, nor considered levels, frequency, or duration of consumer exposures. The Panel submitted airborne dispersion models to support this point. The Panel also contended that EPA's consumer usage survey does not characterize the nature and extent of exposure to acetone from the use of products in which it is contained, and that the data in the NOES survey do not provide a reliable basis for estimating the number of workers exposed to a substance.

EPA does not agree with CMA's Acetone Panel that environmental releases of acetone are not substantial within the meaning of TSCA section 4(a)(1)(B). Section 4(a)(1)(B) of TSCA indicates that a finding can be made if a compound enters, or may reasonably be anticipated to enter, the environment in substantial quantities. The statutory language makes no mention of concentrations which may result as a consequence of these releases. In the proposed rule, annual release of aceton was listed as 195 million pounds for 1987 (56 FR 9108, March 4, 1991). According to TRI data for 1989, 205,019,698 pounds of acetone were released to the environment, of which 199,209,247 pounds were released to air, 1,020,255 pounds were discharged to water, and 4,526,483 pounds were injected underground (Ref. 29). For the reasons set forth in the proposed rule (56 FR 9110–9111, March 4, 1991) and in Unit II.B.5 of this preamble, EPA believes that annual releases of over 19 million pounds of acetone to the environment are "substantial" within the meaning of TSCA section 4(a)(1)(B)(i). In addition, as indicated i the proposed rule, acetone is one of th top 25 chemicals emitted to the air according to the TRI data.

The computer modeling studies submitted by the manufacturers indica that fenceline atmospheric concentrations of acetone were below established occupational exposure guidelines. However, this information does not negate the fact that substantia quantities of acetone are released into the environment. Although the modeling studies may predict that 24-hour concentrations are less than established exposure guidelines, these guidelines are based on an 8-hour wo day and are not meant to protect from continuous 24-hour exposure. Moreover, since the guidelines are bas upon a limited set of test data, they m be inadequate to protect all workers o the general population from the potential health effects of chronic environmental exposure to acetone. E believes that releases of acetone as hig as 37,870 pounds per day, a value utilized in one of the modeling studie (Ref. 4, Appendix C, Hoechst Celenese Narrows, Virginia), released every day represents an emission resulting in substantial entry into the environment for just that single facility. EPA notes that this facility alone exceeds the threshold for substantial environment release of 1 million pounds annually ( FR 28736, May 14, 1993). EPA concludes that TRI release data and th individual site emission data submitte by the Panel both support an environmental release finding under section 4(a)(1)(B)(i)(I) of TSCA.

EPA does not agree with the Panel's comments that NOES data are an inadequate indication of potential occupational exposure to acetone for reasons presented in Units II.A and II.B.4 of this preamble.

The Panel also indicated that EPA's consumer exposure estimates, based on the presence of acetone in 51 consumer products (56 FR 9107, March 4, 1991), do not consider the nature and extent of exposure to acetone from use of the products. EPA used a consumer product usage survey to estimate consumer exposure to acetone, supporting its finding of substantial human exposure" under section 4(a)(1)(B)(i)(II) with 3.7 to 112 million consumers potentially exposed per product. While EPA does not believe that it is required to consider all of the factors cited by the Panel in making its findings under section 4(a)(1)(B)(i)(II), EPA did consider the product use characteristics and the physical/chemical properties of acetone. EPA indicated in the proposed rule (56 FR 9107, March 4, 1991) that acetone has a high vapor pressure (231.5 mmHg), which along with its small, nonpolar structure, will facilitate vaporization and absorption. In addition, EPA discussed how the use of solvent-containing products by consumers often involves close contact with the product, which increases exposure and the likelihood of absorption (Id.). EPA also identified 51 product types (including spot remover, furniture polish, engine cleaner, paint thinner, spray shoe polish) which contained 0.2 to 100 percent acetone (Ref. 62). The use of such products would obviously require the person to be in close contact with the solvent. As explained in Units II.A and II.B.4 of this preamble, EPA believes that extensive analysis of exposure parameters is very resource intensive and considers such an effort more relevant when making a finding for "significant" exposure, or when conducting a comprehensive risk assessment, in which an evaluation of the nature and extent of exposure to acetone would be done with the many products which contain it, for purposes of considering regulatory action, i.e., under TSCA section 6.

CMA's Acetone Panel (Ref. 4) commented that there are sufficient data on acetone to reasonably predict the potential for neurotoxicity. These data, the Panel contended, are of the same extent and quality as data EPA found sufficient to exclude other solvents from this proposed rule. In addition, the Panel stated that existing studies on isopropanol, a chemical which rapidly metabolizes to acetone, provide sufficient evidence that acetone does not cause adverse irreversible effects to the nervous system. The Panel recommended that EPA review all of the available data before finalizing the proposed rule and provided the following list of studies for EPA's review: Bruckner and Peterson (Ref. 5a), De Ceaurriz et al. (Ref. 5b), Dietz (Ref. 4a), Gamis and Wasserman (Ref. 5d), Garcia et al. (Ref. 4b), Geller et al. (Ref. 4c), Geller et al. (Ref. 4d), Goldberg et al. (Ref. 4e), Ladefoged and Perbellini (Ref. 5f), Ladefoged et al. (Ref. 4f) Matsushita et al. (Ref. 4g), Mayhew and Morrow (Ref. 4h), Misumi and Nagano (Ref. 5g), Spencer et al. (Ref. 4i), Seeber et al. (Refs. 68a and 68b), and Stewart et al. (Ref. 68c).

Although EPA agrees that isopropanol metabolizes to acetone, a pharmacokinetics study (Ref. 5h) submitted by CMA showed that unchanged isopropanol remains in the blood for up to 9 hours after the exposure. EPA therefore does not agree that neurotoxicity studies on isopropanol should be used instead of appropriate studies conducted with acetone, because effects observed during the first 9 hours could be due to isopropanol and not acetone. Some unknowns that also preclude the use of isopropanol studies include a lack of clear knowledge of the tissue concentration of acetone following administration of isopropanol, specifically in potential target tissues, and the potential for any metabolic interaction between acetone and isopropanol which may affect the metabolism and toxicity of acetone. EPA believes that there is a potential for extensive exposure to acetone, and thus to be assured of protecting human health, it is necessary to test acetone itself.

EPA reviewed the additional studies (Refs. 43, 4a through 4i, 5a through 5g, 68a through 68c) provided by the Panel and identified a number of problems which made the studies inadequate to satisfy EPA's neurotoxicity data needs for acetone (Refs. 50, 51 and 69). The specific problems are listed in Table 1, Unit III.A.5 of this preamble, and generally include insufficient test duration, insufficient description of methods and results, inadequate methods, inconclusive results, and the evaluation of an insufficient number of tissues and neurotoxicity endpoints. Despite the major limitations of these studies, which would prevent the use of the data in a neurotoxicity risk assessment, they did provide additional evidence that acetone can affect the nervous system.

CMA's Acetone Panel (Ref. 4) commented that the three studies cited in the proposed rule do not support EPA's conclusion that further testing is needed under a section 4(a)(1)(A) finding, but instead support the conclusion that acetone should be excluded from the rule because the quality and quantity of acetone information is superior to the data presented for several of the solvents excluded from the proposed rule. EPA does not agree with the Panel that the studies cited for acetone were superior to those on substances excluded from the proposed rule. All of the studies cited for acetone demonstrated some neurotoxic effects of acetone while being inadequate to fully evaluate the neurotoxicity of acetone even when the data from all of the studies were evaluated together. The study by Bruckner and Peterson (Ref. 5a) used a short exposure period of only 3 hours and the results were presented as average scores for a battery of five tests, making differentiation of effects on motor or sensory functions impossible. Similarly, the study by Glowa and Dews (Ref. 5e) used a short exposure, only 40 minutes, with effects noted on schedule-controlled response at 3,000 ppm and above. Although the Dick et al. (Ref. 5c) study was generally well conducted in humans, only one exposure level was used, and this produced an effect. As the Panel noted in its comments, there was some lack of consistency in this study with effects observed in the first session but not in the second. These data indicate that acetone has a potential to affect the nervous system, but the study was inadequate to assess these effects even for a standard 6–hour acute exposure. EPA contends that the above studies are the kind that fully support a section 4(a)(1)(A) finding and the need for additional data to assure the protection of human health.

EPA therefore concludes that human exposure data, in terms of the number of people potentially exposed, is sufficient for a TSCA section 4(a)(1)(B)(i)(II) finding, and that the available data, combined with the chemical/physical properties of acetone and the use characteristics of products containing acetone support the "risk" portion of the section 4(a)(1)(A)(i) finding. EPA also concludes that available data also support an environmental release finding under section 4(a)(1)(B)(i)(I). EPA notes that any one of these findings is sufficient to support a rule, and EPA believes that support for all three findings provides further impetus for promulgating a rule to require testing of acetone.

*G. n-Amyl Acetate*

CMA's Oxo Process Panel (Ref. 9) commented that EPA should not require the testing of pure *n*-amyl acetate because it is not produced in or imported to the United States. The Panel also commented that Union

Carbide produces a technical grade amyl acetate which is 65 percent *n*-amyl acetate (Ref. 11) and that this mixture should be tested instead. Union Carbide's name for its technical grade *n*-amyl acetate is primary amyl acetate and Union Carbide has reported its production (in excess of 1 million pounds) to EPA under the CAS No. of *n*-amyl acetate (Refs. 30–32). CMA argued that because the production and exposure is to the technical grade *n*-amyl acetate, that it, and not pure *n*-amyl acetate, should be the test substance. Union Carbide stated that it participated in the development of and endorsed CMA's comments.

EPA agrees with CMA and Union Carbide and has accepted their recommendation to test the technical grade *n*-amyl acetate. This rule specifies that the percent *n*-amyl acetate in the test substance must be representative of the technical grade and will be selected by the test sponsor. Because EPA proposed that manufacturers and processors of *n*-amyl acetate other than as an impurity are subject to this rule, Union Carbide is subject to this rule. Although EPA has not identified any other manufacturers of pure *n*-amyl acetate or technical grade *n*-amyl acetate, other manufacturers of *n*-amyl acetate even as a byproduct or in a mixture are also subject to this rule.

CMA's Oxo Process Panel submitted rat inhalation studies (acute, subacute, and subchronic) of primary amyl acetate (Refs. 9j and 9k) and stated that no neurotoxicity was observed in these studies and, therefore, no testing should be required. EPA has reviewed these studies (Ref. 70) and determined that these studies did not adequately describe methods and results or evaluate the test animals for neurotoxic effects. EPA, therefore, does not consider them sufficient to satisfy its data needs for the neurotoxicity of *n*-amyl acetate.

*H. 1-Butanol, n-Butyl Acetate, Ethyl Acetate, and Isobutyl Alcohol*

The Oxo Process Panel of CMA (Ref. 9) commented that for 1-butanol, *n*-butyl acetate, ethyl acetate, and isobutyl alcohol, EPA does not provide an adequate basis for a "B" finding. Specifically, the Panel contends EPA's consumer product usage survey and the NOES do not demonstrate substantial human exposure to these chemicals (for all but 1-butanol) and that the surveys overestimated human exposure. In addition, the Panel and Monsanto (Ref. 17) commented that EPA did not consider likely levels of inhalation exposure or the potential for dermal exposure during the use of consumer products. The Oxo Process Panel (Ref. 9) also maintained that the fact that there are large releases of 1-butanol does not support the finding that it enters the environment in substantial quantities.

As stated in the response to general comments, EPA does not concur with the manufacturers that the NOES data are not an accurate indication of potential worker exposure. For the reasons set forth in Units II.A and II.B.4 of this preamble, EPA believes that the NOES data for 1-butanol, *n*-butyl acetate, ethyl acetate, and isobutyl alcohol indicate that there is or may be substantial worker exposure to these compounds within the meaning of TSCA section 4(a)(1)(B)(i)(II).

In the proposed rule, EPA clearly pointed out that these organic solvents were chosen for consideration for testing under section 4, in part, because they are volatile, relatively small non-polar compounds which are of concern for inhalation exposure and exposure by skin penetration (56 FR 9107, March 4, 1991). In data contained in their own submissions, the manufacturers have acknowledged that these solvents are used in coatings, lacquers, and nail polish products (Refs. 9c, 9h and 10b). For these products, EPA believes that volatilization of the solvent during drying or curing is an intended outcome of their use. EPA also believes that because many of these products are used and applied indoors, there may be consumer exposure both during and after their use, as the vapors may remain within the house. Available data indicate that the concentration of organic solvents may be much higher indoors than it is outdoors (Ref.33). Therefore, it is possible that consumer exposure to these solvents during and after their use may even be higher than indicated in the proposed rule. Therefore, EPA does not concur with the Panel that the potential for inhalation and dermal exposure of consumers to these substances is not substantial within the meaning of TSCA section 4(a)(1)(B)(i)(II). EPA concludes that for 1-butanol, *n*-butyl acetate, ethyl acetate, and isobutyl alcohol, there is substantial human exposure.

For 1-butanol, CMA's Oxo Process Panel (Ref. 9) commented that EPA has not justified its finding that releases to the environment of 1-butanol are substantial within the meaning of TSCA section 4(a)(1)(B). They asserted that a finding of environmental release based on TRI data alone is not sufficient, and submitted airborne dispersion models for acetone and MIBK to support this point.

As indicated in the discussion in Units II.B.5 and II.F. of this preamble, EPA believes that TRI release data are a sufficient indicator of environmental entry and it does not believe that the atmospheric modeling studies refute this point. In the proposed rule, annual release of 1-butanol was listed as 36 million pounds for 1987 (56 FR 9108, March 4, 1991). According to TRI data for 1989, 39 million pounds were released to the environment (Ref. 29). In addition, EPA notes that under section 4(a)(1)(B)(i) of TSCA, either an environmental release finding or a substantial human exposure finding is needed to support a test rule. For 1-butanol, EPA concludes that both findings are valid, and provide further impetus for promulgating a rule.

CMA's Oxo Process Panel (Ref. 9) commented that the studies used by EPA as a basis for an unreasonable risk finding under TSCA section 4(a)(1)(A) for 1-butanol do not support the findings. The Panel contended that the study (Ref. 44) showing motor function impairment only indicated that 1-butanol may induce acute pharmacological effects at high doses. Such short-term suppression of the neurologic system, the Panel maintained, was different from pathologic changes or other long-term effects. It was further maintained that, in the other studies (Refs. 52 and 53), 1-butanol was administered by gavage or injection at large dose levels which would result in very high blood levels of 1-butanol and depression of the CNS. The only inhalation study, by DeCeaurriz et al. (Ref. 34), used exposures of 470 to 965 ppm, which is an order of magnitude higher than the occupational guideline of 50 parts per million (ppm) which is based on irritation. The only effects observed in this study, it was maintained, were due to sensory irritation. The Panel noted that EPA did not refer in the proposed rule to the subchronic oral study (Ref. 9g) used to derive the oral reference dose (RfD) in which hypoactivity and ataxia were observed at a dose of 500 mg/kg and where the NOAEL was 125 mg/kg/day. This NOAEL would correspond to an inhalation exposure of 300 ppm which is considerably higher than the OSHA ceiling of 50 ppm.

EPA agrees that the effects observed in animals exposed to high concentrations or doses of 1-butanol might result from non-specific suppression of the nervous system. However, while these effects do demonstrate some interaction with the CNS, the study designs do not permit the determination of whether there was specific toxicity to the nervous system and whether there would be effects following longer term exposure. These

studies raise concern for the potential neurologic effects of 1-butanol. This concern is further supported by the observation of neurotoxic signs in the subchronic study (Ref. 9g) cited by the Panel. The effects of ataxia and hypoactivity were clearly not the result of transient high blood levels since the effects did not appear until the last 6 weeks of the study. EPA, therefore, concludes that the data it cited in the proposed rule were sufficient to determine that 1-butanol may present an unreasonable risk, and this is further supported by the additional oral subchronic study (Ref. 9g) brought to EPA's attention by the Panel which showed hypoactivity and ataxia. None of these studies, however, was sufficient to satisfy EPA's neurotoxicity data needs for 1-butanol for the reasons presented in Table 1 of Unit III.A.5. These reasons included insufficient number of endpoints examined, only one sex tested, insufficient study duration, and inappropriate route of administration.

The Panel (Ref. 9) commented that the irritation potential of 1-butanol reduces the potential for neurotoxic effects in humans since humans will avoid high concentrations. EPA does not believe that there is evidence that irritation from 1-butanol can be relied upon to protect human health. It is generally known that there is a large degree of individual variation with regard to sensitivity to airborne irritants as well as tolerance to irritation. The ACGIH cited studies that reported workers exposed to 100 ppm of 1-butanol that did not complain of irritation, while other studies reported auditory nerve injury in workers exposed to 80 ppm of 1-butanol (Ref. 35).

In regard to ethyl acetate, CMA's Oxo Process Panel (Ref. 9) commented that this compound is used as a flavoring agent (Ref. 9a), fragrance, and solvent (Ref. 9b), and is on the Food and Drug Administration's (FDA) "generally recognized as safe" (GRAS) list for use as a synthetic flavoring agent and adjuvant (21 CFR 182.60). The Panel cited a review of the toxicity of ethyl acetate by the Cosmetic Ingredient Review (CIR) Expert Panel which, after a review of oral, dermal, intraperitoneal and inhalation animal studies, concluded that ethyl acetate was safe as a cosmetic ingredient "in the present practices of use and concentration" (Ref. 9c). The Oxo Process Panel stated that these data along with low use pattern do not support EPA's section 4(a)(1)(A) finding for ethyl acetate.

EPA believes it provided sufficient data for a section 4(a)(1)(A) finding for ethyl acetate. The CIR Expert Panel reviewed primarily systemic acute and subchronic toxicity studies which did not focus on the nervous system (Ref. 9c). The study by Glowa and Dews (Ref. 5e) referred to in the proposed rule reported effects of ethyl acetate on schedule-controlled response following exposure of mice for 10 minutes to 560 ppm (the decrease in response was 75 percent, while 300 ppm was a no-observed-effect level). Effects produced following such a short exposure time raise concern that ethyl acetate may present an unreasonable risk, particularly when the CIR Expert Panel review (Ref. 9c) indicated that the occupational threshold limit value (TLV) is 400 ppm and consumers may have short-term high levels of exposure since ethyl acetate is present in consumer products at up to 97 percent.

CMA's Oxo Process Panel (Ref. 9) commented that testing is not needed on ethyl acetate since this compound is rapidly metabolized to ethanol for which there is sufficient neurotoxicity data, and that butyl acetate should not be tested if testing is required on 1-butanol since again the acetate is rapidly metabolized to the corresponding alcohol. The Panel provided sufficient data to support the contention that ethyl acetate is rapidly metabolized to ethanol (Refs. 9b, 9h, and 9i), and that this metabolism is facilitated through a first pass effect in the lungs (Ref. 9d). A review (Ref. 9c) noted that one study indicated that following inhalation exposure of rats to ethyl acetate, levels of ethyl acetate in the brain were higher than in the blood. Following an exposure to 10 percent ethyl acetate in air, the concentration of brain ethyl acetate reached a peak of 0.46 mg/g while ethyl acetate in the blood was less than 0.2 mg/g; while ethanol in the blood reached 1.24 mg/g (Ref.59). The Panel maintained that the effects observed in the studies cited in the proposed rule were identical to the symptoms of ethanol toxicity (Ref. 9e). With regard to butyl acetate and 1-butanol, the Panel (Refs. 12) commented that only one substance should be tested because *n*-butyl acetate rapidly hydrolizes to 1-butanol (Refs. 12a and 12b). The Panel (Ref. 9) recommended that butyl acetate be the test compound because of its greater potential for inhalation exposure due to its solvent use and greater volatility.

EPA does not believe that surrogate substances should be recommended for testing in either case. Although it is clear that ethyl acetate is rapidly metabolized to ethanol, the data provided by the Panel demonstrate that ethyl acetate does enter the systemic circulation and that levels are higher in the brain than in blood (Ref. 9c). This would suggest that even over the short exposure period used in an acute study, the brain would be exposed to potentially significant levels of the parent compound which could result in toxic effects. Although it is possible that the effects noted in the studies cited in the proposed rule were due to ethanol, which resulted from the metabolism of ethyl acetate, there are clearly insufficient data to confirm this assumption. In addition, one of the authors of the Glowa and Dews study (Ref. 5e), Dr. J. Glowa, stated in submitted comments that "available evidence for ethyl acetate suggests that it is much more potent in neurobehavioral toxicology measures than is ethanol" (Ref. 20). Dr. Neal (Ref. 25) also noted that the water solubility of the alcohols and esters are different, which may affect the pharmacokinetics of these compounds, that there may be differences in effects on metabolism of endogenous substrates, and even though metabolism of the ester is rapid, there still may be sufficient exposure to the ester to affect the results of *in vivo* testing.

Although EPA believes that the exposure rationale used by the Panel for choosing butyl acetate for testing instead of 1-butanol is appropriate, EPA believes that both butyl acetate and 1-butanol should be tested because the types of concerns EPA has with ethyl acetate also apply to the situation with 1-butanol and butyl acetate. The studies (Refs. 12a and 12b) submitted by the Panel to demonstrate hydrolysis of butyl acetate to butanol were reviewed by EPA (Ref. 41). Although hydrolysis was demonstrated, the rates of hydrolysis would not be competitive with the rates of uptake and distribution of butyl acetate, allowing butyl acetate the time to cause its unique effect on the body. Also, 1-butanol is a greater skin irritant than *n*-butyl acetate, and this difference in irritation potential would influence the response. EPA thus does not believe that butyl acetate or 1-butanol should be tested as a surrogate for the other.

For isobutyl alcohol, CMA's Oxo Process Panel (Ref. 9) commented that EPA did not review the 90-day oral subchronic study in rats (Ref. 9f) that was used as the basis for the oral RfD. In this study, hypoactivity and ataxia were observed at 1,000 mg/kg/day while no effects were noted at the next lowest dose of 316 mg/kg/day. EPA has reviewed this study, which indicated that the degree of hypoactivity decreased markedly after week 4, while ataxia was observed sporadically throughout the study. Although no histologic lesions were reported, the

histologic evaluation of nerve tissue was limited to that which would only detect relatively severe tissue damage. EPA believes this study provides limited evidence that isobutyl alcohol can affect the nervous system and that the nervous system may be the most sensitive biological system. Although EPA is not relying on a TSCA section 4(a)(1)(A) finding to support testing of isobutyl alcohol, EPA believes that these additional data would support such a finding had EPA reviewed the study before it proposed this rule.

The Oxo Process Panel (Ref. 10) also commented that isobutyl alcohol should not be tested because it rapidly oxidizes to isobutyric acid (Refs. 10a, 10b, and 10c) which is not expected to pose an unreasonable risk to health because it is a natural component of food and is the primary metabolite of the essential amino acid valine. Although the submitted studies (Refs. 10a, 10b, and 10c) indicate metabolism of isobutyl alcohol to isobutyric acid, they also report that peak levels of isobutyl alcohol are present in the blood 30 to 90 minutes after exposure and that conversion to isobutyric acid isn't complete until 6 to 8 hours after exposure. EPA is concerned about the possible effects of isobutyl alcohol during the significant period of time before its metabolic conversion to isobutyric acid. Therefore, EPA believes the testing of isobutyl alcohol is still necessary. Also, the Panel did not indicate what foods contain isobutyric acid or in what concentrations. EPA believes that even though a substance may be present in food, it does not mean that at higher concentrations it cannot be toxic and that testing should not be required.

CMA's Oxo Process Panel (Ref. 9) commented that the rule should require that the maximum concentration tested of 1-butanol, *n*-butyl acetate, ethyl acetate, and isobutyl alcohol should not exceed the concentration at which aerosols form because the substance will be deposited on the fur of the test animals and be ingested during preening. The Panel contended that the combined oral and inhalation exposure will make the results of the tests difficult to interpret. EPA agrees that formation of aerosols can present difficulties in the design, conduct, and interpretation of data from inhalation studies. EPA notes, however, that the scientific literature contains many well conducted studies using aerosols, and that some occupational situations which use solvents, such as spray painting, generate aerosols. EPA believes it is not necessary to *a priori* restrict the upper concentration to that which does not produce aerosols. Furthermore, the solvents (1-butanol, *n*-butyl acetate, ethyl acetate and isobutyl alcohol) are relatively volatile with estimated vapor saturation concentrations of between approximately 9,200 and 120,000 ppm (Ref. 36), suggesting that the required testing can likely be conducted using vapor exposure only.

*I. Diethyl Ether*

DEMTG (Ref. 13) commented that EPA failed to present adequate evidence to support a "B" finding for diethyl ether. Objections were made to the use of NOES data and a consumer exposure analysis (Ref. 63) which DEMTG believed overestimated the number of people exposed to diethyl ether. DEMTG stated that because EPA has not made a finding that diethyl ether enters the environment in substantial quantities, human exposure must be the finding triggering the testing.

EPA agrees that human exposure is the issue triggering the finding for diethyl ether, and therefore, an environmental release finding under TSCA section 4(a)(1)(B)(i) is not an issue. Nonetheless, EPA does not concur with DEMTG that NOES data are not an adequate indication of potential occupational exposure. This rationale is discussed fully in Units II.A and II.B.4 of this preamble. EPA notes that its threshold for substantial occupational exposure is 1,000 workers (58 FR 28736, May 14, 1993). According to NOES data cited in the proposed rule, 175,489 workers are potentially exposed to diethyl ether (56 FR 9107, March 4, 1991). Furthermore, as DEMTG points out (Ref. 13 at 26 and Appendix I), the latest NOES data indicate even higher numbers of workers potentially exposed to diethyl ether. EPA believes that NOES data clearly indicate that potential substantial occupational exposure exists, and that a TSCA section 4(a)(1)(B)(i)(II) substantial human exposure finding is valid for diethyl ether.

EPA acknowledges that its consumer exposure analysis may contain a degree of error in its estimate of 67.8 million consumers exposed to diethyl ether from the use of engine starting fluid, the single consumer product which contains diethyl ether. However, the fact remains that 14 million cans of engine starting fluid containing diethyl ether were sold in 1989 and this product has numerous uses other than starting automobile engines; it is also used to start the engines of walk-behind power mowers, lawn tractors/riding mowers, riding garden tractors, rotary tillers, snow throwers, shredder/grinders, chain saws, trimmers/brushcutters, and blowers. EPA believes this wide variety of uses will cause several members of a household to be potentially exposed to diethyl ether, in addition to the person responsible for automobile maintenance. Therefore, EPA does not believe that the presence of diethyl ether in only one consumer product negates the validity of the finding that there is or may be substantial consumer exposure to diethyl ether.

DEMTG (Ref. 13) also challenged EPA's section 4(a)(1)(A)(i) finding for diethyl ether which was based on a study by Essman and Jarvik (Ref. 13g). DEMTG argued that even though the study showed that the administration of diethyl ether interfered with the retention of an avoidance response, EPA should not use the study as an indication of potential neurotoxicity because anesthetic dose levels were used, and EPA had declined to rely on other studies using anesthetic dose levels to characterize the neurotoxic effects of diethyl ether. As discussed in Unit II.D of this preamble, EPA believes that a different measure of adequacy can be applied to studies which it relies on as a basis of concern for toxicity when requiring testing as opposed to studies it considers adequate to satisfy data needs on the potential toxicity of a substance. EPA therefore believes the study by Essman and Jarvik is an adequate basis for a section 4(a)(1)(A)(i) finding. Also, in this case, EPA is interested in the effects of diethyl ether at low level, long term exposure, which cannot be addressed by acute studies run at anesthetic dose levels.

DEMTG (Ref.13) commented that there is sufficient data on the effects of diethyl ether in both human and animal studies and submitted copies of these studies for review.

Human experience with diethyl ether was reviewed by Kirwin and Sandmeyer (Ref. 13i), Reynolds (Ref. 13q), and the ACGIH (Ref. 13b). These reviews provided limited discussion of the anesthetic effects of diethyl ether in humans and the apparent lack of any permanent effects after recovery from acute exposure. Although these reviews suggest that permanent neurotoxic effects do not occur following acute exposure, EPA considers the gross observations inadequate for a comprehensive evaluation of neurotoxic potential because only a limited number of neurotoxic endpoints were considered. EPA agrees with Mergler (Ref. 13n) that few data exist on the effects of prolonged exposure to diethyl ether. The epidemiologic study of Linde et al. (Ref. 13k) that evaluated deaths among early anesthesiologists also does not provide data on potentially subtle

neurologic effects. In this study, the only potential indicators of neurotoxicity are deaths by suicide and accident. EPA does not consider these data adequate to indicate that diethyl ether is not neurotoxic.

De Grosbois et al. (Ref. 13e) studied the effects of diethyl ether on workers at an explosives manufacturing plant. The 68 exposed workers were classified according to 2 exposure levels (≈1,200 mg/m³ and >1,200 mg/mg³), and also according to 3 cumulative exposure indices (moderate, high, and mixed exposure). The results showed that those exposed to diethyl ether concentrations >1,200 mg/m³ had numerous pre-narcotic symptoms (unspecified) during the work week. Those exposed to ≈1,200 mg/m³ complained mainly of headache during the first and last 3 hours of work, as well as eye irritation. Individuals classified as moderately and highly exposed to diethyl ether complained of fatigue, sleepiness, concentration and memory impairment, headaches and dizziness, sexual difficulties, mood instability, and peripheral neuropathies. The 74 control workers were asymptomatic. Although this study shows that diethyl ether may be neurotoxic in humans, it does not satisfy the requirement for SCOB testing nor give a quantitative estimate of the effects of diethyl ether on the nervous system (Ref. 51).

In 18 human volunteers studied by Flemming (Ref.13h), the recognition threshold (concentration at which 50 percent of the individuals recognized the chemical) for diethyl ether was reported to be 1.6 ppm; no other endpoints of neurotoxicity, however, were evaluated.

DEMTG provided a number of additional animal studies of the neurologic effects of diethyl ether. These studies were conducted by Chenoweth et al. (Ref. 13d), Stevens et al. (Ref. 13r), USEPA (Ref. 13f), Banergee and Das (Ref. 13e), Norton and Jewett (Ref. 13p), Lambert and Ven Murthy (Ref. 13j), Wimer and Huston (Ref. 13v), Van Buskirk and McGaugh (Ref. 13t), McGaugh and Alpern (Ref. 13m), Abt et al. (Ref. 13a), and Essman and Jarvik (Ref. 13g).

EPA reviewed these studies and two reviews (Refs. 13l and 13u) provided by DEMTG and EPA still believes that the testing proposed for diethyl ether is necessary. EPA identified problems with the submitted studies which made them inadequate to satisfy its data needs (Refs. 50 and 51). These problems are listed in Table 1, Unit III.A.5 of this preamble and include insufficient description of methods and results, inadequate methods, insufficient number of doses and animals, and the evaluation of an insufficient number of tissues and neurotoxicity endpoints. DEMTG (Ref. 13) expressed concern about the safety of testing diethyl ether, noting the lower explosive limit (LEL) is 1.85 percent (18,500 ppm) which is below the anesthetic concentration. Normal laboratory procedures dictate that testing of flammable material be done at no more than 50 percent of the LEL and that other precautionary measures should be taken. EPA agrees that, for safety reasons, diethyl ether should not be tested above 50 percent of the LEL since there is too great a potential for accidentally generating an explosive atmosphere.

DEMTG (Ref. 13) does not believe that the data generated by the proposed testing will help EPA determine the potential risk from exposure to diethyl ether, or that these data will reduce the uncertainties in assessment of human risk from expected exposure levels. Further, DEMTG contends the non-specific testing procedures proposed will raise difficult issues of data interpretation, particularly the lack of specificity of the SCOB test. These difficulties will be complicated by differences in response between and within test strains of rats and mice. Moser et al. (Ref. 13o) reported differences in baseline functional observational battery (FOB) values not only between strains but between suppliers of a given strain of rats. Differences in response between and within strains have also been reported by Valzelli et al. (Ref. 13s) and Wimer and Huston (Ref. 13v).

EPA must have adequate data for neurotoxicity in order to conduct an adequate risk assessment. Currently, with inadequate neurotoxicity data, it is impossible to determine whether neurotoxicity is a more sensitive indicator of risk from exposure to diethyl ether than other endpoints. The data provided from the tests in this rule should clarify diethyl ether's neurotoxic potential and hence reduce the uncertainties associated with risk assessment. This reduction of uncertainty will occur whether a test for neurotoxicity is specific, such as a test that demonstrates neuropathologic damage to certain nerves, or non-specific, where a test for neurotoxicity demonstrates effects on the general function of the nervous system although a specific physiologic lesion has not been detected. Further, EPA does not believe that strain difference, as reported in the above studies, should unduly complicate the interpretation of results. Strain differences, both inter and intra, are commonly observed in biologic tests, and it is precisely for this reason that concomitant control groups are used in testing rather than historical controls and that laboratories, as a general practice, use animals from a single supplier. As noted by Moser et al. (Ref. 13o), "although some behavioral and physiological parameters showed strain and supplier differences .... conclusions concerning its [the tested substance] neurotoxic potential in a screening context would be similar".

DEMTG (Ref. 13) commented that EPA has underestimated the economic impact of the proposed rule. The manufacturers estimate that the cost of testing will represent 3.4 percent of gross revenues. This estimate was made by dividing the cost of testing by the 2-year period from initiation of testing to submitting results. The difference in reported economic impact results from DEMTG asserting that all costs will be paid out in the years that they are accrued, while EPA estimated that costs will be annualized over a 15-year period. EPA believes that costs of this type would normally be annualized and has included in the estimate a cost-of-capital figure to cover annualization.

*J. Methyl Isobutyl Ketone*

CMA's Ketones Panel (Ref. 7) commented that EPA has not justified its "B" finding that there is substantial human exposure to, and release to the environment of methyl isobutyl ketone (MIBK). The Panel contended that TRI release data are not sufficient for a determination that MIBK enters the environment in substantial quantities, and presented an atmospheric modeling study to support its claims. The Ketones Panel also maintained that EPA must consider the nature, extent, frequency, and circumstances of MIBK's use, and not just the number of people exposed to the substance, in making its substantial human exposure finding under section 4(a)(1)(B)(i).

As stated in Unit II.B.4 of this preamble, EPA believes that NOES data are a useful tool in estimating occupational exposure to a chemical. EPA believes that 375,906 workers potentially exposed to MIBK, according to NOES data (56 FR 9107, March 4, 1991), constitutes substantial worker exposure to MIBK within the meaning of TSCA section 4(a)(1)(B)(i)(II). For the reasons set forth in Units II.A, II.B.4, II.B.5 and II.F of this preamble, EPA believes that a TSCA section 4(a)(1)(B)(i)(II) substantial human exposure finding is valid for MIBK.

EPA does not agree with the Ketones Panel that TRI data is not a sufficient basis for a section 4(a)(1)(B)(i)(I) finding. In the proposed rule, annual release of

MIBK was listed as 29 million pounds for 1987 (56 FR 9108, March 4, 1991). According to TRI data for 1989, 31 million pounds were released to the environment (Ref. 29). The computer modeling cited by the Panel (Ref. 7) indicated that fenceline concentrations of MIBK were below established occupational exposure guidelines. However, section 4(a)(1)(B)(i)(I) of TSCA indicates that a finding can be made if a compound enters, or may reasonably be anticipated to enter, the environment in substantial quantities, and it makes no mention of concentrations which may result as a consequence of those releases. Although the modeling studies may predict that 24–hour concentrations are less than established occupational exposure guidelines, these guidelines are based on an 8–hour work day and are not meant to protect from continuous 24–hour exposure. In addition, they do not take into account long-term environmental burden. EPA believes that releases of the size described in the modeling study, on a daily basis, represent substantial entry into the environment.

Moreover, submissions provided by CMA's Ketones Panel indicated that MIBK is used in coatings, adhesives, cleaning agents, and printing inks (Refs. 7f, 7i, and 7j). MIBK must be present in a large number of commercial products as the Ketones Panel, in discussing *de minimus* exclusions for MIBK under TSCA section 12(b), stated that a test rule "would be burdensome for thousands of formulators". Also, for most coatings, adhesives, and printing inks, EPA believes that volatilization of a solvent like MIBK is an intended outcome of the use of these products. This volatilization will result in additional amounts of MIBK entering the environment above and beyond the reported releases in the TRI.

EPA concludes that the annual release of 29 million pounds of MIBK to the environment in 1987 and 31 million pounds in 1989 is sufficient for a section 4(a)(1)(B)(i)(I) finding that MIBK enters, or may be reasonably expected to enter, the environment in substantial quantities. Its potential for release from commercial and consumer products strengthens this conclusion.

CMA's Ketone Panel (Ref. 7) provided additional studies on the neurotoxicity of MIBK and believes that these data justify excluding MIBK from the proposed rule. These studies were conducted by Seikoe et al. (Ref. 8b), Geller et al. (Refs. 7e and 8a), Spencer et al. (Ref. 8c), Spencer and Schaumburg (Ref. 7j), De Ceaurriz et al. (Ref. 7d), Abou-Donia et al. (Ref. 7a), Phillips et al. (Ref. 7i), MacEwen et al. (Ref. 7h), Carnegie-Mellon Institute of Research (CMIR) (Refs. 7b and 7c), and Hjelm et al. (Ref. 7f).

EPA reviewed the additional information provided by the Panel and still believes that the testing proposed for MIBK is necessary (Refs. 50, 51 and 60). EPA identified problems with the submitted studies which made them inadequate to satisfy its data needs. These problems are listed in Table 1, Unit III.A.5 of this preamble and include insufficient number of doses and animals, insufficient description of methods, no perfusion *in situ*, use of only one sex, use of a nonmammal, and evaluation of an insufficient number of neurotoxicity endpoints.

CMA's Ketone Panel (Ref. 7) commented that EPA did not acknowledge that the study (Ref. 45) cited in the proposed rule to support the section 4(a)(1)(A) finding was conducted as a result of a voluntary testing agreement following recommendation of MIBK to EPA by the ITC. The agreed upon testing included the developmental test cited in the proposed rule, a 90–day subchronic toxicity test, and mutagenicity studies. The Panel maintained that a 90–day study is generally accepted by EPA, for section 4 purposes, for determining chronic risk. Following completion of these studies, EPA stated in a letter to the House of Representatives Subcommittee on Environment, Energy and Natural Resources that the "data are complete" for MIBK. The Panel contended that EPA should explain why EPA has chosen to reopen testing, without any new data, following the voluntary testing agreement and the assessment of the completeness of the data. The Panel did not consider the hindlimb paralysis observed in the developmental study cited in the proposed rule as new data indicating a potential for neurotoxicity because the paralysis occurred only at near lethal doses and was reversible.

EPA does not agree with the Panel that the developmental study cited in the proposed rule is not new data which suggests the potential for MIBK to be neurotoxic. Paralysis, both permanent and reversible, is a gross, and not very sensitive, sign of neurotoxicity. Even though the effects were observed at high doses, the design of the developmental toxicity study did not permit assessing more sensitive endpoints of neurotoxicity which may have occurred at lower doses. Likewise, there was only an indication that the paralysis was reversible; however, regaining the ability to use the hindlimbs does not assure that permanent damage was not done to some nerve fibers, and that following repeated exposure this damage may accumulate and result in dysfunction. Furthermore, when EPA indicated that data were complete, this related solely to the completion of the negotiated testing agreement and indicated that the tests agreed upon had been submitted to EPA. Neurotoxicity was not an issue at the time because EPA had not evaluated the neurotoxicity data needs of MIBK because it had no neurotoxicity test guidelines in place. EPA believes that evaluation of testing needs for a chemical is a progressive process which is influenced by many scientific and social concerns, and because of this, it would be unlikely that a statement could ever be made that complete data are available on any chemical. For example, EPA anticipates that some substances considered to have been thoroughly tested are good candidates to be evaluated for immunotoxicological effects, but EPA does not currently have test guidelines to assess such effects.

*K. 2-Ethoxyethanol*

CMA's Glycol Ethers Panel (Ref. 6) commented that the proposed rule overstates the potential for exposure to 2–ethoxyethanol (2–EE) and that imminent regulation of 2–EE by OSHA will further reduce occupational exposure (Ref. 6e). The Panel provided on-site monitoring data to support its exposure claims (Refs. 6, 6f, 6g, and 6j). The Panel maintained that production levels of 2-ethoxyethanol have dropped from 1983 to 1990, 187 million to 108 million pounds, and that this decline has resulted in fewer uses and less exposure. The Panel (Ref. 6) commented that 2–EE is no longer used in consumer products, but only in industrial products. The Panel also maintained that release of 2–EE to the environment has decreased substantially from 1987 to 1989, 2.9 million pounds to 1.8 million pounds (Refs. 6 and 29), and that future emissions are likely to drop below EPA's release threshold of 1 million pounds. EPA agrees with the Glycol Ethers Panel that, when the OSHA regulation becomes effective, occupational exposure to 2–EE is likely to be lower than estimated in the proposed rule, and appreciates the additional information on worker and consumer exposure submitted for review. However, EPA does not agree that a substantial human exposure finding under TSCA section 4(a)(1)(B)(i)(II) is inappropriate.

The Panel (Ref. 6) commented that NOES data indicating that 233,418 workers are potentially exposed to 2–EE is overstated and based on outdated data. The Panel estimated that less than

10,000 workers are potentially exposed to 2–EE in the workplace, with 400 of this number involved in production and distribution (Ref. 6). EPA notes that its threshold for substantial worker exposure is 1,000 workers (58 FR 28736, May 14, 1993) and that the estimate of worker exposure provided by the Panel exceeds this threshold by an order of magnitude (tenfold). Other data which also demonstrate worker exposure to 2–EE were presented in OSHA's proposed glycol ethers standard (58 FR 15526, March 23, 1993) and its supporting documentation. Table VIII–2 (58 FR 15582 and 15583, March 23, 1993) presented data estimating that 45,786 workers are exposed to four glycol ethers, of this number 21,992 workers are exposed to 2–EE (Ref. 71). EPA concludes that worker exposure data contained in the proposed rule, the data provided by the manufacturers, and the data in OSHA's proposed standard clearly indicate that there is or may be substantial occupational exposure to 2–EE, which provides adequate support for a TSCA section 4(a)(1)(B)(i)(II) substantial human exposure finding for 2–EE.

The Glycol Ethers Panel also commented that occupational exposure was in the range of 0.03 to 0.7 ppm and that this compared so favorably with OSHA's permissible exposure limit (PEL) of 200 ppm that EPA's exposure finding was not justified (Ref. 6). EPA, however, did not make a finding for "significant" occupational exposure based on concentrations to which workers are exposed. Instead, EPA made a finding for "substantial" exposure based on the number of workers potentially exposed. Also, although CMA cited the future OSHA regulation of 2–EE as a reason for not testing, CMA failed to mention the possibility that the revised OSHA standard might include a lower PEL thus weakening their argument that actual exposure concentrations are well within the permissible limit. Subsequent to CMA's submission of these comments, OSHA proposed a health standard for 2–EE which did indeed include a much lower PEL of 0.5 ppm as an 8–hour time–weighted average (58 FR 15526, March 23, 1993).

In a letter dated April 23, 1993, the Panel cited OSHA's proposed health standard for glycol ethers (58 FR 15526, March 23, 1993) and claimed that most workplace exposures are generally low, i.e., below 1.0 ppm (Ref. 73). EPA reviewed OSHA's proposed health standard which presented data on exposure by job category. The data showed that of 25 job categories with exposure to 2–EE, four have exposures in the range of 1.98 to 7.9 ppm (58 FR 15582, March 23, 1993), and an estimated 1,949 workers are exposed to 2–EE over the proposed PEL (Ref. 72). Based on these data, it appears that, although not proposed, EPA could have made a finding for "significant" exposure as well as "substantial" exposure to 2–EE.

The Panel also challenged EPA's exposure finding by commenting that production levels have declined from 187 to 108 million pounds and that solvent use has declined from 7 to 6 percent. EPA notes that 6 percent of 108 million is 6.5 million pounds which is still considerable use for solvent purposes. The Panel also commented that 43 percent of 2–EE is exported, the implication being that no American workers or consumers are exposed during the use of 2–EE. This information has a bearing on the exposure of the end user of 2–EE, but it does not affect the exposure of the workers involved in the manufacture, processing, and distribution of 2–EE, which industry concedes is less than 10,000 workers and OSHA estimates to be nearly 22,000 workers. When 10,000 to 22,000 workers are engaged in the annual production, processing and distribution of 108 million pounds, EPA believes there is substantial potential exposure.

Concerning consumer exposure, the Glycol Ethers Panel (Ref. 6) provided labels from the two manufacturers of 2–EE indicating that 2–EE should not be used in consumer products, but did not indicate how the manufacturers can be certain their warnings are heeded. No survey of customers was performed to determine if 2–EE is formulated into consumer products. The Panel also provided a 1984 letter from the CPSC to EPA (Ref. 6) stating that 2–EE is not in consumer products, but another submission from the Panel (Ref. 6h) indicated that as of 1990, the CPSC regarded consumer exposure to 2–EE as "likely or possible." Given the insufficient and conflicting nature of this information, EPA could not conclude that there is no potential consumer exposure to 2–EE. Consequently, EPA questioned purchasers of 2–EE concerning the possible formulation of 2–EE into consumer products. Although every purchaser of 2–EE could not be contacted, EPA did not discover any consumer use of 2–EE (Ref. 74). Therefore, EPA is not making a section 4(a)(1)(B)(i)(II) finding for 2–EE based on consumer exposure.

EPA does not agree with the Panel that releases of 2–EE to the environment are not substantial within the meaning of TSCA section 4(a)(1)(B)(i)(I). The Panel (Ref. 6) commented that TRI data indicated that emissions of 2–EE are declining, and that 1990 releases are likely to be below EPA's threshold of 1 million pounds. EPA believes that the Panel's estimates of future emissions are speculative. Moreover, EPA does not believe that the Panel provided sufficient data to support its argument that environmental releases will have decreased by approximately 50 percent in 1 year. EPA notes that manufacturers provided 1989 TRI data indicating that 1.8 million pounds of 2–EE were released to the environment. This value clearly exceeds the environmental release threshold of 1 million pounds specified by EPA (58 FR 28736, May 14, 1993). Given the available data, EPA concludes that a TSCA section 4(a)(1)(B)(i)(I) substantial release finding is also valid for 2–EE.

EPA does not agree with the Glycol Ethers Panel that imminent OSHA regulation negates the need for testing under TSCA. OSHA regulations seek to protect only the worker population and are based on available toxicity data. The fact that an Agency decides to regulate based on available data does not preclude EPA from seeking testing under TSCA for significant health and environmental effects data gaps which may identify a more sensitive endpoint. Also, OSHA's regulation on 2–EE is only in the proposal stage and a final rule may not be promulgated for 1 to 2 years. What OSHA's final rule will require concerning level of protection, controls, or monitoring can not be determined at this time although EPA agrees with the Panel that the future OSHA rule should reduce worker exposure. However, a reduction may not be guaranteed in every case when engineering and administrative controls are not feasible and personal protective equipment is relied on to achieve compliance with the OSHA standard. There is some uncertainty concerning the actual protection provided by gloves and respirators because the employee must be motivated to use the equipment and use it properly for it to be effective. Because of the uncertainties involved at this stage of OSHA's regulatory efforts, EPA believes that it is justified in requiring development of test data to assess the potential risks posed by the continued potential for substantial occupational exposure to 2–EE.

CMA's Glycol Ethers Panel (Ref. 6) commented that the available toxicology data demonstrate that there is no need for additional testing because existing data are sufficient and provided copies of additional studies for consideration. These studies were conducted by Barbee

et al. (Ref. 6a), Foster et al. (Ref. 6c), Werner et al. (Ref. 6i), Gill and Negley (Ref. 6d), and Doe et al. (Ref. 6b).

EPA reviewed the additional studies provided by the Glycol Ethers Panel regarding the possible neurotoxic effects of 2–EE and still believes the testing proposed for 2–EE is necessary. EPA identified problems with the submitted studies which made them inadequate to satisfy its data needs (Refs. 50 and 51). These problems are listed in Table 1, Unit III.A.5 of this preamble and include insufficient exposure duration, insufficient description of methods, no *in situ* perfusion, and the evaluation of an insufficient number of neurotoxicity endpoints.

Dr. Gill (Ref. 6) commented that the summary of the Nelson et al. studies, used by EPA as the basis for its TSCA section 4(a)(1)(A)(i) finding for 2–EE, overstated the significance of the studies and incorrectly inferred that exposure concentration-related changes were observed in tests of neuromuscular function, exploratory activity, and aversive learning. EPA did state that the reported changes were statistically significant according to Nelson et al., and that more effects were seen at the higher dose, but it did not state or infer that these changes demonstrated a dose-response relationship, which in some cases they did not. Nelson et al. (Refs. 38 and 39) exposed pregnant Sprague-Dawley rats to 0, 100, or 200 ppm 2–EE (14–16/group) during gestation days 7–13. Behavioral testing was conducted on the pups up to 60 days of age. In the pups, rotarod performance was impaired at the two highest concentration levels of 2–EE, but the effect was not dose-related. Open field activity was decreased at 200 ppm only on one of the test days. Open field latency was increased only in the 100 ppm group. Results from the ascent test were mixed in the 200 ppm group with increased performance on day 10, but decreased performance on day 12. Avoidance crosses in a shuttle box were decreased in the 200 ppm group, whereas the mean number of shocks received in 20 trials and mean seconds shocked were not different among groups. Operant behavior was not significantly altered by 2–EE treatment. As with some neurobehavioral studies, the results are not easy to interpret. The results from Nelson et al. (Refs. 38 and 39) show some effects on neuromotor responses of the pups after prenatal exposure to 2–EE, but dose-response relationships were not clearly established. In general, as indicated by Nelson et al. (Ref. 39) and also by Dr. Gill (Ref. 6), these results fit a pattern of decreased neuromotor function, which EPA believes also supports its TSCA section 4(a)(1)(A)(i) finding.

*L. Testing Program*

1. *Tiering of tests.* CMA (Ref. 3) commented that a tiered approach to testing would be more cost effective for this and future neurotoxicity endpoint rules. CMA argued that a tiered approach would permit screening tests to be performed first, and only if the results of the screening tests are positive should additional second tier testing be required. CMA suggested that the first tier consist of a subchronic functional observational battery (FOB) and neuropathology; a second tier, decided on a case-by-case basis, could include motor activity (MA) and behavior tests. CMA also suggested that a subchronic study of 28 days duration may be appropriate since the Office of Pesticide Programs (OPP) recently revised its guidelines for delayed neurotoxicity for organophosphorus substances from 90 to 28 days in duration and OECD guidelines allow for a range of test durations.

Similar comments were expressed in reference to MIBK by CMA's Ketones Panel (Ref. 7). DuPont (Ref. 15) also suggested a two-tier approach, except that the first tier should be acute FOB and MA tests and the second tier should be a subchronic FOB, MA, and neuropathology. Du Pont further stated that a tier approach was outlined in the OTA report on neurotoxicity, used in a previous TSCA test rule on unsubstituted phenylenediamines (40 CFR 799.3300), and has been used for other toxicologic endpoints such as mutagenicity in other test rules (52 FR 21516, June 8, 1987; 53 FR 913, January 14, 1988). Monsanto (Ref. 17) also commented that testing should be tiered with the first tier consisting of a subchronic FOB test and neuropathology and the second tier required on a case-by-case basis consisting of cognitive function and behavior tests along with acute testing and assessments of reversibility of effects after acute exposure. In the tiered approach proposed by The Dow Chemical Company (Ref. 14), three tiers would be used. The first would be a classical subchronic study with FOB, MA, and neuropathology (fixation by immersion), the second tier would be a subchronic study with the high dose set below doses which cause systemic toxicity which would hamper data interpretation and with FOB, MA, neuropathology (perfusion), and evoked potentials battery included, and the third tier would assess cognitive functions in a subchronic study.

As indicated in the proposed rule, EPA has a concern about the neurotoxicity of solvents as a class, and this is supported by the discussion in Casarett and Doull's Toxicology (Ref. 47) which was cited in the proposed rule. Because EPA believes the likelihood is high that neurotoxic effects will be produced, there is less justification to use a tiered approach. A tiered approach will result in delays in receiving valuable data due to the added time needed to review first tier data, and because tests would not be performed concurrently. While EPA agrees that tiered testing is a valid and cost effective method of screening substances, and appreciates the value of this approach as indicated by its use of tiered testing in other test rules, the different tests proposed for first and second tiers in the above comments indicate that there is no universal agreement on what constitutes a first tier battery. In addition, while tiered testing is particularly useful for screening a large number of substances for which there is no indication that positive results will be produced, EPA believes that there is a high probability that these compounds are neurotoxic agents. For these reasons, EPA believes the tests required in this rule constitute a justifiable testing program that will result in the development of testing data necessary to reasonably determine or predict the neurotoxic effects of these solvents.

2. *Dose selection.* CMA (Ref. 3) commented that interpretation of data from the high dose group would be difficult as the high dose group is currently defined in the proposed rule, because substances which are highly irritating may affect breathing patterns and this, in turn, may have an effect on neurobehavioral, learning and memory endpoints in the test animals. CMA suggested that the concentration which results in a reduction in breathing rate (RD50) be used as the high dose rather than a concentration which results in clear neurotoxic effects or is near life threatening.

EPA believes that clearly demonstrated behavioral effects are valid criteria for the high dose. EPA acknowledges, however, that the occurrence of toxic effects on other organ systems in addition to the nervous system would require careful analysis to determine whether the behavioral effects were secondary to toxicant induced changes in other organ systems or more directly neurotoxic.

3. *Observation/testing times.* Dow (Ref. 14) commented that EPA should modify the neurotoxicity test guidelines for scientific and technical reasons. Dow

noted that the guidelines for the testing of acute motor activity require testing to be conducted at times that include the peak signs of toxicity. Dow stated that the time of peak signs is likely to be during exposure, but testing cannot be conducted until after the chamber has been vented which takes 30 to 35 minutes. If the elimination of the solvent from the brain is rapid, then the results that are generated may be worthless. Dow believes that other tests (e.g., evoked potential or EEG) should be substituted which can be used while the animal is being exposed. Although EPA would prefer to have the motor activity and SCOB tests conducted during exposure, EPA does not consider it practical to require testing in the inhalation chamber at this time. Therefore, EPA requires that testing be done as quickly as possible after exposure. EPA also believes that Dow's estimate of 30 to 35 minutes to vent a chamber seems an unusually lengthy period of time and that some adjustment here might allow peak signs to be measured sooner in the post-exposure observation/testing period. EPA is interested in motor activity as a quantified index of arousal of the test animal and does not accept that Dow's proposal has justified using other tests (e.g., evoked potential or EEG) instead of acute motor activity.

Dow also commented that for the FOB test, observations are required at 1, 6, and 24 hours, and commented that it is not clear if these times start from the beginning of exposure or start at the end of the 6-hour exposure. If the time starts at the beginning, then it is not possible to make all of the observations at 1 hour, which is during the exposure, and if time starts at termination of exposure, then the observations at 6 hours would require an extended work day. The time for FOB observations for the acute FOB and for the first exposure in the subchronic FOB is at the termination of exposure, although it is an established scientific practice to record those observations that can be made during the exposure period. To clarify further, according to the guideline, all animals should be observed prior to initiation of exposure. Also, subsequent to the first exposure in the subchronic FOB, all observations should be made before the daily exposure. Concerning the length of the work day, EPA believes extended work days occur in many testing situations and this should not be a major obstacle to conducting the required tests.

4. *Schedule-controlled operant behavior test.* AIHC (Ref. 1), CMA's Glycol Ethers Panel (Ref. 6), Du Pont (Ref. 15), Monsanto (Ref. 17), Union Carbide (Ref. 19), and Dr. R.A. Neal from Vanderbilt University (Ref. 25) commented that the validity of the schedule-controlled operant behavior (SCOB) test conducted under EPA guidelines has not been firmly established by systematic studies. EPA does not agree. SCOB has been used for over 40 years to study nervous system function. SCOB has been shown to be affected by brain lesions, many toxicants, and by virtually every category of psychoactive drugs, hundreds of which have been cited in the open literature. Moreover, SCOB has had extensive use as a tool for assessment of the role of specific brain regions/pathways, lesioning techniques, and biochemical pre-treatments such as receptor antagonists, in studying the mechanism or action of drug effects on behavior. There are, moreover, considerable toxicity data on SCOB and solvents, pesticides, and metals which have been gathered in many laboratories over the last 20 years. Clearly, there is a long standing research tradition and rich data base on SCOB as compared to many methods in use in regulatory toxicology.

CMA's Glycol Ethers Panel (Ref. 6), Du Pont (Ref. 15), Monsanto (Ref. 17), Union Carbide (Ref. 19), and Dr. R.A. Neal from Vanderbilt University (Ref. 25) considered some definitions in the guidelines to be unclear, i.e, whether or not a change in response rate represents an adverse effect. As asked by Wenger (Ref. 42) "is a decrease always bad and an increase always good?" Although the answer may not be perfectly clear in every case, EPA believes that there are no special difficulties in the interpretation of SCOB data. Disruptions in the rate or pattern of an organism's behavior obtained in studies that are scientifically valid, i.e., found to be statistically and toxicologically significant, are generally considered to be adverse. This is easily understood by analogy to the depressant effects of alcohol, the confused behavior of people under the influence of alcohol, or the stimulant effects of several cups of coffee. Of course, ultimately what is "adverse" can be a social judgment, but it is reasonable to assume that most people would not desire such effects from inadvertent exposures, and that public safety would also argue against them.

The AIHC (Ref. 1) provided references to several studies which have not demonstrated a consistent relationship between SCOB performance and neurotoxicity as measured by other tests. In response, EPA notes that it is not particularly uncommon that conflicting results are obtained between different tests of neurotoxicity. This is to be expected, since the different tests are evaluating different functions of the nervous system, and the reason for requesting different tests is based on the assumption that some tests may provide negative results while others will provide positive results or significant differences in the dose-response relationship. For example, the well known neurotoxicant tetrodotoxin completely blocks sodium channels leading to blockage of the action potential, paralysis, and death. Neuropathological assessments of the nerves by histological methods, or even by the use of electron microscopy of animals treated with this compound, do not reveal any alterations in the nerve fibers. Another example would be that the measures of motor function, such as grip strength, would not be modified if a few axons in the motor nerve were undergoing degeneration, although neuropathology would detect these changes. These examples support the rationale that batteries of tests should be used in assessing neurotoxicity, and that there is no *a priori* reason that the SCOB test would not be a useful addition to such a battery of tests.

The AIHC (Ref. 1) stated that "data generated under the SCOB guideline as proposed by EPA will not permit any inferences to be made about learning and memory because animals will be exposed to the chemicals after being trained to perform a task." Similar opinions were expressed by CMA (Ref. 3), CMA's Ketone Panel (Ref. 7), CMA's Oxo Process Panel (Ref. 9), Dow (Ref. 14), Du Pont (Ref. 15), Monsanto (Ref. 17), Union Carbide (Ref. 19), and DEMTG (Ref. 13). EPA does not agree. Although the SCOB measures the effect on the performance of a complex task, operant behavior refers to behavior that is acquired, i.e., learned and maintained by its consequences, more generally, rewards and punishments. Schedules of reinforcement refer to rules that specify what responses will be reinforced and when. SCOB is a set of methods for assessing the sensitivity of organisms to environmental conditions that may be varied in a number of ways to study the ability of organisms to adapt to change. The data base on SCOB compiled over the last 50 years has shown that schedules of reinforcement determine both the rate and pattern of responses over time. These rates and patterns have been shown to have broad generality across species and to be reliably affected by many environmental changes, different classes of drugs and several other classes of substances. Learning refers to the increase in probability of a

response following the association of the response with either an eliciting stimulus (Pavlovian conditioning) or with reinforcement (operant conditioning). Memory refers to the likelihood of a learned response after some temporal delay following training. Learning and memory cannot be directly observed but can only be inferred from changes in behavior. Learning and memory are broad constructs that cover many varied and complex functions that cannot be simply studied in humans, let alone in animals. A comprehensive assessment of learning and memory requires an extensive test battery. Regular performance under a schedule of reinforcement is a complex pattern of learned behavior and is an index of the organism's memory of the task as well as a measure of its ongoing moment by moment adaptation to its environment. Thus, deficits in performance of a complex task represent a failure of an ongoing adaptation to the environment fundamental to the learning process. EPA therefore believes the SCOB is currently the best single test for the assessment of complex behavior dependent on learning and memory.

Dr. D. Cory-Slechta from the University of Rochester (Ref. 23), though supportive of the inclusion of the SCOB test in the rule, disagreed with the type of schedule proposed, i.e., the multiple fixed-ratio, differential reinforcement of low rate (mult FR DRL) schedule. She commented that this schedule will mostly reflect changes in response rate per se rather than measure learning and memory and recommended the use of a multiple fixed-ratio, fixed-interval (mult FR FI) schedule. Dr. Weiss of the University of Rochester also considered the mult FR FI schedule to be an equally valid choice (Ref.24). The more extensive data base of the mult FR FI was an additional reason presented to support this choice (Refs. 22 and 23). Dr. Cory-Slechta also preferred the multi FR FI because changes in DRL response rates will affect the rate of reinforcement, which may evoke compensatory mechanisms that would prevail over test substance effects. Moreover, long interresponsive times (IRT) resulting from decreases in response rates at high doses will produce apparent increases in the animal's ability to space its responses in real time (Ref. 42).

EPA has reviewed the comments on the advantages and disadvantages of different schedules and has decided to revise its modification of § 798.6500(d)(8)(v) and require the mult FR FI schedule of reinforcement which was discussed under issues for comment in the proposed rule as a possible alternative schedule. EPA has several reasons for selecting this schedule. The multi FI FR schedule, as noted by several commenters, has a broad data base. Also, quality assurance questions can be easily addressed by analysis of rate and pattern of performance because the characteristic pattern of FI and FR performance has broad generality across species, and does not depend to any great degree on the particular response or reinforcer used in a study. SCOB response rates maintained by FI schedules can also be increased as well as decreased by solvents. In addition, disruptions in the FI or FR response patterns provide evidence of a specificity of effect on the nervous system that cannot be ascribed to changes in motivation, malaise, or an inability to perform. Finally, FI and FR schedules have been extensively used to study the effects of many solvents, and quantitative approaches have already been advanced by Dews, et al. (Ref. 56) and Glowa (Ref. 57) for quantitative risk assessment, i.e., benchmark doses, making better use of the data than conventional NOELs.

AIHC (Ref.1) commented on the large number of animals that would be necessary to conduct a SCOB test according to the guideline requirements and the attendant logistical problems. EPA understands these concerns and has decided that an acceptable alternative to the guideline requirement would be the testing of animals of the same sex if at least 10 animals per dose level and control are used. This alternative is listed under § 799.5050(b)(1)(iii).

5. *SCOB as a first tier test.* The AIHC (Ref. 1) commented that the SCOB is not appropriate for inclusion in a neurotoxicity screening battery. The AIHC states that although the SCOB test has a definite role in neurotoxicity testing, "its role should be reserved for more advanced questions about the behavioral effects of a compound and not as an initial assessment." This opinion was shared by the CMA's Ketone Panel (Ref. 7), CMA's Oxo Process Panel (Ref. 9), Du Pont (Ref. 15), Monsanto (Ref. 17), and Dr. R.A. Neal (Vanderbilt University) (Ref. 25). The submitters further cited a study by Moser and MacPhail (Ref. 28) in which the investigators examined the sensitivity of three tests (FOB, motor activity, and SCOB), for identifying the low observed effect levels (LOAELs) for six known neurotoxicants. This study is cited by the submitters as evidence that SCOB should only be included after other neurotoxicity tests have been completed.

EPA reviewed the study by Moser and MacPhail (Ref. 28) and found that although each of the six substances tested had a similar effective dose range across the different tests, the three test methods clearly assess different aspects of the overall nervous system function of the rat. For the chemicals tested, the FOB was an equally or more sensitive test than the motor activity or operant tests, while the motor activity and operant behavior tests were equally sensitive in most cases. Moser and MacPhail (Ref. 28) concluded that although the FOB and motor activity may be expected to adequately detect neurotoxicity of unknown substances, operant behavior testing can also characterize the actions and possible mechanisms of action of neurotoxicants. The conclusions of Moser and MacPhail (Ref. 28) are in agreement with earlier remarks of an expert subpanel of the Science Advisory Panel of the Office of Pesticide Programs regarding neurotoxicity testing that motor activity and SCOB do not always measure the same thing and that some effects might be missed if SCOB were a second tier test (Ref. 40). EPA, therefore, concludes that the SCOB test can provide valuable information about the neurotoxic properties of the substances in this rule. This rule does not require a simple screening test program, but is aimed at the specific kinds of neurotoxicity known or suspected to be associated with chronic solvent exposure. As such, inclusion of SCOB will provide meaningful data with respect to complex neurobehavioral and cognitive function.

*M. Cost of Testing*

CMA and its Glycol Ethers Panel (Refs. 3 and 6) commented that there is insufficient experience with the SCOB test for either EPA or CMA to reliably estimate the cost of testing. CMA noted that although a reliable estimate cannot be made, industry scientists believe the true cost could be twofold to threefold greater than EPA has indicated. Dow (Ref. 14) believed EPA's estimate was low because several subchronic studies (about $150,000 each) may have to be conducted on each chemical, and there will be development costs for pilot research which could add an additional $75,000 to the overall costs of the study.

EPA believes that it has made a reasonable estimate of the cost of the SCOB test. EPA has used the best information available, and the comments by CMA have provided no substantial data to demonstrate that EPA's estimate is too low. The estimate by Dow for the cost of subchronic testing is very similar to that used by

EPA. EPA does not agree with Dow that several subchronic tests will be required for each substance. EPA believes these multiple studies would only be required if the tiered testing approach proposed by Dow and outlined above were adopted in the final rule. In addition, as noted by EPA in the proposed rule, it is anticipated that the sponsor might combine subchronic tests, which would reduce the cost of testing for a given substance. EPA also believes it is likely that other types of cooperation will occur between sponsors that will substantially reduce the cost of any pilot research not considered in the economic analysis.

*N. Laboratory Capacity*

AIHC (Ref. 1), CMA (Ref. 3), CMA's Oxo Process Panel (Ref. 9), Dow (Ref. 14), DEMTG (Ref. 13), and Monsanto (Ref. 17) commented that there is insufficient laboratory space to conduct the required testing since laboratories are required that have expertise in both inhalation toxicology and neurotoxicology. The commenters stated that the surveys used by EPA to assess laboratory capacity assessed the capacity to conduct neurotoxicity and inhalation studies separately, while an informal survey conducted by AIHC of nine major contract testing laboratories indicated that only one or two could conduct the required testing. In addition, the commenters noted that EPA recently announced a data-call-in for neurotoxicity tests for certain pesticides and also announced requiring neurotoxicity testing for pesticides requiring new registration. The commenters maintained that any available laboratory capacity would be eliminated by these other EPA actions. Du Pont (Ref. 15) also indicated that laboratory capacity may be limited if the SCOB test is not deleted from the final rule, and further requested at least a 9-month extension on each test to allow for scheduling of laboratory space (it was noted that this is the time needed to reserve space in their laboratory).

Dr. D. McMillan (Ref. 22) commented that there are sufficient scientists available to staff new contract laboratories in neurotoxicity and that there is adequate laboratory space to conduct tests on 20 substances/year; however, he believes that space may become severely limited if tests were required on as many as 50 substances/year. Dr. D. Cory-Slechta (Ref. 23) suggested the time frame for obtaining results for this first set of substances in the endpoint rule might be increased to allow for the hiring and establishment of additional qualified personnel, but maintained that if subsequent chemicals are added to the rule, the time frame as outlined in the proposed rule should be adequate.

EPA believes that there will be sufficient laboratory space to comply with this rule (Refs. 48 and 49). EPA anticipates that despite the demand for laboratories to conduct neurotoxicity testing under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA), there will be adequate capacity to accommodate neurotoxicity testing of 10 additional substances under this rule. However, to assist the test sponsor in scheduling laboratory space, EPA has decided to extend the due dates for the SCOB test from 21 to 24 months for three of the chemicals, from 21 to 30 months for three other chemicals, and from 21 to 36 months for the remaining four chemicals. The order in which these chemicals should be tested is as follows:

First set of three chemicals:

acetone
1-butanol
ethyl acetate

Second set of three chemicals:

methyl isobutyl ketone
2-ethoxyethanol
diethyl ether

Third set of four chemicals:

*n*-butyl acetate
isobutyl alcohol
tetrahydrofuran
*n*-amyl acetate

The criteria used for establishing the above order were proposed in Unit IV.D of the proposed rule. The substances to be tested first would be those with 4(a)(1)(A) and 4(a)(1)(B) findings and ranked according to production volume as reported in the proposed 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 the proposed rule. No comment was received on this method of prioritizing the chemicals for testing.

*O. Export Notification Requirements*

CMA (Ref. 3) commented that requiring exporters, under TSCA section 12(b), to notify EPA annually of the substances they export which are subject to this rule will be very burdensome and that a *de minimis* exemption should be allowed for substances present in small concentrations in exported products.

EPA realizes that annual export notification for the substances to be tested under this rule may be burdensome. EPA has proposed to offer some relief to exporters by requiring a one-time notice instead of an annual notice. That proposal was published in the **Federal Register** on July 12, 1989 (54 FR 29524). Currently, EPA is in the process of issuing a final rule.

## III. Final Testing Requirements

*A. Findings*

EPA is basing the final health effects testing requirements on the authority of section 4(a)(1)(A) and (B) of TSCA. EPA finds that: available data indicate that six of the substances may present an unreasonable risk of injury to human health based on preliminary information suggesting that these substances may produce neurotoxic effects and upon the potential human exposure to these substances. EPA also finds that all 10 substances are produced in substantial quantities; there is or may be substantial human exposure to all 10 substances; and there is or may be substantial environmental release of four of these substances. Moreover, EPA has concluded that there are insufficient data and experience to reasonably determine or predict the neurotoxic effects from manufacturing, processing, use, and disposal of these substances, and testing is necessary to develop these data.

EPA published a general policy statement under TSCA section 4(a)(1)(B)(i) (the "B" policy) in which it articulated its criteria for making findings under this provision (58 FR 28736, May 14, 1993). The "B" policy was developed in response to the April 12, 1990 decision in *CMA v. EPA* (Ref. 26) in which the Court remanded to EPA the TSCA section 4 rule for cumene 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 articulated the criteria for substantial production and substantial and significant human exposure in the "B" policy.

EPA proposed the neurotoxicity test rule under TSCA section 4(a)(1)(B) without waiting for the "B" policy to be proposed and published in the **Federal Register** for comment by exercising the option of articulating the criteria used in making findings under TSCA section 4(a)(1)(B) in the specific proposed rule (56 FR 9110–9111, March 4, 1991). EPA did not base its section 4(a)(1)(B) finding in this rule on the "B" policy.

although the findings in this rule are consistent with the policy. For the reasons set forth in the proposed rule (Id.), in the response to the comments section of this notice, and in the discussion below, EPA believes that it has clearly articulated the bases for its findings under sections 4(a)(1)(A) and (B) of TSCA in support of the required testing.

1. *All 10 substances are or will be produced in substantial quantities.* The production volumes of all of the substances subject to this 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 (see Economic Impact Analysis). EPA has reviewed these data and has found that the reported production volume of each substance (9.4 million to 2.4 billion pounds per year) is substantial. EPA believes it is reasonable to interpret substantial production to mean large production, and that 9.4 million pounds is a large amount of production. Furthermore, only 11 percent of the substances reported in connection with the TSCA section 8(b) inventory of the substances in commerce have annual production volumes over 1 million pounds (Ref. 64). EPA believes that it is reasonable to conclude that this small group of substances (i.e., the top 11 percent according to production volume), clearly are substances with substantial production.

2. *There is or may be substantial human exposure to each of the 10 substances.* With the exception of 2-ethoxyethanol, EPA finds there is potential for substantial consumer exposure to these substances from their widespread presence in consumer products. Consumer uses of these solvents include engine starting fluid, and solvent for paint, lacquer, ink, and enamel (56 FR 9106–9107, March 4, 1991). EPA has determined that these substances are present in 1 to 51 consumer products and has estimated that at least 3.7 million consumers are exposed to each product (56 FR 9107, March 4, 1991). EPA believes that it is reasonable to interpret the term "substantial human exposure" to mean widespread human exposure, or in other words, a large number of people. EPA believes that exposure of 3.7 million people is substantial exposure because where millions of people are exposed to a substance, it is reasonable that EPA should have data on the potential hazards associated with the substance.

EPA also finds there is or may be substantial occupational exposure to each of these substances. The industrial uses of these substances include extraction solvent, chemical synthesis, lube oil additive, solvent for coatings, adhesives, plastics, PVC cement and ink (56 FR 9106–9107, March 4, 1991). The NOES data indicate that at least 172,000 workers may be exposed to each of these substances (56 FR 9107, March 4, 1991). 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. Thus, to be considered substantial, exposure does not have to be as widespread for workers as for consumers or the general population. EPA believes that exposure of 172,000 workers is widespread enough to necessitate testing to determine the potential hazards of the substances.

EPA finds that exposure of over 100,000 workers and 3.7 million consumers is "substantial" as that term is used in TSCA section 4(a)(1)(B)(i)(II). Furthermore, these substances have a propensity to penetrate the skin, and have high volatility, which facilitates inhalation. Available data on skin absorption and the vapor pressures of these substances support this conclusion.

3. *Four of the substances enter or may reasonably be anticipated to enter the environment in substantial quantities.* 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 believes that the term "substantial" used in connection with environmental releases means large release and is intended to capture substances with extensive release to the environment. 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 TRI 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. 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 therefore finds that the releases of these four substances are "substantial" as that term is used in TSCA section 4(a)(1)(B)(i)(I).

4. *Activities involving six of the substances may present an unreasonable risk of injury.* 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 the proposed rule and Unit II of this preamble for acetone, 1-butanol, diethyl ether, 2-ethoxyethanol, ethyl acetate, and methyl isobutyl ketone, and the worker and/or 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. 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. 5c) and the dose-related functional decrements observed in rats and mice after exposure to 1,000 to 56,000 ppm acetone (Refs. 43 and 5e). The finding that 1-butanol may present a risk is based on its observed impairment of motor control in rats (Refs. 52 and 53) and motor performance in mice (Refs. 34 and 44). The finding that diethyl ether may present a risk is based on its interference with the acquisition of an avoidance response in mice (Ref. 13g). 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. 38 and 39). 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. 5e). Also, intravenous injection of ethyl acetate depressed the vestibulo-ocular reflex in rats (Ref. 54). 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. 45). The specific effects observed in these studies indicate that each of these substances presents a potential to cause neurotoxic effects.

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 subchronic exposures from manufacturing, processing, use, and disposal of these substances.

EPA believes that the guidelines found at 40 CFR part 798 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, including some submitted to EPA during the public comment period, do not adequately assess the neurotoxic effects of the

substances subject to this rule (see Refs. 50, 51, 60, 73 and 74 for a detailed discussion of EPA's assessment). EPA has summarized its reasons for its finding for data insufficiency in the following Table 1:

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

| Name | Data Insufficiency | References |
|---|---|---|
| acetone (67–64–1). | a | 43 |
| | h | 4a |
| | d,h,i,j | 4b |
| | d,k,m | 4c |
| | l,m | 4d |
| | a,n | 4e |
| | p | 4f |
| | d,h,l | 4g |
| | h,r,y,z,aa | 4h |
| | h,m,q | 4i |
| | o,u | 5a |
| | d,k | 5b |
| | l,t | 5c |
| | d | 5d |
| | a,b,d,n,u | 5e |
| | b | 5f |
| | m,s,t | 5g |
| | d,t | 68a |
| | d,t | 68b |
| | m,ff,gg | 68c |
| *n*-amyl acetate, technical grade (628–63–7). | d,h,n,o | 9j |
| | h,n,o | 9k |
| 1-butanol (71–36–3). | a,n | 44 |
| | n | 9g |
| | a,d | 34 |
| | d,n | 52 |
| | a,d,s | 53 |
| *n*-butyl acetate (123–86–4). | g. | |
| diethyl ether (60–29–7). | a,d,m,n,t,bb | 13g |
| | a,d,m,t,bb | 13v |
| | a,m,t,bb | 13a |
| | n | 13b |
| | bb,cc,dd | 13c |
| | h,n,o | 13d |
| | c,bb | 13e |
| | h,r,y,z,aa | 13f |
| | n | 13h |
| | n | 13i |
| | ee | 13j |
| | n | 13k |
| | a,m,t,bb | 13m |
| | a,t,dd | 13p |
| | n | 13q |
| | h,n,o | 13r |

TABLE 1.— DATA INSUFFICIENCY FINDINGS UNDER TSCA 4(A)(1)(A)(II) AND (B)(II)—Continued

| Name | Data Insufficiency | References |
|---|---|---|
| | a,m,t,bb | 13t |
| 2-ethoxyethanol (110–80–5). | c,e,f,l | 38 |
| | c,e,f,l | 39 |
| | h,n,r,z,aa | 6a |
| | f,n | 6b |
| | n | 6c |
| | x | 6d |
| | h,n | 6i |
| ethyl acetate (141–78–6). | a,b,d,n | 5e |
| | n | 9c |
| isobutyl alcohol (78–83–1). | n | 9f |
| methyl isobutyl ketone (108–10–1). | f | 45 |
| | ee | 7a |
| | a,h,m,n,t,ff | 7b |
| | a,m,r,t,z,aa | 7c |
| | a,n,ff | 7d |
| | b,l,m,t | 7e |
| | c,ff | 7f |
| | a | 7h |
| | h,r,aa | 7i |
| | h,m,n,s,w,dd | 7j |
| | b,l,m,t | 8a |
| | v | 8b |
| | m,q,t | 8c |
| tetrahydrofuran (109–99–9). | n | 2a |
| | n | 2b |
| | n | 2c |
| | f,n | 2d |

a. Only one sex was tested.
b. Animals were exposed to more than one chemical.
c. Dose-response not clearly established.
d. Insufficient duration of exposure; not a subchronic test.
e. Provided data on effects to offspring only.
f. This is primarily a developmental toxicity test.
g. No study addressing neurotoxicity was found.
h. Description of methods insufficient to allow evaluation of test.
i. Inconclusive results.
j. No statistical treatment of results provided, or not possible given available data.
k. Relevance of results to human health uncertain.
l. Significance of results is unknown.
m. Small number of animals/subjects.
n. Insufficient number of neurotoxicity endpoints evaluated.
o. Description of results insufficient to allow evaluation of test.
p. Longer treatment durations should have been explored.
q. Sex of study animals not reported.
r. In situ perfusion not done.
s. Inappropriate route of administration used.
t. Only one dose level.
u. Short exposure period.
v. An *in-vitro* study.
w. Effects of treatment at end of study not determined.
x. Study of a structurally similar but less toxic chemical (Refs. 50 at 77 and 37).
y. Animals were not stored in preservative at 4° C for 8–12 hours prior to removal of the cranium and vertebral column.
z. Tissue sampling was inadequate.
aa. No special stains were used.
bb. Not a test of schedule-controlled operant behavior.
cc. Number of test animals not specified.
dd. Concentration/dose of test substance not specified.
ee. Test animal was not a mammal.
ff. Test not comparable to functional observational battery.
gg. Exposure levels and durations were inconsistent across subjects.

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 required testing will be relevant to a determination as to whether acute or subchronic exposure to these substances during manufacturing, processing, use, and disposal does or does not present an unreasonable risk of injury to human health.

*B. Test Standards*

Given the section 4(a)(1)(B) 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 requiring only neurotoxicity testing for the substances included in this final 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.

The following Table 2 lists the tests to be conducted on each substance.

TABLE 2.— TEST REQUIREMENTS

| Name | Required Test | Test Guideline |
|---|---|---|
| acetone (67–64–1) | Functional observational battery, acute and subchronic | 798.6050 |
| | Motor activity, acute and subchronic | 798.6200 |
| | Neuropathology, subchronic | 798.6400 |

TABLE 2.— TEST REQUIREMENTS—Continued

| Name | Required Test | Test Guideline |
|---|---|---|
| ..... | Schedule-controlled operant behavior, subchronic | 798.6500 |
| *n*-amyl acetone, technical grade (628–63–7). | Functional observational battery, acute and subchronic | 798.6050 |
| ..... | Motor activity, acute and subchronic | 798.6200 |
| ..... | Neuropathology, subchronic | 798.6400 |
| ..... | Schedule-controlled operant behavior, subchronic | 798.6500 |
| 1-butanol (71–36–3) | Functional observational battery, acute and subchronic | 798.6050 |
| ..... | Motor activity, acute and subchronic | 798.6200 |
| ..... | Neuropathology, subchronic | 798.6400 |
| ..... | Schedule-controlled operant behavior, subchronic | 798.6500 |
| *n*-butyl acetate (123–86–4) | Functional observational battery, acute and subchronic | 798.6050 |
| ..... | Motor activity, acute and subchronic | 798.6200 |
| ..... | Neuropathology, subchronic | 798.6400 |
| ..... | Schedule-controlled operant behavior, subchronic | 798.6500 |
| diethyl ether (60–29–7) | Functional observational battery, acute and subchronic | 798.6050 |
| ..... | Motor activity, acute and subchronic | 798.6200 |
| ..... | Neuropathology, subchronic | 798.6400 |
| ..... | Schedule-controlled operant behavior, subchronic | 798.6500 |
| 2-ethoxyethanol (110–80–5) | Functional observational battery, acute and subchronic | 798.6050 |
| ..... | Motor activity, acute and subchronic | 798.6200 |
| ..... | Neuropathology, subchronic | 798.6400 |
| ..... | Schedule-controlled operant behavior, subchronic | 798.6500 |
| ethyl acetate (141–78–6) | Functional observational battery, acute and subchronic | 798.6050 |
| ..... | Motor activity, acute and subchronic | 798.6200 |
| ..... | Neuropathology, subchronic | 798.6400 |
| ..... | Schedule-controlled operant behavior, subchronic | 798.6500 |
| isobutyl alcohol (78–83–1) | Functional observational battery, acute and subchronic | 798.6050 |
| ..... | Motor activity, acute and subchronic | 798.6200 |
| ..... | Neuropathology, subchronic | 798.6400 |
| ..... | Schedule-controlled operant behavior, subchronic | 798.6500 |
| methyl isobutyl ketone (108–10–1). | Functional observational battery, acute and subchronic | 798.6050 |
| ..... | Motor activity, acute and subchronic | 798.6200 |
| ..... | Neuropathology, subchronic | 798.6400 |
| ..... | Schedule-controlled operant behavior, subchronic | 798.6500 |
| tetrahydrofuran (109–99–9) | Functional observational battery, acute and subchronic | 798.6050 |
| ..... | Motor activity, acute and subchronic | 798.6200 |
| ..... | Neuropathology, subchronic | 798.6400 |
| ..... | Schedule-controlled operant behavior, subchronic | 798.6500 |

EPA is requiring that the above-referenced neurotoxicity test guidelines in Table 2, and modifications to these guidelines noted in this rule or granted in the future, be the test standards for testing these substances. The testing must also be conducted in accordance with EPA's TSCA Good Laboratory Practice Standards (GLPs) in 40 CFR part 792.

The testing shall be performed in rats with inhalation as the route of administration. The duration of exposure for acute testing will be 6 hours per day for 1 day; duration of exposure for subchronic testing will be 6 hours per day for 5 days per week for 13 weeks (90 days).

*C. Test Substances*—

With the exception of *n*-amyl acetate, EPA is requiring that the purity of the test substances be at least 99 percent or greater. In the case of *n*-amyl acetate, the test sponsor will be required to select and test a technical grade containing a representative percent of *n*-amyl acetate. The test sponsor will indicate the percent of *n*-amyl acetate in the test substance in the test protocol. EPA believes that the percent purities listed in the following Table 3 are readily available.

TABLE 3.— AVAILABLE PURITY OF TEST SUBSTANCE

| Substance | CAS No. | Available percent purity |
|---|---|---|
| acetone | 67–64–1 | 99.9 |
| *n*-amyl acetate | 628–63–7 | 60.0–70.0 |
| 1-butanol | 71–36–3 | 99.9 |
| *n*-butyl acetate | 123–86–4 | 99.9 |
| diethyl ether | 60–29–7 | 99.9 |

TABLE 3.— AVAILABLE PURITY OF TEST SUBSTANCE—Continued

| Substance | CAS No. | Available percent purity |
|---|---|---|
| 2-ethoxyethanol | 110–80–5 | 99.0 |
| ethyl acetate | 141–78–6 | 99.9 |
| isobutyl alcohol | 78–83–1 | 99.9 |
| methyl isobutyl ketone. | 108–10–1 | 99.5 |
| tetrahydrofuran | 109–99–9 | 99.5 |

With the exception of *n*-amyl acetate, 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. In the case of *n*-amyl acetate, EPA has specified that a representative technical

grade be tested because that is the substance which is produced and to which there is exposure.

*D. Persons Required to Test*

Because of the findings in Unit III.A of this preamble, EPA is requiring 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 rule. This period is defined in 40 CFR 791.3(h). Byproduct manufacturers and importers of one or more of these substances will 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, will be required to submit letters of intent or exemption applications. Pursuant to an amendment to part 790, small quantity research and development manufacturers are not required to submit letters of intent or exemption applications initially (40 CFR 790.42 to 790.48). Such manufacturers should consult the **Federal Register** of May 7, 1990 (55 FR 18881) for further details.

EPA is not requiring the submission of equivalence data as a condition for exemption from the testing requirements for these substances. With the exception of *n*-amyl acetate, EPA is interested in evaluating the effects attributable to the substances themselves and has specified relatively pure substances for testing.

*E. Reporting Requirements*

As required in 40 CFR 799.10, all data developed under the final rule must be developed, reported and retained in accordance with the TSCA GLPs which appear in 40 CFR part 792.

As required by TSCA section 4(b)(1)(C), EPA is requiring specific reports for each of the tests as follows. Final reports of acute testing under 40 CFR 798.6050 and 798.6200 will be due 9 months from the effective date of the final rule; interim progress reports will be due 6 months from the effective date of the final rule.

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

For subchronic testing under 40 CFR 798.6500, final reports for acetone, 1-butanol, and ethyl acetate will be due 24 months from the effective date of the final rule, final reports for methyl isobutyl ketone, 2-ethoxyethanol, and diethyl ether will be due 30 months from the effective date of the final rule, and final reports for *n*-butyl acetate, isobutyl alcohol, tetrahydrofuran, and *n*-amyl acetate will be due 36 months from the effective date of the final rule. Interim progress reports will be due at 6-month intervals beginning 6 months from the effective date of the final rule.

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 required in this rule (Ref. 48). If test sponsors can document that the neurotoxicity testing required in this rule needs to be staggered due to insufficient laboratory availability and that reporting deadlines cannot be met, they must request an extension of the deadline by submitting a written request. If the testing must be staggered, EPA anticipates that it will first grant requests for those substances which lack a 4(a)(1)(A) finding and have the lowest production as reported in the proposed rule (56 FR 9107–9108, March 4, 1991).

TSCA section 14(b) governs EPA disclosure of all test data submitted pursuant to section 4 of TSCA. Upon receipt of data required by this rule, EPA will publish a notice of receipt in the **Federal Register** as required by section 4(d).

Persons who export a chemical substance or mixture subject to a section 4 test rule are subject to the export reporting requirements of TSCA section 12(b). Final regulations interpreting the requirements of section 12(b) are in 40 CFR part 707. In brief, as of the effective date of this test rule, an exporter of any of the substances listed in this rule must report to EPA upon the first annual export of the compound to any one country. EPA will notify the foreign country about the test rule for the substance.

*F. Enforcement Provisions*

EPA considers failure to comply with any aspect of a section 4 rule to be a violation of section 15 of TSCA. Section 15 of TSCA makes it unlawful for any person to fail or refuse to comply with any rule or order issued under section 4. Section 15(3) of TSCA makes it unlawful for any person to fail or refuse to (1) establish or maintain records, (2) submit reports, notices, or other information, or (3) permit access to or copying of records required by TSCA or any regulation or rule issued under TSCA.

Additionally, TSCA section 15(4) makes it unlawful for any person to fail or refuse to permit entry or inspection as required by section 11. Section 11 applies to any "establishment, facility, or premises in which chemical substances or mixtures are manufactured, processed, stored, or held before or after their distribution in commerce ..." EPA considers a testing facility to be a place where the substance is held or stored, and therefore, subject to inspection. Laboratory inspections and data audits will be conducted periodically in accordance with the authority and procedures outlined in TSCA section 11 by duly designated representatives of the EPA for the purpose of determining compliance with this final test rule. These inspections may be conducted for purposes which include verification that testing has begun, that schedules are being met, that reports accurately reflect the underlying raw data, interpretations and evaluations, and to determine compliance with TSCA GLP Standards and the test standards established in the rule.

EPA's authority to inspect a testing facility also derives from section 4(b)(1) of TSCA, which directs EPA to promulgate standards for the development of test data. These standards are defined in section 3(12)(B) of TSCA to include those requirements necessary to assure that data developed under testing rules are reliable and adequate, and such other requirements as are necessary to provide such assurance. EPA maintains that laboratory inspections are necessary to provide this assurance.

Violators of TSCA are subject to criminal and civil liability. Persons who submit materially misleading or false information in connection with the requirement of any provision of this rule may be subject to penalties which may be calculated as if they never submitted their data. Under the penalty provision of section 16 of TSCA, any person who violates section 15 could be subject to a civil penalty of up to $25,000 for each violation with each day of operation in violation constituting a separate violation. This provision would be applicable primarily to manufacturers or processors that fail to submit a letter of intent or an exemption request and that continue manufacturing or processing after the deadlines for such submissions.

This provision would also apply to processors that fail to submit a letter of intent or an exemption application and continue processing after EPA has notified them of their obligation to

submit such documents (see 40 CFR 790.48(b)).

Knowing or willful violations could lead to the imposition of criminal penalties of up to $25,000 for each day of violation, imprisonment for up to 1 year, or both. In determining the amount of penalty, EPA will take into account the seriousness of the violation and the degree of culpability of the violator as well as all the other factors listed in TSCA section 16. Other remedies are available to EPA under section 17 of TSCA, such as seeking injunction to restrain violations of TSCA section 4.

Individuals as well as corporations could be subject to enforcement actions. Sections 15 and 16 of TSCA apply to "any person" who violates various provisions of TSCA. EPA may, at its discretion, proceed against individuals as well as companies. In particular, this includes individuals who report false information or who cause it to be reported. In addition, the submission of false, fictitious, or fraudulent statements is a violation under 18 U.S.C. 1001.

## IV. Economic Analysis

To assess the potential economic impact of this rule, EPA has prepared an economic analysis (Ref. 67) that evaluates the potential for significant economic impacts of this testing on test sponsors. The economic analysis estimates the costs of conducting the required testing for each of the 10 substances, including both laboratory and administrative costs, and evaluates the potential for significant adverse economic impacts as a result of those 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 4:

TABLE 4.—COST RANGE OF TSCA NEUROTOXICITY TESTS

| Test | Cost Range in Dollars |
|---|---|
| Functional observational battery. | |
| Acute, 40 CFR 798.6050 | 16,500–23,325 |
| Subchronic, 40 CFR 798.6050. | 92,013–170,625 |
| Motor Activity. | |
| Acute, 40 CFR 798.6200 | 18,625–26,388 |
| Subchronic, 40 CFR 798.6200. | 86,275–162,388 |
| Neuropathology. | |
| Subchronic, 40 CFR 798.6400. | 112,638–200,125 |
| Schedule-controlled operant behavior. | |
| Subchronic, 40 CFR 798.6500. | 168,138–292,250 |

Actual test costs per substance should be lower since EPA assumed that each test would be done independently of one another. However, 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 required 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 $96,081 for each of the 10 substances.

Dividing these annualized costs by the appropriate production volumes listed for each substance in Table 3 of the proposed rule (56 FR 9105, March 4, 1991), and then dividing these amounts by the appropriate price per pound in the following Table 5, the percent price increase per pound due to testing was estimated.

TABLE 5.—ECONOMIC ANALYSIS

| Chemical | CAS No. | Chemical Price/Pound (Dollars) | Percent Chemical Price Increase/Pound |
|---|---|---|---|
| acetone | 67–64–1 | 0.310 | 0.0071–0.0126 |
| *n*-amyl acetate, technical grade | 628–63–7 | 0.660 | CBI |
| 1-butanol | 71–36–3 | 0.380 | 0.0077–0.0138 |
| *n*-butyl acetate | 123–86–4 | 0.430 | 0.0648–0.1147 |
| diethyl ether | 60–29–7 | 0.515 | 0.1916–0.3392 |
| 2-ethoxyethanol | 110–80–5 | 0.750 | 0.0594–0.1052 |
| ethyl acetate | 141–78–6 | 0.410 | 0.0514–0.0911 |
| isobutyl alcohol | 78–83–1 | 0.380 | 0.0863–0.1528 |
| methyl isobutyl ketone | 108–10–1 | 0.450 | 0.0535–0.0948 |
| tetrahydrofuran | 109–99–9 | 1.220 | 0.0289–0.0511 |

Table 5 shows that for the 10 substances, unit test costs are substantially lower than 1 percent of price. For these 10 substances, it appears that the costs of testing will have little significant adverse economic impact.

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.

## V. Availability of Test Facilities and Personnel

EPA has determined that test facilities and personnel are available to perform the testing specified in this final rule (Refs. 48 and 49). EPA also anticipates that laboratory capacity will increase to accommodate the demand created by future rulemaking.

## VI. Rulemaking Record

EPA has established a record for this rulemaking (docket number OPPTS–42134B). In addition, each substance in the rule has a separate docket number. This record contains the basic information considered by EPA in developing this final rule and appropriate **Federal Register** notices.

A public version of the record, from which all Confidential Business Information (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 a.m. to 12 noon, and 1 p.m. to 4 p.m., 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 (48 FR 31786, July 11, 1983).

(c) Notice of proposed multi-substance rule for the testing of neurotoxicity (56 FR 9105, March 4, 1991).

(d) Notice of TSCA section 4(a)(1)(B)(i) statement of policy (58 FR 28736, May 14, 1993).

(e) Notice of proposed test rule for chloromethane (45 FR 48524, July 18, 1980).

(f) Notice of proposed OSHA health standard for 2-ethoxyethanol (58 FR 15526, March 23, 1993).

(2) TSCA test guidelines cited as test standards for this rule.

(3) Communications consisting of:

(a) Contact reports of telephone conversations.

(b) Meeting summaries.

(4) Support documents consisting of:

(a) Economic impact analysis for the substances contained in this final rule.

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

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## VII. 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 test rule is not major because it does not meet any of the criteria set forth in section 1(b) of the Order; i.e., it will not have an annual effect on the economy of at least $100 million, will not cause a major increase in prices, and will not have a significant adverse effect on competition or the ability of U.S. enterprises to compete with foreign enterprises.

This 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., EPA is certifying that this test rule will not have a

significant impact on a substantial number of small businesses because: (1) They are not likely to perform testing themselves, or to participate in the organization of the testing effort; (2) they will 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 final 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.

**List of Subjects in 40 CFR Part 799**

Chemicals, Chemical export, Environmental protection, Good laboratory practices, Hazardous substances, Laboratories, Reporting and recordkeeping requirements, Testing.

Dated: July 12, 1993.

**Victor J. Kimm,**

*Acting Assistant Administrator for Prevention, Pesticides and Toxic Substances.*

Therefore, 40 CFR, chapter I, subchapter R, part 799 is 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 adding § 799.5050 to subpart D to read as follows:

**§ 799.5050 Multi-test requirements for specific chemical substances.**

(a) *General testing provisions*—(1) *Identification of test substance.* Table 1 in paragraph (a)(5) of this section identifies those chemical substances that shall be tested in accordance with this section. The purity of each test substance shall be 99 percent or greater, unless otherwise specified in Table 1.

(2) *Persons required to submit study plans, conduct tests, and submit data.* All persons who manufacture (including import) or process or intend to manufacture or process, including persons who manufacture or process or intend to manufacture or process one or more of the substances listed in Table 1 in paragraph (a)(5) of this section as a byproduct, or who import or intend to import products which contain one or more of the substances listed in Table 1 in paragraph (a)(5) of this section after the effective date specified in Table 1 under paragraph (a)(5) of this section to the end of the reimbursement period, shall submit letters of intent to conduct testing, submit study plans, conduct tests and submit data, or submit exemption applications, as specified in this section, subpart A of this part, and parts 790 and 792 of this chapter for single-phase rulemaking. Persons who manufacture, import, or process one or more of the substances listed in Table 1 in paragraph (a)(5) of this section only as an impurity are not subject to these requirements.

(3) *Applicability of test guidelines.* The guidelines and other test methods cited in Table 1 under paragraph (a)(5) of this section are referenced here as they exist on the effective date listed in Table 1 for that specific test.

(4) *Reporting requirements.* All testing requirements in this section are subject to the submission of interim progress reports every 6 months beginning 6 months after the effective date for that specific test listed in Table 1 under paragraph (a)(5) of this section. The date for the submission of final reports is specified as the number of months after the effective date for the specific test listed in Table 1 under paragraph (a)(5) of this section.

(5) *Designation of specific chemical substances and applicable testing requirements.* The substances identified by name and CAS number in Table 1 of this paragraph shall be tested in accordance with the designated testing requirements and any additional requirements and limitations specified in the following Table 1:

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 | Final Reports Due | Effective dates |
|---|---|---|---|---|---|---|
| 60–29–7 | Diethyl Ether | | | | | |
| | Health effects testing: | | | | | |
| | Acute neurotoxicity: | | | | | |
| | Functional observational battery | § 798.6050, except paragraphs (d)(1)(i), (5) and (6). | (1)(i), (6)(i), (9)(i) ... | ..... | 9 mo. | (9/9/93) |
| | Motor activity ..... | § 798.6200, except paragraphs (d)(1)(i), (5) and (6). | (1)(i), (6)(i), 2)(i) .... | ..... | 9 mo. | (9/9/93) |
| | Subchronic neurotoxicity: | | | | | |
| | Functional observational battery | § 798.6050, except paragraphs (d)(1)(i), (5) and (6). | (1)(i), (6)(ii), 2)(i) ... | ..... | 21 mo. | (9/9/93) |
| | Motor activity ..... | § 798.6200, except paragraphs (d)(1)(i), (5) and (6). | (1)(i), (6)(ii), 2)(i) ... | ..... | 21 mo. | (9/9/93) |

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 | Final Reports Due | Effective dates |
|---|---|---|---|---|---|---|
| | Neuropathology | §798.6400, except paragraphs (d)(1)(i), (5) and (6). | (1)(i), (6)(ii), 2)(i) | | 21 mo. | (9/9/93) |
| | Schedule-controlled operant behavior | §798.6500, except paragraphs (d)(2)(i)(A), (iii)(A), (6), (7) and (8)(v). | (1)(i), (3)(i), (6)(ii), (vi), 2)(i). | | 30 mo. | (9/9/93) |
| 67-64-1 | Acetone | | | | | |
| | Health effects testing: | | | | | |
| | Acute neurotoxicity: | | | | | |
| | Functional observational battery | §798.6050, except paragraphs (d)(1)(i), (5) and (6). | (1)(i), (6)(i), 2)(i) | | 9 mo. | (9/9/93) |
| | Motor activity | §798.6200, except paragraphs (d)(1)(i), (5) and (6). | (1)(i), (6)(i), 2)(i) | | 9 mo. | (9/9/93) |
| | Subchronic neurotoxicity: | | | | | |
| | Functional observational battery | §798.6050, except paragraphs (d)(1)(i), (5) and (6). | (1)(i), (6)(ii), 2)(i) | | 21 mo. | (9/9/93) |
| | Motor activity | §798.6200, except paragraphs (d)(1)(i), (5) and (6). | (1)(i), (6)(ii), 2)(i) | | 21 mo. | (9/9/93) |
| | Neuropathology | §798.6400, except paragraphs (d)(1)(i), (5) and (6). | (1)(i), (6)(ii), 2)(i) | | 21 mo. | (9/9/93) |
| | Schedule-controlled operant behavior | §798.6500, except paragraphs (d)(2)(i)(A), (iii)(A), (6), (7) and (8)(v). | (1)(i), (3)(i), (6)(ii), (vi), 2)(i). | | 24 mo. | (9/9/93) |
| 71-36-3 | 1-Butanol | | | | | |
| | Health effects testing: | | | | | |
| | Acute neurotoxicity: | | | | | |
| | Functional observational battery | §798.6050, except paragraphs (d)(1)(i), (5) and (6). | (1)(i), (6)(i), 2)(i) | | 9 mo. | (9/9/93) |
| | Motor activity | §798.6200, except paragraphs (d)(1)(i), (5) and (6). | (1)(i), (6)(i), 2)(i) | | 9 mo. | (9/9/93) |
| | Subchronic neurotoxicity: | | | | | |
| | Functional observational battery | §798.6050, except paragraphs (d)(1)(i), (5) and (6). | (1)(i), (6)(ii), 2)(i) | | 21 mo. | (9/9/93) |
| | Motor activity | §798.6200, except paragraphs (d)(1)(i), (5) and (6). | (1)(i), (6)(ii), 2)(i) | | 21 mo. | (9/9/93) |
| | Neuropathology | §798.6400, except paragraphs (d)(1)(i), (5) and (6). | (1)(i), (6)(ii), 2)(i) | | 21 mo. | (9/9/93) |
| | Schedule-controlled operant behavior | §798.6500, except paragraphs (d)(2)(i)(A), (iii)(A), (6), (7) and (8)(v). | (1)(i), (3)(i), (6)(ii), (vi), 2)(i). | | 24 mo. | (9/9/93) |
| 78-83-1 | Isobutyl Alcohol | | | | | |
| | Health effects testing: | | | | | |
| | Acute 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 | Final Reports Due | Effective dates |
|---|---|---|---|---|---|---|
| | Functional observational battery | § 798.6050, except paragraphs (d)(1)(i), (5) and (6). | (1)(i), (6)(i), 2)(i) | | 9 mo. | (9/9/93) |
| | Motor activity | § 798.6200, except paragraphs (d)(1)(i), (5) and (6). | (1)(i), (6)(i), 2)(i) | | 9 mo. | (9/9/93) |
| | Subchronic neurotoxicity: | | | | | |
| | Functional observational battery | § 798.6050, except paragraphs (d)(1)(i), (5) and (6). | (1)(i), (6)(ii), 2)(i) | | 21 mo. | (9/9/93) |
| | Motor activity | § 798.6200, except paragraphs (d)(1)(i), (5) and (6). | (1)(i), (6)(ii), 2)(i) | | 21 mo. | (9/9/93) |
| | Neuropathology | § 798.6400, except paragraphs (d)(1)(i), (5) and (6). | (1)(i), (6)(ii), 2)(i) | | 21 mo. | (9/9/93) |
| | Schedule-controlled operant behavior | § 798.6500, except paragraphs (d)(2)(i)(A), (iii)(A), (6), (7) and (8)(v). | (1)(i), (3)(i), (6)(ii), (vi), 2)(i). | | 36 mo. | (9/9/93) |
| 108-10-1 | Methyl Isobutyl Ketone | | | | | |
| | Health effects testing: | | | | | |
| | Acute neurotoxicity: | | | | | |
| | Functional observational battery | § 798.6050, except paragraphs (d)(1)(i), (5) and (6). | (1)(i), (6)(i), 2)(i) | | 9 mo. | (9/9/93) |
| | Motor activity | § 798.6200, except paragraphs (d)(1)(i), (5) and (6). | (1)(i), (6)(i), 2)(i) | | 9 mo. | (9/9/93) |
| | Subchronic neurotoxicity: | | | | | |
| | Functional observational battery | § 798.6050, except paragraphs (d)(1)(i), (5) and (6). | (1)(i), (6)(ii), 2)(i) | | 21 mo. | (9/9/93) |
| | Motor activity | § 798.6200, except paragraphs (d)(1)(i), (5) and (6). | (1)(i), (6)(ii), 2)(i) | | 21 mo. | (9/9/93) |
| | Neuropathology | § 798.6400, except paragraphs (d)(1)(i), (5) and (6). | (1)(i), (6)(ii), 2)(i) | | 21 mo. | (9/9/93) |
| | Schedule-controlled operant behavior | § 798.6500, except paragraphs (d)(2)(i)(A), (iii)(A), (6), (7) and (8)(v). | (1)(i), (3)(i), (6)(ii), (vi), 2)(i). | | 30 mo. | (9/9/93) |
| 109-99-9 | Tetrahydrofuran | | | | | |
| | Health effects testing: | | | | | |
| | Acute neurotoxicity: | | | | | |
| | Functional observational battery | § 798.6050, except paragraphs (d)(1)(i), (5) and (6). | (1)(i), (6)(i), 2)(i) | | 9 mo. | (9/9/93) |
| | Motor activity | § 798.6200, except paragraphs (d)(1)(i), (5) and (6). | (1)(i), (6)(i), 2)(i) | | 9 mo. | (9/9/93) |
| | Subchronic neurotoxicity: | | | | | |
| | Functional observational battery | § 798.6050, except paragraphs (d)(1)(i), (5) and (6) | (1)(i), (6)(ii), 2)(i) | | 21 mo. | (9/9/93) |

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 | Final Reports Due | Effective dates |
|---|---|---|---|---|---|---|
| | Motor activity | § 798.6200, except paragraphs (d)(1)(i), (5) and (6). | (1)(i), (6)(ii), 2)(i) | | 21 mo. | (9/9/93) |
| | Neuropathology | § 798.6400, except paragraphs (d)(1)(i), (5) and (6). | (1)(i), (6)(ii), 2)(i) | | 21 mo. | (9/9/93) |
| | Schedule-controlled operant behavior | § 798.6500, except paragraphs (d)(2)(i)(A), (iii)(A), (6), (7) and (8)(v). | (1)(i) (3)(i), (6)(ii), (vi), 2)(i). | | 36 mo. | (9/9/93) |
| 110-80-5 | 2-Ethoxyethanol | | | | | |
| | Health effects testing: | | | | | |
| | Acute neurotoxicity: | | | | | |
| | Functional observational battery | § 798.6050, except paragraphs (d)(1)(i), (5) and (6). | (1)(i), (6)(i), 2)(i) | | 9 mo. | (9/9/93) |
| | Motor activity | § 798.6200, except paragraphs (d)(1)(i), (5) and (6). | (1)(i), (6)(i), 2)(i) | | 9 mo. | (9/9/93) |
| | Subchronic neurotoxicity: | | | | | |
| | Functional observational battery | § 798.6050, except paragraphs (d)(1)(i), (5) and (6). | (1)(i), (6)(ii), 2)(i) | | 21 mo. | (9/9/93) |
| | Motor activity | § 798.6200, except paragraphs (d)(1)(i), (5) and (6). | (1)(i), (6)(ii), 2)(i) | | 21 mo. | (9/9/93) |
| | Neuropathology | § 798.6400, except paragraphs (d)(1)(i), (5) and (6). | (1)(i), (6)(ii), 2)(i) | | 21 mo. | (9/9/93) |
| | Schedule-controlled operant behavior | § 798.6500, except paragraphs (d)(2)(i)(A), (iii)(A), (6), (7) and (8)(v). | (1)(i), (3)(i), (6)(ii), (vi), 2)(i). | | 30 mo. | (9/9/93) |
| 123-86-4 | n-Butyl Acetate | | | | | |
| | Health effects testing: | | | | | |
| | Acute neurotoxicity: | | | | | |
| | Functional observational battery | § 798.6050, except paragraphs (d)(1)(i), (5) and (6). | (1)(i), (6)(i), 2)(i) | | 9 mo. | (9/9/93) |
| | Motor activity | § 798.6200, except paragraphs (d)(1)(i), (5) and (6). | (1)(i), (6)(i), 2)(i) | | 9 mo. | (9/9/93) |
| | Subchronic neurotoxicity: | | | | | |
| | Functional observational battery | § 798.6050, except paragraphs (d)(1)(i), (5) and (6). | (1)(i), (6)(ii), 2)(i) | | 21 mo. | (9/9/93) |
| | Motor activity | § 798.6200, except paragraphs (d)(1)(i), (5) and (6). | (1)(i), (6)(ii), 2)(i) | | 21 mo. | (9/9/93) |
| | Neuropathology | § 798.6400, except paragraphs (d)(1)(i), (5) and (6). | (1)(i), (6)(ii), 2)(i) | | 21 mo. | (9/9/93) |
| | Schedule-controlled operant behavior | § 798.6500, except paragraphs (d)(2)(i)(A), (iii)(A), (6), (7) and (8)(v). | (1)(i), (3)(i), (6)(ii), (vi), 2)(i). | | 36 mo. | (9/9/93) |

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 | Final Reports Due | Effective dates |
|---|---|---|---|---|---|---|
| 141-78-6 | Ethyl Acetate | | | | | |
| | Health effects testing: | | | | | |
| | Acute neurotoxicity: | | | | | |
| | Functional observational battery | § 798.6050, except paragraphs (d)(1)(i), (5) and (6). | (1)(i), (6)(i), 2)(i) | | 9 mo. | (9/9/93) |
| | Motor activity | § 798.6200, except paragraphs (d)(1)(i), (5) and (6). | (1)(i), (6)(i), 2)(i) | | 9 mo. | (9/9/93) |
| | Subchronic neurotoxicity: | | | | | |
| | Functional observational battery | § 798.6050, except paragraphs (d)(1)(i), (5) and (6). | (1)(i), (6)(ii), 2)(i) | | 21 mo. | (9/9/93) |
| | Motor activity | § 798.6200, except paragraphs (d)(1)(i), (5) and (6). | (1)(i), (6)(ii), 2)(i) | | 21 mo. | (9/9/93) |
| | Neuropathology | § 798.6400, except paragraphs (d)(1)(i), (5) and (6). | (1)(i), (6)(ii), 2)(i) | | 21 mo. | (9/9/93) |
| | Schedule-controlled operant behavior | § 798.6500, except paragraphs (d)(2)(i)(A), (iii)(A), (6), (7) and (8)(v). | (1)(i), (3)(i), (6)(ii), (vi), 2)(i). | | 24 mo. | (9/9/93) |
| 628-63-7 | *n*-Amyl Acetate | | | | | |
| | Health effects testing: | | | | | |
| | Acute neurotoxicity: | | | | | |
| | Functional observational battery | § 798.6050, except paragraphs (d)(1)(i), (5) and (6). | (1)(i), (6)(i), 2)(i), (10)(i). | | 9 mo. | (9/9/93) |
| | Motor activity | § 798.6200, except paragraphs (d)(1)(i), (5) and (6). | (1)(i), (6)(i), 2)(i), (10)(i). | | 9 mo. | (9/9/93) |
| | Subchronic neurotoxicity: | | | | | |
| | Functional observational battery | § 798.6050, except paragraphs (d)(1)(i), (5) and (6). | (1)(i), (6)(ii), 2)(i), (10)(i). | | 21 mo. | (9/9/93) |
| | Motor activity | § 798.6200, except paragraphs (d)(1)(i), (5) and (6). | (1)(i), (6)(ii), 2)(i), (10)(i). | | 21 mo. | (9/9/93) |
| | Neuropathology | § 798.6400, except paragraphs (d)(1)(i), (5) and (6). | (1)(i), (6)(ii), 2)(i), (10)(i). | | 21 mo. | (9/9/93) |
| | Schedule-controlled operant behavior | § 798.6500, except paragraphs (d)(2)(i)(A), (iii)(A), (6), (7) and (8)(v). | (1)(i), (3)(i), (6)(ii), (vi), 2)(i), (10)(i). | | 36 mo. | (9/9/93) |

(b) *Additional testing requirements.* In addition to the testing requirements specified in Table 1 under paragraph (a)(5) of this section, the following additional requirements also apply when specified for a particular chemical substance in the "(b) Additional testing requirements" column of Table 1:

(1) *Test species and strains.* If a species other than the one specified is used, the test sponsors shall provide justification/reasoning to the Agency for their selection. Commonly used laboratory strains shall be employed. Commonly used species include the mouse, rabbit and hamster. The test species shall be the:

(i) Rat.

(ii) [Reserved]

(2) *Age.* [Reserved]

(3) *Sex.* (i) Approximately equal numbers of male and female animals are required for each dose level and control group. As an alternative, one sex may be tested, if 10 animals per dose and control are used.

(ii) [Reserved]

(4) *Numbers per dose group.* [Reserved]

(5) *Control groups.* [Reserved]

(6) *Duration and frequency of exposure.* (i) Animals shall be exposed for 6 hours per day for 1 day.

(ii) Animals shall be exposed for 6 hours per day, 5 days per week for a 90-day period.

(iii)–(v) [Reserved]

(vi) A multiple fixed-interval fixed-ratio schedule shall be used. Fixed-ratio and fixed-interval contingencies shall alternate throughout daily test sessions of at least 60 minutes duration.

(7) *Dose levels and dose selection.* [Reserved]

(8) *Test substance and administration.* [Reserved]

2) *Route of exposure.* (i) Animals shall be exposed via the inhalation route.

(ii) [Reserved]

(10) *Percent purity.* (i) A technical grade of *n*-amyl acetate shall be the test substance. The percent *n*-amyl acetate in the test substance shall be representative of the technical grades and shall be selected by the test sponsor. The test sponsor shall specify the percent *n*-amyl acetate in the test substance in the test protocol.

(ii) [Reserved]

(11) *Observation period.* [Reserved]

(12) *Test Procedures.* [Reserved]

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