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OFFICE OF  
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Proposed Design for a Retrospective Study  
of PMN Hazard Predictions

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Attached for review by the Science Advisory Board's Environmental Health Committee is the Office of Pesticides and Toxic Substances' proposed design for a retrospective study of PMN hazard predictions. The purpose of the proposed study is to obtain some measure of the validity of the Office of Toxic Substances' use of structure activity relationships in its assessment of the potential hazards posed by Premanufacture Notification (PMN) chemicals submitted under section 5 of the Toxic Substances Control Act.

The document presents an introduction to and background information on the task facing OPTS in its efforts to assess the risks posed by "new" chemicals. This is followed by a description of the experimental design proposed for the study and includes discussion of the tests selected by OPTS for use in the study, the strategy for selecting a set of 100 chemicals from the PMN universe of over 4,000 chemicals, and the analytic approach which OPTS contemplates using in measuring the correlations between SAR-based hazard predictions and the results of the proposed laboratory testing.

In reviewing the proposed design the Environmental Health Committee is requested to focus on the appropriateness of: (1) the testing battery selected by OPTS within an approximate funding limit of \$50,000 per chemical; (2) the selection criteria and strategy for sampling 100 chemicals from the PMN universe; and (3) the approach proposed for analyzing the concordance of the SAR-based hazard predictions with the results of laboratory testing.

The OPTS in preparing the proposed design for the study has relied heavily on the helpful comments and suggestions offered by the Environmental Health Committee at the May 10, 1984, public meeting, in the July 19 letter reporting the Committee's formal positions, recommendations, and questions, and at the July 24 briefing of the committee by OPTS. I believe that the Science Advisory Board can continue to provide OPTS with critical review and comment on the technical merits of the design proposed for the retrospective study of PMN hazard predictions.

The results of this study are expected to provide information vital to an evaluation of the strengths and weaknesses of the current use of SAR in the PMN program. Moreover, the study might provide some indication of the costs and benefits to be derived from a limited set of testing in terms of its potential for (1) improving the present PMN hazard assessment process versus (2) creating economic barriers to the introduction of innovative PMN chemicals. Finally, as noted by the Environmental Health Committee in its formal comments, the test data generated through this proposal are expected to provide useful toxicologic information which could be used to improve the quality of the overall TSCA section 5 chemical assessment process.

In closing, I want to bring two OPTS activities to the attention of the Environmental Health Committee. The first concerns the possible development in OPTS of an expert system for hazard analysis, an enterprise that was suggested to OPTS by the Committee. This past summer, the Office was fortunate to have the services of Dr. Eden Fisher of Carnegie-Mellon University, an American Association for the Advancement of Science/EPA Environmental Science and Engineering Fellow, who prepared an evaluation of the potential role of expert systems in the new chemical hazard assessment process. Dr. Fisher is in the process of preparing a written report of her conclusions, a copy of which can be provided to the Committee if so desired. The second activity concerns a workshop that OPTS is sponsoring jointly with

the EPA Office of Research and Development's Health Effects Research Laboratory to be held in Research Triangle Park on October 25-26, 1984. The purpose of the workshop is to develop an Agency research strategy for the improved application of quantitative structure activity relationships (QSARs) and other computational techniques as tools for predicting health effects. Invited extramural participants<sup>1</sup> at the workshop include spokespersons for many of the state-of-the-art techniques presently being employed in computational studies to predict the biological chemistry of xenobiotic substances.

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<sup>1</sup>Drs. Corwin Hansch, Arnold Hagler, Peter Jurs, Gilles Klopman, Milan Randic, Gilda Loew, Paul Craig, Carrol Johnson, Harel Weinstein, Todd Wipke, and Peter Politzer.

## Proposed Design for a Retrospective Study of PMN Health Hazard Predictions

This paper proposes a design for a retrospective study of the approach used by the Environmental Protection Agency (EPA) in evaluating the hazards of new chemicals submitted to EPA under section 5 of the Toxic Substances Control Act (TSCA). More specifically, the purpose of this study is to obtain some measure of the validity of EPA's use of structure activity relationships in its assessment of the potential health hazards posed by "new" or Premanufacture Notification (PMN) chemicals submitted under TSCA section 5.

Under the proposed study, EPA plans to conduct a selected set of laboratory toxicity tests on a representative sample of the PMN chemicals. Test data obtained from the study will be compared with previously generated EPA PMN health hazard predictions in order to determine (1) the concordance of those predictions with results obtained by testing and (2) the extent to which EPA's health hazard assessments would have changed if similar test data had been available at the time that the PMN was reviewed.<sup>1</sup> It is hoped that the proposed project can contribute to the resolution of some of the major uncertainties surrounding the use of structure activity relationships as the basis for the hazard assessment of new chemicals. In addition to supporting the objectives of this project, the proposed testing is expected to generate useful toxicologic information which will expand the data base available to the overall TSCA section 5 chemical assessment process.

The testing approach proposed for this study may also be useful in indicating the types of test data that should be considered for inclusion in future PMN submissions. Moreover, the results of such a study might provide some basis for evaluating the relative costs and benefits of requiring limited testing on new chemicals.<sup>2</sup>

## INTRODUCTION

The Toxic Substances Control Act was passed by the Congress and signed by President Ford in 1976. The stated purpose of the Act is to "protect human health and the environment by requiring testing and necessary use restrictions on certain chemical substances" (P.L. 94-469, 1976). Under TSCA, the Congress decided to distinguish between so-called "new" and "existing" chemicals.<sup>3</sup> New chemicals, that is, those not appearing on an inventory of existing chemicals, are subject to premanufacture reporting requirements under section 5 of TSCA. Since publication of the inventory of existing chemicals in July 1979, Premanufacture Notifications have been received on some 4,000 new chemicals (see Figure 1).

TSCA section 5 requires that manufacturers and importers of new chemicals submit a Premanufacture Notification (PMN) to the EPA 90 days before they intend to commence manufacture or import. TSCA thus provides EPA with a 90-day review period, extendable with cause to 180 days, in which to complete its risk determination on each PMN chemical. (The task before EPA in regulating chemicals under TSCA is to distinguish between "reasonable" and "unreasonable" risks; as used in TSCA, "risk" is some function of hazard, i.e., toxicity, and exposure, and includes consideration of economics.) Under TSCA section 5, certain information must be provided in the notification, as follows:

- a description of the new chemical substance, its chemical identity, molecular structure, and common or trade name;
- the estimated total amount to be manufactured or processed;
- the proposed categories of use and the estimated amount to be used for each such category;
- a description of the by-products resulting from manufacture, processing, use, or disposal;
- the number of individuals expected to be exposed in their place of employment and estimates of the expected duration of exposure;
- the manner and methods of disposal; and
- any test data in the possession or control of the notifier related to the health or environmental effects of the substance (15 U.S.C. 2604(d)).

As can be seen in the above listing, TSCA does not require that submitters conduct toxicity testing prior to submission of the PMN; rather they need only supply any health or environmental test data which are available to them at the time of submission. Presently, EPA receives test data on fewer than 50% of all PMNs submitted; when provided, the data most commonly consist of acute lethality and local irritation studies (see subsequent discussion on this point).<sup>4</sup>

Given the general paucity of submitted test data on PMN chemicals, EPA has come to rely on structure activity relationships (SAR) in its evaluation of the potential hazards posed by these chemicals. The analysis performed by EPA in its use of SAR involves the following components:

- review of submitted test data, if any, on the PMN chemical;
- review of test data available on structurally analogous substances (these can be identified by either EPA or the submitter);
- use of quantitative SAR methods where available and applicable;
- the professional judgments of scientific assessors in interpreting and integrating the above, plus consideration of factors derived directly from the structure of the PMN chemical. These factors can include, for example, molecular shape and size, fundamental physical/chemical properties, log P, presence and positioning of reactive chemical functional groups, metabolic pathways, and so on (see Arcos, 1983; Arcos and Auer, in press).

The task before EPA is to determine, despite a paucity (oftentimes an absence) of test data, whether PMN chemicals, under their projected conditions of use, manufacturing, or processing, "may" or "will" present an unreasonable risk of injury to health or the environment. Under the former (TSCA section 5e or "may present") finding, the Agency can prohibit or limit manufacture processing, use, or disposal of the new chemical pending development of test data sufficient to permit a reasoned evaluation of the risks posed by the chemical (15 U.S.C. 2604(e)). In the event that EPA can support the finding that a

new chemical "will present" an unreasonable risk, the Agency can take action under TSCA section 5f to prohibit manufacture altogether or to limit its use or release without a requirement for development of additional test data (15 U.S.C. 2604(f)). To date, EPA has issued two TSCA section 5f orders (involving 3 PMN chemicals), and 7 unilateral TSCA section 5e orders (involving 15 PMN chemicals); 23 voluntary or consent 5e orders (involving 150 PMN chemicals) have also been instituted.<sup>5</sup> In addition, 77 PMN chemicals have been voluntarily withdrawn by the submitter in the face of a likely TSCA section 5e or 5f order. (EPA, 1984a).

In the event that EPA chooses not to take any action to control or otherwise limit a PMN chemical, the submitter is free to manufacture or import the chemical following expiration of the 90-day review period. Upon commencement of manufacture or import, the submitter is required to provide written notification of this fact to the EPA, after which the chemical will be placed on the inventory of existing chemicals. To date, a notice of commencement of manufacture or import has been received on approximately 50% of all PMNs submitted to the Agency (see Figure 2).

EPA's use of SAR in reaching PMN hazard assessment conclusions has been the subject of questioning and some criticism from the Congress, environmental groups, and others (Office of Technology Assessment, 1983; Government Accounting Office, 1984; American Chemical Society, 1984) who point out the many uncertainties associated with the approach. In response to these concerns as well as EPA's desire to have some measure of how well it is doing in predicting new chemical hazards, a design is hereby proposed for conducting a retrospective study of PMN hazard predictions. The objective of this effort is to obtain some indication of the validity of EPA's use of SAR in assessing the potential hazards posed by new chemicals.

## BACKGROUND

### The PMN Assessment Process

Figure 3 presents a schematic of the overall PMN risk assessment process employed by EPA. The first step in the process is a determination that all necessary information has been included in the notification. This is followed by a series of three meetings which bring senior level expertise to bear on the questions of chemistry, hazard, and exposure within the first 15 days of the 90-day period available to EPA for the assessment of each PMN chemical. Although generally characterized as "professional judgment" meetings, the initial discussions are supported by a variety of information gathering activities including: (1) identification of previously received PMN chemicals which structurally (or otherwise) resemble the newly submitted chemical; (2) substructure and nomenclature-based searches to identify potential analogues; (3) searches in handbooks and bibliographic data bases to identify pertinent literature on the PMN chemical and/or its potential analogues; (4) critical review of submitted test data with special emphasis on toxicologic testing; (5) calculation of a variety of physical chemical properties including water solubility (Banerjee et al., 1980) Koc, vapor pressure (Lyman et al., 1982), log P (Chou and Jurs, 1979), bioconcentration factor (Veith et al., 1979), etc.

The first of these meetings, known as Chemistry Review and Search Strategy (CRSS), (1) confirms the chemical identity of the substance in terms matching the name with the structural depiction provided, (2) considers (or develops as needed) the PMN chemical's industrial synthetic process to identify by-products or impurities which might be present (if by-products and/or impurities are identified by the submitter, the task is one of explaining and expanding on the information provided), (3) collects and/or estimates values of various physical chemical properties, and (4) attempts to understand how the substance

functions chemically in its projected use applications. The second professional judgment meeting is known as the Structure Activity Team (SAT) and is responsible for the initial assessment of the potential hazards posed by the chemical. The SAT is composed of senior scientists who specialize in organic chemistry, environmental chemistry, metabolism of xenobiotic chemicals, chemical carcinogenesis and mutagenesis, systemic toxicity, teratogenesis, and environmental toxicology. SAT consideration of a PMN chemical commences with a presentation by the CRSS chairman of the findings of that group. This is followed by discussions of (1) environmental fate, (2) health effects, and (3) environmental effects. The health effects discussion considers uptake, metabolism, distribution, excretion, and any specific toxicities suggested by the PMN chemical's structure or identified through preliminary information searches; test data provided with the notice are also discussed and evaluated at this time. The environmental effects discussion considers acute and chronic aquatic toxicity, bioconcentration potential, and terrestrial toxicity. The final professional judgment meeting is termed the Exposure Analysis Meeting (EXAM) and is responsible for consideration of the nature and magnitude of (1) occupational exposures associated with manufacture, processing, and use of the new chemical, (2) environmental releases resulting from these activities as well as disposal of chemical wastes, (3) consumer and environmental exposures (including drinking water), and (4) environmental fate (transport and transformations).

The three professional judgment meetings are followed by the initial risk assessment meeting, termed the Focus meeting. The Focus meeting is chaired by a regulatory decision-maker and brings together the chairpersons from the chemistry, hazard, and exposure meetings for synoptic presentations of the conclusions from each previous meeting followed by open discussion of the risk potential presented by the PMN chemical. Using the information and/or judgments developed to this point, a decision

is reached at the Focus meeting to either drop the chemical from further consideration (approximately 60% (EPA, 1984a) of all cases) or to pursue further review of the chemical, a process known as a "Detailed Review."<sup>6</sup> Thus at the crucial initial stages of the PMN review period, EPA has devised a "screening" procedure which relies on senior expertise to identify those PMN chemicals which are potentially hazardous and/or might have significant exposure and release potential, from other chemicals considered unlikely to present a significant risk of injury to health or the environment.

During the Detailed Review, those aspects of the case identified for further consideration at the Focus meeting are examined in depth by discipline experts. All available data on the PMN substance and its analogues are gathered and reviewed by the experts who prepare a written evaluation of the data and make appropriate recommendations. These recommendations are then reviewed by senior scientific and managerial staff who determine the nature and magnitude of potential hazards and then examine whether there is sufficient exposure such that the chemical might pose a significant risk. If the decision is reached that the chemical might pose such a risk, the case is presented to senior regulatory decision-makers at a "Disposition" meeting who decide whether the risk is "unreasonable." The possible outcomes of this meeting include: (1) control the chemical pending completion of needed testing under TSCA section 5e, (2) directly control the chemical under TSCA section 5f, or (3) drop the case from further consideration. All of the above decisions turn on the strength of the case made for an "unreasonable risk" determination with, as noted before, TSCA section 5e requiring a "may present" finding, TSCA section 5f a "will present" finding, and a drop resulting from the inability to meet either of these tests.

## Test Data Received in PMNs

As noted earlier, TSCA section 5 does not require the provision of test data with incoming PMN submissions. Rather, submitters must provide any test data that are available to them at the time of submission. Table 1 presents summary statistics for test data submitted with PMNs. As can be seen, 52% of all PMNs contain no test data of any type; the situation is somewhat better for nonpolymeric PMN chemicals, of which only 39% do not contain any test data. In general, health test data are more commonly provided than ecotoxicological or environmental fate data. Among the various types of health test data provided, the most commonly received studies are various acute tests (specifically, oral and dermal acute toxicity and skin and eye irritation studies), with mutagenicity, dermal sensitization, and "other" health studies appearing less frequently. "Other" health test data include repeated dose toxicity studies, teratogenicity assays, phototoxicity studies, and a variety of other toxicity studies. (The reader is also referred to an earlier evaluation of the test data provided in PMNs prepared by the Office of Technology Assessment, 1983.)

Table 2 provides a summary of the combinations of different health test data that are most commonly encountered among PMNs containing health data. Thus, this table gives an indication of the extent of the testing that is undertaken for those cases that contain health test data. The most frequently encountered combinations of tests submitted with PMNs consist of acute toxicity (any route) and local irritation studies (34% of the 1560 PMN cases containing health test data); these for the most part take the form of the battery required for labeling purposes under the Federal Hazardous Substances Act (16 CFR 1500). An equal number (522 or 33%) of the health data-containing cases include acute toxicity (any route) and irritation studies (both skin and eye) in combination with any one or more of sensitization, mutagenicity, or "other" health test data. Sixty (or 4%) of the

data-containing cases contain only sensitization, mutagenicity, and/or "other" health test data (thus they do not contain acute or local toxicity testing). Table 3 reports the number of PMNs which contain one category of health test data, two categories of test data, and so on through the eight health test data categories included in TDIS, an EPA in-house PMN information system.

The amount and types of health test data provided with PMNs can be contrasted with the data estimated (National Research Council, 1984) to be available on chemical substances contained in the TSCA inventory of existing chemicals. Table 4 presents estimated percentages of TSCA existing chemicals which have undergone various types of health effects testing with the results of the testing being publicly available (i.e., additional test data may exist in restricted access files). The table also presents corresponding figures for the set of PMN chemicals. As Table 4 illustrates, compared with a published estimate of available data on TSCA existing chemicals (NRC, 1984), relatively more data are available on the set of PMN chemicals than is the case for TSCA existing chemicals. However, in absolute terms, available data on PMN chemicals for endpoints other than acute toxicity and local irritation are limited. This is a serious limitation since studies such as sensitization, mutagenicity, reproductive/developmental toxicity, repeated dose toxicity, and so on, are generally viewed as being more critical to an overall assessment of health hazards than are acute studies.

#### The Use of SAR in PMN Health Hazard Assessments

Given the limitations of the test data which are provided with PMNs, EPA has evolved a reliance on structure activity relationships (SAR) in its evaluation of the potential hazards posed by PMN chemicals.<sup>7</sup> EPA's operational definition of "structure activity relationships" was described above as being comprised of four components. The first of these components,

submitted test data, has already been discussed. The second of the components, data on analogous substances, deserves some comment. In order for an analogue to be useful to EPA, it must resemble the PMN chemical in one or more critical aspects (e.g., structurally, substructurally, physicochemically, etc.) and at the same time must have pertinent toxicologic data available on it in the scientific literature. It has been EPA's experience, and the point was recently confirmed by the NRC (1984), that available test data are very limited for most chemicals, but especially so for TSCA chemicals. This factor becomes a major limitation on the usefulness of many potential analogues.

Analogous substances may be identified by either EPA or the submitter. The latter instance most often takes the form of test data on structurally related substances which are existing chemicals produced by the submitter. The data provided tend to resemble in scope the types described earlier as typically accompanying PMN submissions (i.e., acute toxicity and local irritation studies, occasionally mutagenicity or repeated dose toxicity studies). EPA relies on two sources in its internal efforts to identify chemical analogues. These consist of analogue recommendations offered by members of the Structure Activity Team and other technical staff, and structural analogues retrieved from several publicly available automated chemical substructure and nomenclature search systems.<sup>8</sup> In the former instance, the proposed analogues often provide a rich source of pertinent information which can be applied to the assessment effort. The Structure Activity Team and other technical staff also provide guidance in constructing the strategy for the automated analogue searches. This guidance consists of the identification, based on experience and professional judgment, of the putative toxicophore(s) within the PMN chemical's structure. Potential analogues resembling the PMN chemical in the structure or function<sup>9</sup> of the putative toxicophore(s) are then identified via an automated searching capability. When attempting to select analogues for literature searching and

subsequent assessment purposes, similarity in the structure or function of the toxicophore is an essential element. Physical chemical properties, especially those that are known or suspected of contributing to a chemical's biological activity, as well as other major aspects such as projected metabolic pathways for the potential analogues as compared with those of the PMN chemical are also considered in selecting potential analogues.

One of the major limitations of the available substructure and nomenclature search systems is that they restrict the searchable parameters to chemical names, name fragments, substructural components, molecular formulae, and so on. Sizeable data bases of physical chemical properties are not available in a readily searchable environment, although several are under development (Eakin and Johnson, 1981; Milne and Heller, 1980; Magnuson *et al.*, 1981; Howard *et al.*, 1982; Page, 1983; Page and Kissman, 1984). Thus automated screening of the analogue search outputs using quantitative measures of physical chemical properties to select potential analogues is not presently available. Consequently EPA relies on manual screening using a variety of quantitatively and/or qualitatively applied factors which can be used for comparison between the potential analogues and the PMN chemical. These factors can include relative differences in, for example, molecular weight, molecular topology, log P (Hansch and Leo, 1979), presence and positioning of reactive or potentially reactive groups, possible steric effects, presence of aromatic systems, and presence of ionizable (Perrin, 1965; Perrin, 1972; Serjeant and Dempsey, 1979) or zwitterionic groups. Once potential analogues have been selected, they are subjected to automated literature searching using a variety of readily available bibliographic systems and data bases in the hopes of uncovering pertinent toxicity information. Only those analogues yielding test data are carried forward in the assessment process.

The use of the third component, quantitative SAR methods, is at present limited to the estimation of certain physical chemical properties (such as water solubility (Banerjee et al., 1980), Koc, vapor pressure (Lyman et al., 1982), log P (Chou and Jurs, 1979)) and ecotoxicity (prediction of acute LC50s in aquatic organisms (Veith et al., 1983; Lipnick and Dunn, 1983; Hermans, 1983; Konemann, 1981; Hutzinger et al., 1978) and estimation of bioconcentration factors (Veith et al., 1979)).

The last of the four components, the knowledge and professional judgments of scientific assessors in the interpretation and integration of available information, is most critical in terms of the overall success of the evaluation effort. Given that the three preceding components, even when combined, will generally produce a limited set of useful information, the importance of the knowledge and professional judgments of the scientific assessors becomes apparent. This is especially so in the case of information developed on analogous substances which must be critically evaluated and interpreted in terms of the weight that should be applied to each analogue as a function of its "closeness" to the PMN chemical. Thus the assessors' task is to evaluate the toxicologic potentialities of the PMN chemical using submitted data and extrapolations of data available on suitable analogues. In performing this task the assessors must consider a variety of parameters as they apply to the PMN chemical and, in comparison, to the analogue chemicals. These parameters include those applied previously in selecting potential analogues as well as:

- ° potential for skin, pulmonary, and gastrointestinal absorption;
- ° biotransformation pathways;
- ° distribution and excretion;

- consideration of the possible mechanisms of toxicity, and other parameters (Arcos, 1983; Arcos and Auer, in press;).

Recently, an evaluation of EPA's use of SAR in the PMN process was prepared by Adrien Albert (1983) at EPA's request. Professor Albert, author of Selective Toxicity: the Physico-Chemical Basis for Therapy, is one of the foremost international authorities on structure activity relationships. The report identified four major approaches or tools that are available for predicting biological activity from chemical structure and physical chemical properties:

- professional expertise of scientific assessors;
- attempting to relate the whole molecule to a class of chemicals for which adequate biological data exist (analogues are chosen to be as close as possible in size, overall molecular structure, and component parts); consideration of biotransformation enters here;
- searching for structural analogues that have a "domain" (or substructure) similar to the domain thought to be responsible for biological activity in the submitted chemical (in other words, the putative toxicophore); biotransformation is a factor in this approach as well;
- quantitative structure activity relationships (QSARs) as exemplified by Hansch analysis.

Albert concluded that EPA relied to the greatest degree on the first 3 of the available approaches in assessing the hazards of PMN chemicals. While he recognized and accepted the reasons for EPA's limited use of QSARs, Albert recommended that EPA

attempt to expand its utilization of QSAR approaches to toxicity assessment. The major factor identified by Albert as limiting EPA's use of QSARs was the need, as yet largely unmet, to develop a large data bank containing toxicologic test data, physical chemical property data, and QSAR descriptors. Albert, in addition, called attention to the limitations of and potential pitfalls in an over reliance on the "domain" approach.

In making projections about the toxicity of the PMN chemical, EPA is hampered by the limited data that are generally available on the PMN chemical and its analogues. Because of this, EPA's hazard predictions tend to take the form of conservative, worst case analyses which reflect the uncertainties inherent in a process which uses limited test data. The TSCA section 5e "may present" language recognizes the uncertainties that are likely to confront EPA in assessing PMN chemicals and thus allows a less robust regulatory finding to suffice in requiring the development of the test data needed to adequately assess the risks posed by new chemicals.

#### PROPOSED DESIGN<sup>10</sup>

The stated purpose of this retrospective study of PMN health hazard predictions is to obtain some measure of the validity of EPA's use of structure activity relationships in its assessment of the potential hazards posed by PMN chemicals. The study is not intended to validate PMN hazard predictions in an absolute sense. Rather the study is more limited in scope and is intended to provide EPA with an indication of the validity of its hazard predictions relative to a limited set of toxicity testing. In this way, EPA may begin to determine the strengths and weaknesses of the present SAR-based approach under TSCA section 5. The study will also provide an indication of the types of toxicity testing, if any, that can best complement, or, if indicated, are needed to supplement, EPA's assessment capabilities. Finally,

given that EPA's charge under TSCA is to protect public health and the environment without unduly impeding or creating economic barriers to technological innovation, the study attempts to provide an indication of the relative costs and benefits of limited testing if such a requirement were to be contemplated for future PMN chemicals.

The discussions that follow lay out the major factors that were considered in formulating the study and proposes a study design which in EPA's judgment can best meet the objectives of the project within the limitations outlined.

### General Design Considerations

The major factors serving to limit the scope of the retrospective study are the resource limitations of available funding, time, and personnel that can be committed to the project. At this time EPA envisions a project that would involve approximately one hundred (100) PMN chemicals, each subjected to around \$50,000 worth of testing (EPA, 1984c), for an initial cost of \$5.0 million. Subsequent analysis of the data, report preparation, and other costs associated with the study are expected to approximately double the cost to \$10.0 million for the completed project.

In an initial exposition presented to the EPA Science Advisory Board's Environmental Health Committee (SAB-EHC) on the design of a retrospective study of PMN health hazard assessments, EPA (1984b) proposed focusing the effort on determination of a "false negative" rate among EPA's PMN hazard predictions. A false negative prediction is one that, either by omission or commission, incorrectly characterizes a "toxic" chemical as nontoxic in one or more effect areas. The rationale offered for this proposal was that false negative hazard predictions are of public health concern due to their potential for contributing to underestimation of the risk potential posed by such chemicals.<sup>11</sup>

False positive predictions, on the other hand, were characterized as contributing to, if anything, overestimation of risk potential (and possibly to unwarranted regulation). Several reviewers (SAB-EHC, 1984) of the initial discussion of the project (EPA, 1984b) noted that, while determination of a false negative rate is certainly desirable, to focus the effort on this aspect to the exclusion of determining a false positive rate would weaken the overall study. EPA has decided to broaden the study to include testing of both positive and negative hazard predictions.

### Approach to Data Analysis

In general, the analysis of the data from the study will focus on the following basic objectives:

1. estimate the degree of agreement in the scoring of chemicals by the two scoring methods (i.e., EPA's SAR-based hazard predictions versus laboratory testing);
2. test whether the estimated degree of agreement is statistically significant (i.e., could the degree of agreement be attributed solely to chance);
3. if the laboratory tests can be viewed as a more reliable scoring method, then estimate the false positive and false negative rates of the SAR-based method relative to the laboratory tests. Note that these rates would have a limited meaning since the reliability of the selected laboratory tests (see subsequent discussion of the tests chosen for this study) with respect to the actual response of the chemicals in confirmatory assays would not be known.

Let the following table represent the cross classification of the SAR-based hazard predictions and the corresponding laboratory test results for a selected sample of PMN chemicals where a, b, c, and d represent the number of PMN chemicals in each quadrant and N represents the total number of PMN chemicals in the sample.

		Test Results		
		+	-	
SAR-Based Hazard Predictions	+	a	b	a + b
	-	c	d	c + d
		a + c	b + d	N

Also let

$$p_o = \frac{a + d}{N}$$

be the proportion of PMN chemicals in the sample which are scored the same by both scoring methods.

$$p_c = \frac{(a + c)(a + b) + (b + d)(c + d)}{N^2}$$

is the proportion of PMN chemicals that would be expected to be scored the same by chance alone. The statistic K, where

$$K = \frac{p_o - p_c}{1 - p_c}$$

represents the degree of agreement after allowing for chance. If  $K < 0$ , this means that the sample had less than the number of agreements than would have been expected by chance alone. If  $K > 0$ , this indicates the observation of more than chance agreements.  $K = 0$  is then indicative of only chance agreement.

The statistical significance of  $K$  can be tested by calculating

$$\chi^2 = \frac{K^2}{\text{Var}(K)}$$

where  $\text{Var}(K) =$

$$\frac{p_c + p_c^2 - 1/N^3 [(a + c)(a + b)(2a + b + c) + (b + d)(c + d)(2c + b + d)]}{N(1 - p_c)^2}$$

If  $\chi^2$  exceeds 3.84, the value needed for significance at the 0.05 level, the conclusion would be that  $K$  is significantly different from zero.

If one views the lab tests as a more reliable method, then one can estimate the false positive and false negative rates of the SAR-based predictions viz a viz the laboratory tests when

$$\text{false positive rate} = \frac{b}{a + b}$$

$$\text{false negative rate} = \frac{c}{c + d}$$

and their standard errors of estimate are, respectively,

$$\sqrt{\frac{ab}{(a + b)^3}}$$

and

$$\sqrt{\frac{cd}{(c + d)^3}}$$

The preceding is the simplest kind of analysis that could be done and it is presented to illustrate the general approach which is contemplated for data analysis. The actual analysis of data would probably include more complex versions of this basic analysis. Examples include:

1. applying the analysis for each of several different toxicological endpoints and/or types of laboratory tests or combinations of laboratory tests.
2. classifying the outcomes of the SAR-based predictions and/or the laboratory tests into more than two categories (for example, the 2 X 2 cross classification matrix described above could be expanded into 2 X 3, 3 X 3, etc. matrices; a simple example involves keeping the present classification of SAR-based predictions and classifying the test results into +, -, and ± categories yielding a 2 X 3 matrix).
3. expanding the dimensions of the analysis; an example is to include consideration of chemical class.

### Selection of Chemicals

One of the major design factor in this study concerns selection of the PMN chemicals that will be tested as part of the effort. In the initial discussion of the project, EPA (1984b) proposed a series of exclusion criteria which could be used to eliminate certain PMN chemicals from consideration on the basis of low hazard potential or low risk potential. The SAB-EHC (1984) in written comments expressed concern regarding the proposed exclusions and requested that EPA reconsider the issue. EPA has done so and the following discussion presents EPA's planned approach to chemical selection.

## The PMN Universe

Over 4,000 chemicals have been submitted to EPA under section 5 of TSCA since mid-1979. The ratio of polymeric to nonpolymeric PMN chemicals is approximately 40:60. For the set of nonpolymeric PMN chemicals, the mean molecular weight is approximately 450 daltons while the mode is between 200 and 300 daltons; the range of molecular weights extends from 104 to over 4000 daltons (see Figure 4). Information as to health test data availability on the set of PMN chemicals was previously discussed and presented in Tables 1 through 3.

## Considerations in Developing the Sampling Strategy

Among the PMN chemical categories proposed for exclusion in the initial discussion of this project (EPA, 1984b) was a subset of the polymeric PMN chemicals. This subset of polymers can be characterized as high molecular weight (less than 5 weight percent below 500 daltons), nonreactive, and essentially insoluble in water. For the set of polymeric PMN chemicals (n = 1739), approximately 600 (or 35%) meet these criteria. Essentially all polymeric PMN chemicals meeting these requirements have been identified by EPA as presenting a low degree of toxicity based primarily on the view that they will not be bioavailable. EPA has decided to exclude this subset of polymers from the sampling universe due to the expectation that they are likely to possess a low degree of toxicity.

A major consideration in developing the sampling strategy for the project is the question of the likelihood of obtaining specimens of PMN chemicals for testing. An important limitation in this regard is the fact that in the absence of Agency receipt of a notice of commencement of manufacture or import, only "small quantities" of the PMN chemicals will be available.<sup>12</sup> EPA anticipates that it would encounter substantial difficulties in obtaining specimens of chemicals which have not entered commercial production. EPA has,

therefore, decided to include in the sampling universe only those PMN chemicals which have entered into commercial production as evidenced by receipt of a notice of commencement of manufacture or import (known hereafter as "NOC chemicals"). At present, the set of NOC chemicals contains 1504 or 50% of the PMN chemicals (both polymeric and nonpolymeric) received by the Agency. Since the restriction to the set of NOC chemicals could introduce biases into the overall result, an attempt will be made to study if such a bias does exist and, if so, to estimate its magnitude. Various analyses are presently underway to determine the presence of any significant bias(es) between the set of NOC chemicals and the balance of the PMNs. In these analyses, the set of NOC chemicals will be contrasted with the set of "non-NOC" PMN chemicals in terms of such parameters as the presence of health test data, the presence of health concerns (Structure Activity Team "level of concern" rankings will be used to identify cases having health concerns; see discussion of this point below), and the ratio of polymers to nonpolymers. If there is any indication of significant bias(es) between the sets of NOC and non-NOC chemicals, an appropriate number of additional chemicals will be sampled from the set of non-NOC PMN chemicals (once again, excluding certain polymers) and a substantial effort will be made to obtain specimens of these chemicals. The subset of non-NOC chemicals would then be subjected to the testing scheme described previously and appropriate analysis of the testing results undertaken.

Employing the exclusions as described above is estimated to yield a sampling universe containing somewhere between 1,200 to 1,400 PMN chemicals. Note that these figures do not include PMN chemicals received in fiscal year 1984; this will eventually add approximately 500 chemicals to the sampling universe.

## Sampling of PMN Chemicals

A valid probability sampling will be made of the PMN sampling universe to select chemicals for testing. A simple random sampling procedure would achieve data analysis objectives (1) and (2) (described above in the section entitled "Approach to Data Analysis"); however, to best achieve data analysis objective (3) as well as objectives (1) and (2) a stratified random sampling procedure will be used. First, two strata will be defined; one stratum will consist of chemicals in the sampling universe for which EPA identified one or more adverse health concerns (i.e., "positive" SAR-based hazard predictions) and the other stratum will consist of chemicals in the sampling universe for which EPA had low or no health concerns (i.e., "negative" SAR-based hazard predictions). The total sample will then be allocated to the two strata in proportion to the relative size of these strata in the PMN universe as long as both groups are large enough so that this approach will not result in too small a sample to calculate one or the other of the error rates. A systematic sampling with a random start (NRC, 1984, p. 45) will then be made from a chronologically ordered listing of the PMN chemicals within each stratum; this latter step will be, in effect, a further stratification of the sample through time. Additional strata will also be developed if indicated; for example, it may be useful to stratify on the basis of polymeric versus nonpolymeric PMN chemicals.

PMN chemicals having "positive" SAR-based hazard predictions will be separated from those having "negative" SAR-based hazard predictions on the basis of the health effects "level of concern" estimate provided on each PMN chemical as part of the deliberations of the Structure Activity Team. The SAT level of concern estimates were originally developed for use by management in assigning assessment resources to individual PMN cases. The operational assumption was that if the senior scientists on the SAT identified certain PMN chemicals as being of "low" health concern relative to other PMN chemicals, then one might want to direct technical

resources toward other PMN chemicals which received a "moderate" or "high" health concern ranking from the SAT. Although the SAT level of concern rankings have limitations in separating "toxic" from "nontoxic" chemicals, for the purpose of stratifying PMN chemicals as described above, the health level of concern rankings provided by the SAT are thought to be an adequate discriminator for the purposes of this project.

### Selection of Tests

In the initial discussion of the "Selection of Tests" issue, EPA (1984b) suggested that one could structure the retrospective study of PMN health hazard predictions "(1) to test for a predetermined set of toxicologic endpoints... or (2) to test for the set of toxicologic endpoints which are identified by SAR as being of potential concern...." The decision reached by EPA is to structure the study to incorporate both of these approaches, with emphasis placed on the former. Accordingly, the study will employ a "core set" of laboratory toxicity tests that will be run on every chemical selected, but will allow some additional testing which is to be undertaken as described below.

### "Core Set" of Testing

The task before EPA in devising a core set of toxicity testing is to develop the best set of tests that can be assembled within a given dollar amount. EPA proposed (1984c) and has adopted \$50,000 as the testing budget for the core set of tests on a per chemical basis. Final recommendations for a \$50,000 core set of tests were developed at a working meeting held at the National Institute of Environmental Health Sciences (NIEHS) in Research Triangle Park, NC in August 1984. Participants at the meeting included personnel from EPA, NIEHS, the National Toxicology Program, and the Chemical Industry Institute of Toxicology (EPA, 1984d). At the meeting, general agreement was reached to include in the core set of testing a series of

mutagenicity assays which would serve to identify potential carcinogens, an acute toxicity screen, a 28-day repeated dose toxicity study, and a dermal sensitization assay.

The decision was reached at the meeting to table discussion on selection of the short-term test(s) for developmental toxicity. The meeting concensus was that none of the available short-term assays for developmental toxicity have been widely accepted by the scientific community as being adequately and appropriately validated for use as a screening tool. The participants recommended, however, that the issue of selecting an adequate screening assay for developmental toxicity be revisited within the next year. Another aspect of the decision to table consideration of a developmental toxicity assay is the fact that the other tests recommended at the meeting already totaled more than the targeted \$50,000 per chemical.

The specific assays recommended at the August meeting are listed below along with the basis for their selection. The recommended testing was as follows:

- o A series of three short-term mutagenicity screening tests for identifying potential carcinogens.
  - Ames Salmonella/mammalian microsome test using 5 strains of Salmonella, both with and without metabolic activation (EPA, 1983a). Estimated cost \$2,000.
  - in vitro sister chromatid exchange (SCE) assay using the CHO line of Chinese hamster cells, both with and without metabolic activation (EPA, 1983b). Estimated cost: \$9,000.
  - in vitro gene mutation test using the L5178Y line of mouse lymphoma cells, both with and without activation (EPA, 1983c). Estimated cost: \$12,000.

- o Two general toxicity assays for acute and repeated dose toxicity in the rat.
  - acute oral toxicity test (EPA, 1984e). Estimated cost: \$2,100.
  - 28-day repeated dose oral toxicity study using a modified OECD (1981a) protocol. Estimated cost: \$25,000.
  
- o A dermal sensitization assay in the guinea pig.
  - the Buehler (1965) or "closed patch" test. Estimated cost: \$3,500.

The total cost for the above set of tests is estimated to be \$53,600 on a per chemical basis.

The tests chosen for identification of potential carcinogens include two tests for gene mutations, one in prokaryotes (Ames Salmonella/mammalian microsome test) and the second in mammalian cells in culture (L5178Y mouse lymphoma test), and an in vitro SCE test. Although the ultimate mechanism of SCE formation is unknown, the endpoint is visualized as effects on the chromosome. These three assays were chosen because they are routinely available, relatively inexpensive, have a large data base of tested chemicals, and are performed under standard protocols allowing for interlaboratory replication of data (Brusick and Auletta, 1984). Most importantly these assays correlate well with in vivo carcinogenicity. Phase II of the Gene-Tox Program (EPA, 1983d) has found that the Ames assay has an overall correlation with carcinogenicity of 81% (121/151 carcinogens tested were correctly identified), the L5178Y mouse lymphoma test has an overall correlation of 90% (18/20 carcinogens correctly identified), and the in vitro SCE assay has

an overall correlation of 97% (40/41 carcinogens correctly identified). The combination of the Ames assay with an assay in mammalian cells in culture is known to yield increased sensitivity over that of the Ames assay alone. For example, the International Collaborative Study (de Serres and Ashby, 1981) found that the use of a mammalian cell assay in addition to an Ames assay enhanced detection of known carcinogens, so that the majority of carcinogens not detected in the Ames assay were detected in eukaryotic in vitro systems. The mammalian cell assays examined by de Serres and Ashby included assays for both gene mutation and effects such as cytogenetics and SCE. Finally, in conducting the in vitro SCE assay, the technique used to prepare cells for SCE analysis is compatible with the way cells are prepared for chromosomal analysis, thus both SCE and chromosomal aberrations can often be seen and scored on the same slide. The combination of the Ames Salmonella/mammalian microsome assay, the in vitro SCE assay, and the in vitro gene mutation assay in L5178Y mouse lymphoma cells covers a spectrum of genetic events and enhances the possibility of detecting potential carcinogenic agents over that which exists with any one of the tests. It should be remembered that one is dealing here with sensitivity (the ability to detect known carcinogens) and that an assessment of specificity (the ability to accurately assess noncarcinogens) is limited by the paucity of valid negative in vivo data. The Gene-Tox data base (EPA, 1984f), for example, lists fewer than 10 chemicals as having been tested with enough rigor to be classified as noncarcinogens. However, the assays selected will detect potential in vivo carcinogens and within these limits they are valuable aids in identifying potentially hazardous agents.

The utility of determining acute effects of industrial chemicals to assess potential effects of both routine and accidental exposure, especially in the workplace, serves as the basis for inclusion of the rat acute toxicity test (3 dose groups, 5 animals per sex per dose, 14-day observation period).

This test will, in addition, provide information needed to set the doses for the 28-day repeated dose study. The 28-day repeated dose oral (gavage) toxicity study in the rat (3 dose groups plus control, 5 animals per sex per dose) is a screening test for potential chronic effects other than cancer, mutagenicity, and teratogenicity. The 28-day study is seen as a less costly but a less detailed alternative to the 90-day subchronic toxicity test, and, despite its limitations, is expected to identify most of the organs or systems that will be affected following repeated exposures over a limited time period. One of the limitations of the 28-day study is that, unlike the 90-day subchronic assay, it is not viewed as providing reliable information regarding a chronic No Observed Effect Level (NOEL) and thus will not give an indication of acceptable lifetime exposure levels for humans. Based on their studies, Weil and McCollister (1963) and Weil et al. (1969) have suggested that one may transfer the results of shorter term animal tests with measured confidence into a prediction of the "no ill effect" levels for the corresponding longer term animal studies.

The Buehler sensitization study was selected because it is: widely used; does not involve intradermal injection (and thus is more difficult to vitiate by improper technique); does not require highly trained animal handlers/technicians; requires fewer animals and is the least expensive of the seven methods considered acceptable by both EPA (1982) and the OECD (1981b); and provides data on both the incidence and severity of sensitization reactions.

#### "Tailored" Testing

In a Status Report presented to the SAB-EHC, EPA (1984c) noted that it was considering the use of tailored testing in the retrospective study. The "tailored" tests would be run in addition to the core set of tests and would be selected on the basis of the specific chemical or chemical class and the predicted

effect(s) of concern. At that time EPA indicated that tailored testing needs would be identified on a case by case basis. At the August meeting at NIEHS (EPA, 1984d), it was recommended that tailored testing decisions operate at a chemical class or physical chemical property level rather than on a case by case basis. Thus, for example, organophosphates might be identified as a class for determination of blood cholinesterase levels (Weir and Hazleton, 1982) as part of the clinical biochemistry in the 28-day repeated dose toxicity study. Glycol ethers, on the other hand, might be identified as a class for which teratogenicity and reproductive toxicity testing may be indicated (EPA, 1984g). The specific applications of tailored testing in the retrospective study will be developed at a subsequent point in the project.

### Operational Procedures

Questions remain as to the actual procedures that will be used to obtain the testing outlined in this report. EPA recently approached the National Toxicology Program with a request for assistance in this project and the preliminary response was favorable (EPA, 1984i). Laboratory testing will most likely be performed by laboratories under contract to the government; the specifics have not been worked out. EPA has an item in its preliminary budget for fiscal year 1986 to provide support for the project; some fraction of the funding will likely go to support laboratory testing, while the balance will be used to support management of the project and data evaluation.

Evaluation of laboratory studies and comparison of testing results with EPA's hazard predictions is anticipated to proceed in the following general fashion:

1. Laboratories performing the testing will be responsible for evaluation of the individual test results (using

established criteria provided by EPA; these are yet to be developed) and for preparation of laboratory reports. The laboratories will be blind to the chemical structures and to EPA's hazard assessment documents.

2. A second group (likely a contractor under EPA supervision) will next evaluate the set of test results using established criteria provided by EPA and will prepare a written evaluation of the toxicity of each tested chemical. This group will be aware of chemical structures and will interpret the results of the testing using the knowledge of any correlations known to exist between the chemical class tested and its response in the short-term tests used in this study. They will not, however, have access to EPA assessment documents.
3. A third group (once again, likely an EPA contractor) will review EPA's PMN hazard assessment documents on each tested chemical (while being blind to the results of the testing) and extract conclusions as to the presence or absence of concerns about health effects for each tested PMN chemical.
4. Correlations will be derived (as described previously) between the results of groups (1) and (3) and groups (2) and (3), above. The results of these analyses will be used to determine the validity of EPA's SAR-based hazard predictions as compared with the results of a limited set of testing.
5. Other data analyses may also be undertaken.

Table 1. Test Data Submitted with Premanufacture Notices<sup>a</sup>

<u>Type of Data</u>	<u>Percent of PMNs</u>		
	<u>All</u>	<u>Non-Polymer</u>	<u>Polymer</u>
Health data (some)	46%	58%	30%
Acute Toxicity			
Oral	39%	51%	24%
Dermal	21%	26%	14%
Inhalation	8%	10%	7%
Local Toxicity			
Eye irritation	34%	45%	22%
Dermal irritation	37%	48%	23%
Sensitization	9%	12%	5%
Mutagenicity	13%	19%	5%
Other <sup>b</sup>	8%	12%	4%
Ecotoxicological data (some)	10%	14%	6%
Acute lethal vertebrate	7%	11%	4%
Acute lethal invertebrate	3%	4%	2%
Fate data (some)	10%	12%	5%
Biodegradation	6%	9%	3%
Log P	3%	6%	1%
No test data of any type	52%	39%	68%

<sup>a</sup>Based on the full set of 3,578 PMNs received to date (6/84).

<sup>b</sup>The "other" health category includes acute toxicity studies by other routes (ip, iv, etc.), repeated dose toxicity studies (generally 28 days or less in duration), teratogenicity studies, phototoxicity, neurotoxicity, and a variety of other endpoint studies.

(EPA, 1984h)

Table 2. Most Frequently Encountered Combinations of Health Test Data Submitted with PMNs<sup>a,b</sup>

Specific Testing Combinations<sup>c</sup>

Number of PMNs	Acute Toxicity			Irritation		SENS	MUTA	OTHR
	ORL	DRM	IHL	DRM	EYE			
256	X			X	X			
177	X	X		X	X			
121 <sup>d</sup>	X	X	X	X	X	X	X	X
100	X	X	X	X	X			
72	X							
70	X	X		X	X		X	
63	X			X	X		X	
50	X			X	X	X		
34				X	X			
33							X	
31	X	X		X				
28	X	X	X	X	X		X	
28	X			X	X	X	X	
28	X			X				
26	X			X	X		X	
25	X	X		X	X	X		X
24	X			X	X	X		
21	X			X	X		X	X
20	X	X		X	X	X	X	
19	X	X		X	X			X
19	X		X	X	X			
18	X	X		X	X	X	X	X
17								X

<sup>a</sup> Based on 1646 PMN cases containing some type of health test data (8/84).

<sup>b</sup> Abbreviations as follows: ORL-oral; DRM-dermal; IHL-inhalation; EYE-eye; SENS-sensitization; MUTA-mutagenicity; OTHR-other health studies.

<sup>c</sup> Approximately 400 cases contain 94 other combinations of health test data.

<sup>d</sup> Includes 106 synfuels received as a group.

(EPA, 1984h)

Table 3. The Number of PMNs Containing 1 Through n Different Categories of Test Data<sup>a</sup>

Number of Test Data Categories Submitted <sup>b</sup>	1	2	3	4	5	6	7	8
Number of PMNs	151	109	383	370	333	126	53	121 <sup>c</sup>

<sup>a</sup> Based on 1646 PMN cases containing some type of health test data (8/84).

<sup>b</sup> Test data categories include: acute lethal oral, acute lethal dermal, acute lethal inhalation, eye irritation, local skin irritation, sensitization, mutagenicity, and other. This table does not reflect the possible submission of multiple tests in a single category (for example, a notice containing a single mutagenicity study is not distinguished from other notices containing more than one such study).

<sup>c</sup> Includes 106 synfuels received as a group. (EPA, 1984h)

Table 4. Comparison of Available Health Test Data for TSCA Existing Chemicals versus PM Chemicals

TEST TYPE	Reported Production Volume		All Cases	Non-Polymers	Polymers
	≥ 10 <sup>6</sup> lb/yr	< 10 <sup>6</sup> lb/yr			
Acute <sup>a</sup>	20(15-25)	22(15-29)	40	51	24
Subchronic <sup>a</sup>	10(7-14)	8(5-13)	11	16	5
Chronic	4(3-7)	3(2-6)	< 1	< 1	< 1
Repro/Develop. <sup>f</sup>	6(3-9)	4(2-7)	< 1	< 1	< 1
Mutagenicity	9(6-13)	10(5-15)	13	19	5
Minimal Toxicity Information <sup>g</sup>	22(18-26)	24(18-30)	42	54	25
No Toxicity Information <sup>h</sup>	78(73-84)	76(69-83)	54	42	70

<sup>a</sup> Figures taken from NRC (1984, p. 84).

<sup>b</sup> Figures taken from EPA (1984h).

<sup>c</sup> For existing chemicals, the sample size reports the number of chemicals from the full TSCA inventory of 48,523 chemicals which underwent a standardized screening procedure to identify available toxicity information (see NRC, 1984, p. 45-50). For PM chemicals, the number represents the count as of July 1984.

<sup>d</sup> Existing chemical estimates are expressed as means with upper and lower 90% confidence limits. For PM chemicals the values reported include test data submitted with the notice and thus do not reflect any testing that is subsequently undertaken.

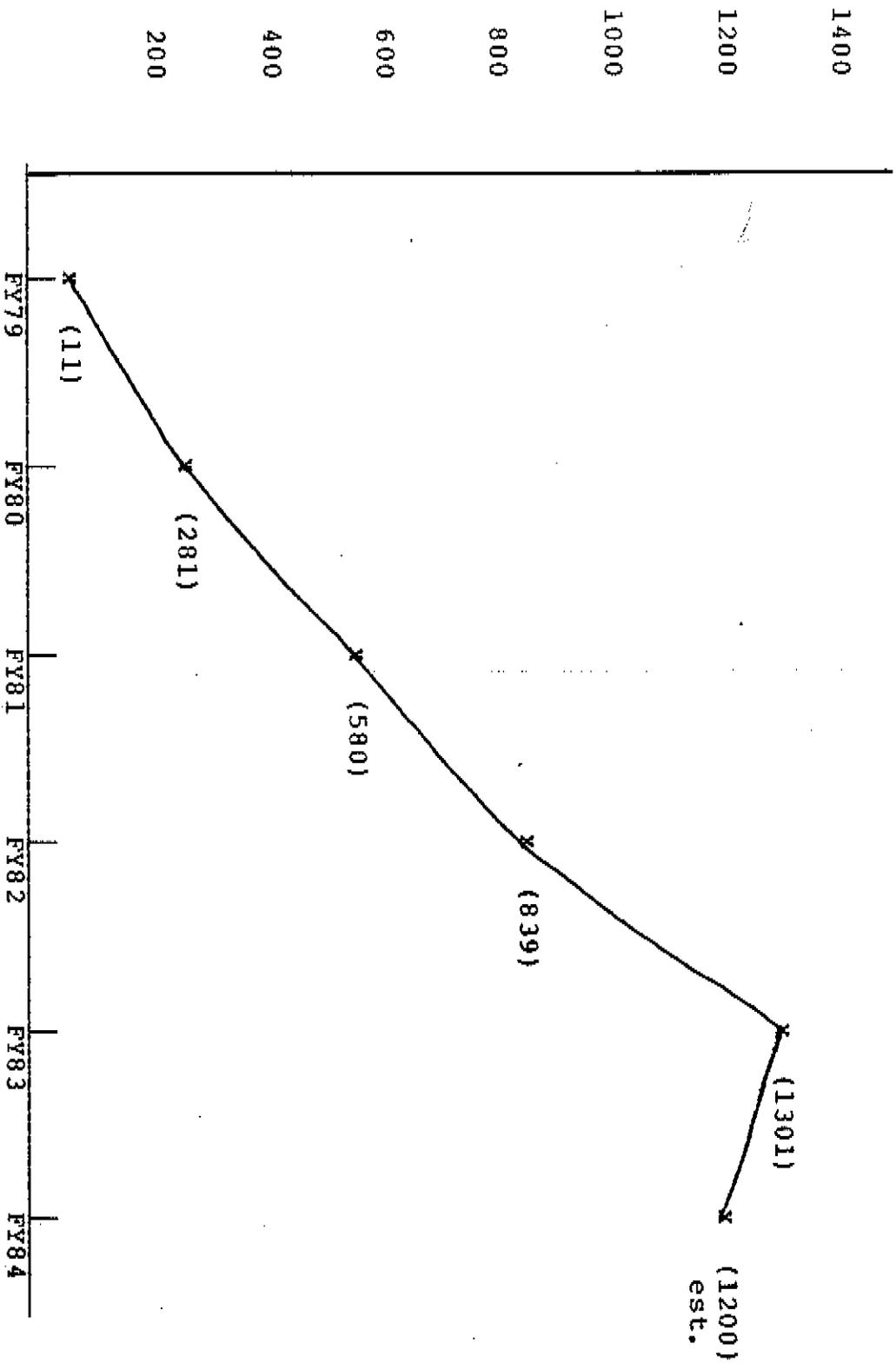
<sup>e</sup> Acute toxicity studies are defined as single administration via any route within 24 hours. Subchronic toxicity studies include 28- and 90-day repeated dose studies (oral, dermal) and guinea pig sensitization tests (from NRC, 1984, p. 47).

<sup>f</sup> Reproductive/developmental toxicity.

<sup>g</sup> NRC (1984, p. 47) defined "minimal toxicity information" for TSCA existing chemicals as the availability of any one or more of the 5 study types included in this table.

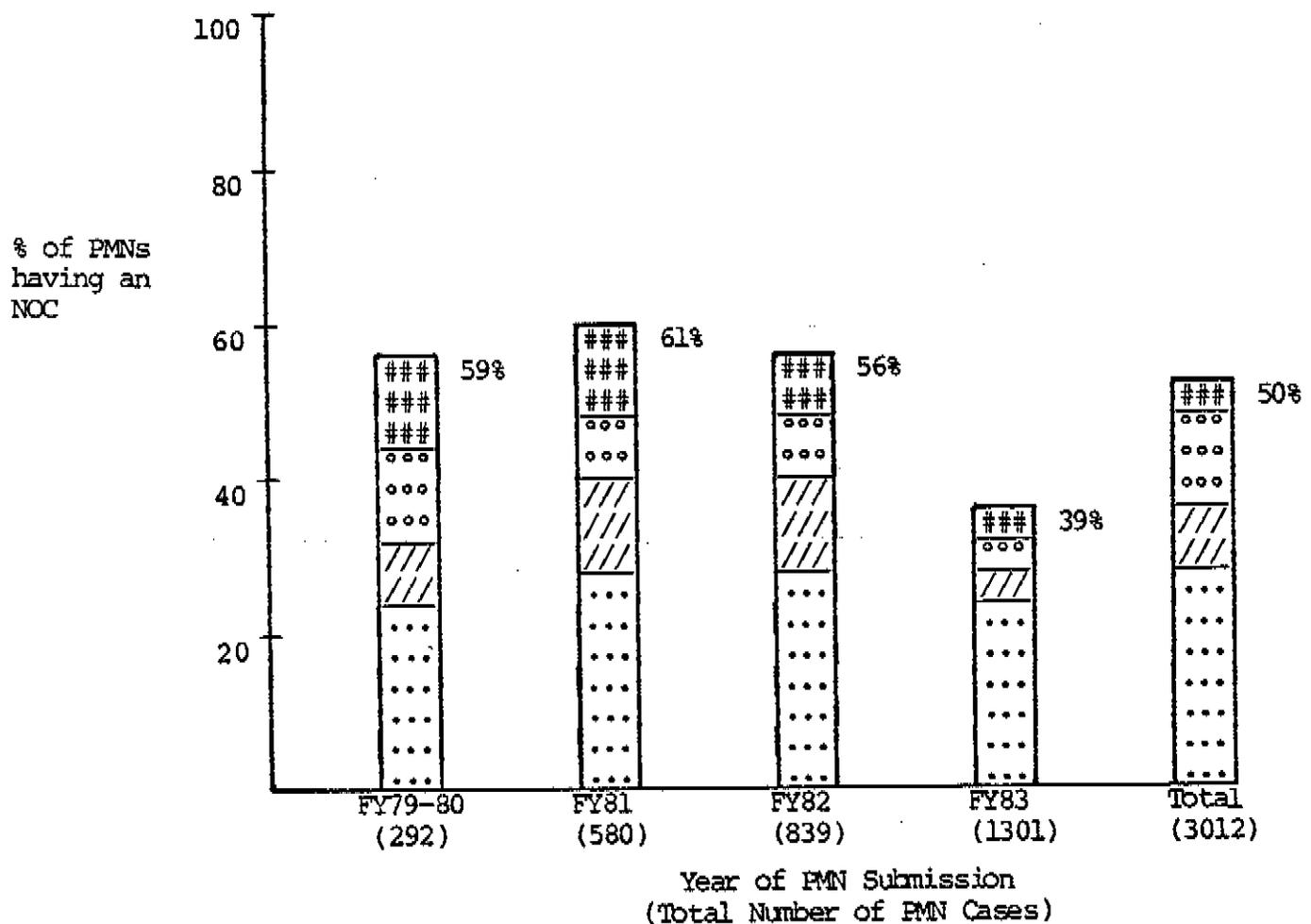
<sup>h</sup> For TSCA existing chemicals, NRC (1984) noted that additional information might exist in restricted access files.

Figure 1. Annual Receipt of PMNS from FY79 Through FY84a



a Fiscal Year  
(EPA, 1984h)

Figure 2. Statistics on Receipt of Notices of Commencement of Manufacture or Import (NOC)<sup>a</sup> for PMNs Received Between FY79 and FY83



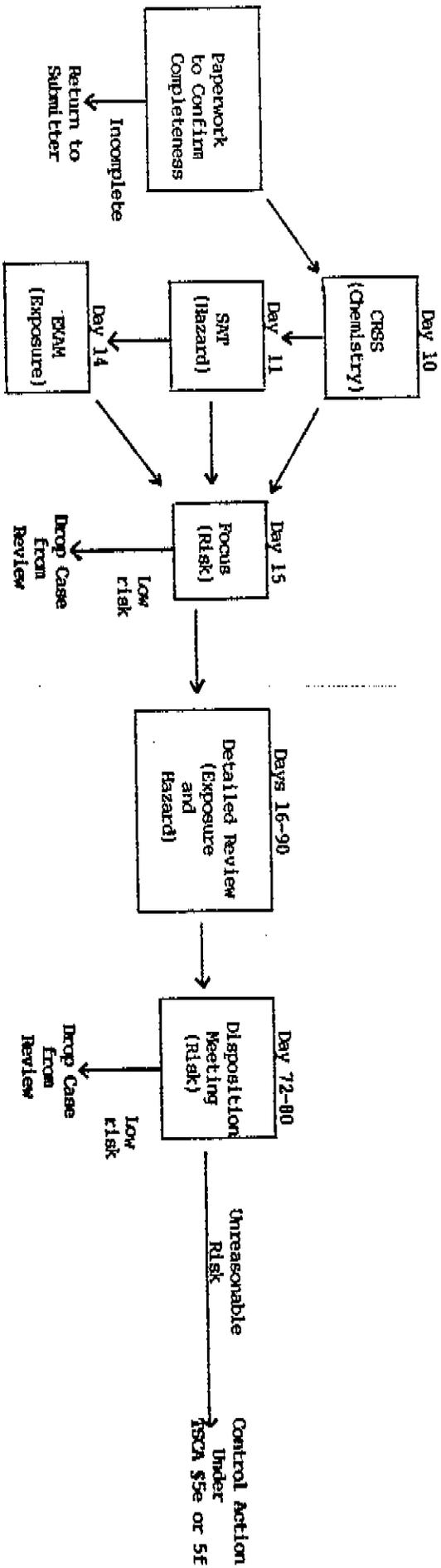
Legend: Days after day 90 that the Notice of Commencement is received.

###	days > 365
ooo	days 181-365
///	days 91-180
...	days 1-90

<sup>a</sup> see explanation of an NOC in the text.

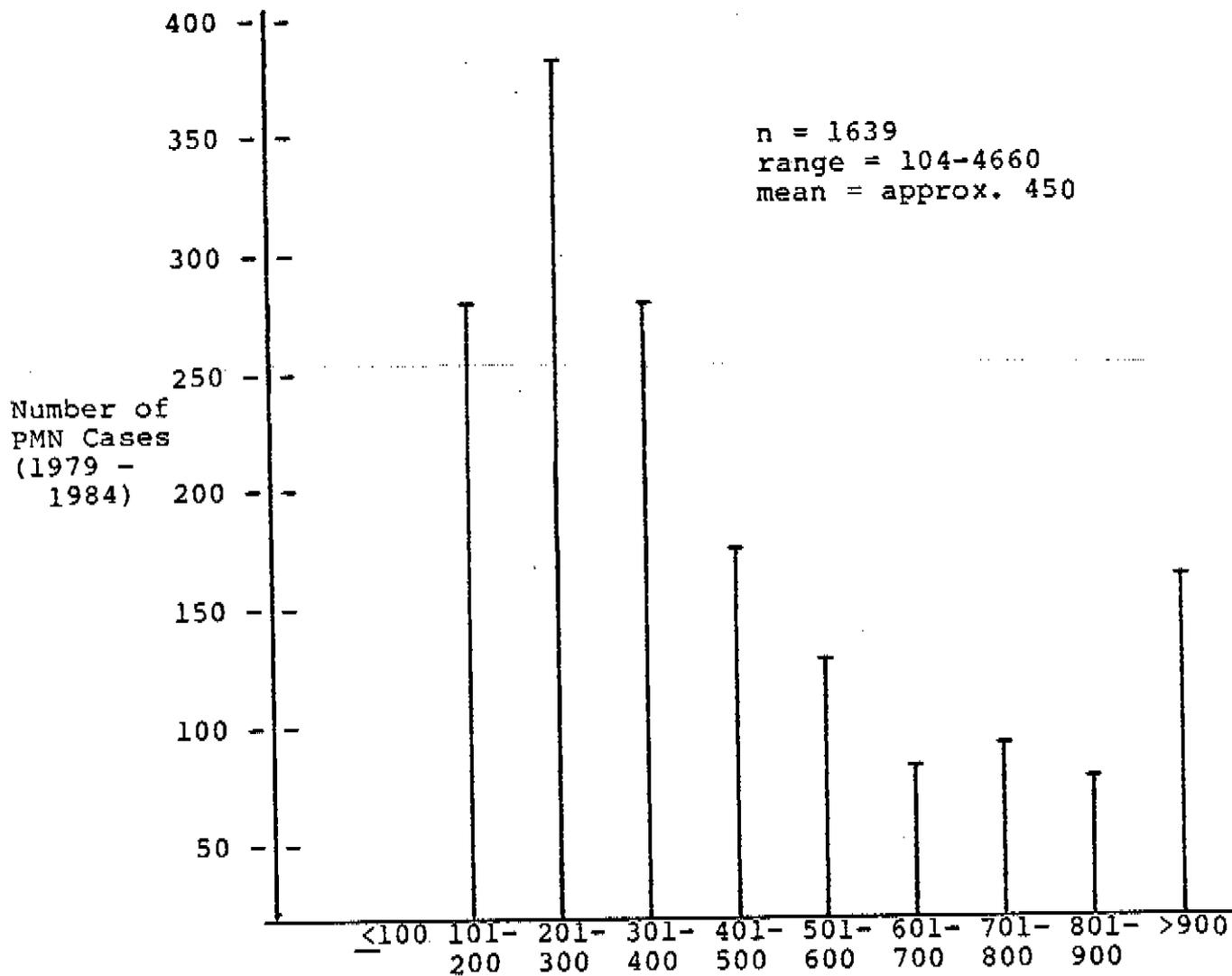
FY - Fiscal Year  
(EPA, 1984h)

Figure 3. PMN Assessment Process



Legend:  
 CRSS - Chemistry Review and Search Strategy  
 SMP - Structure Activity Team  
 EXAM - Exposure Analysis Meeting

Figure 4. Molecular Weight Distribution (in daltons) for Nonpolymeric Chemicals (EPA, 1984h)



## FOOTNOTES

<sup>1</sup>The extent to which testing obtained under this project indicates that certain health hazard determinations were not appropriate does not in isolation indicate that the overall risk decision made for each such case was wrong. Risk decisions must consider both hazard (i.e., toxicity) potential and exposure potential. An analysis to determine the effect of additional test data on historical risk decisions is beyond the scope of this project.

<sup>2</sup>As noted, one of the major objectives of this study is to determine the extent to which EPA's predictions of toxicity would have changed if the results of certain tests were included in each PMN. Information obtained via this project might be useful in analyses to study whether the submission of test data should be required under section 5 of TSCA. In the course of such analyses the benefits of the information gained by such testing must be weighed against their costs and the impact of these costs on the introduction of innovative PMN chemicals. For example, while long term bioassays directed at multiple endpoints would provide much greater certainty concerning the toxicity of new chemicals, the cost to industry of requiring such testing on all new chemicals militates against such a requirement. For this reason, the study design presented in this paper focuses on test methods which are relatively inexpensive in comparison to long term bioassay tests.

<sup>3</sup>pesticides, drugs, foods, food additives, cosmetics, and certain other chemicals which are controlled by other statutes are not within the purview of TSCA (see 15 U.S.C. 2602(2)).

<sup>4</sup>The TSCA "premanufacture" reporting requirements can be contrasted with the European Communities (EC) "premarketing" notification requirements (EC Directive 79/831/EEC, 6th Amendment, 1979). As the terms indicate, premanufacture notification under TSCA is required at an earlier point in the development of a chemical than is the case for the EC's premarket notification procedure. Many of the information reporting requirements under the EC's directive are similar to those outlined earlier in TSCA with the major difference being that the EC Directive (1979) requires as a mandatory part of the premarketing notification a specified "base set" of health, environmental, and physical chemical test data. A minimum set of test data is thus available on premarket notification (EC) chemicals, whereas the hazard assessment of TSCA premanufacture chemicals often starts out with fewer or no data.

5 A "consent" 5(e) order is one in which in which EPA negotiates the terms of the order with the company that submitted the PMN. The company agrees to be bound by the order and waives its rights to file objections to the order. This waiver does not affect any other rights that the company may have under TSCA. The company at a later date can request a modification of the consent order. This is contrasted with a unilateral order under which EPA takes action to restrict or prohibit the manufacture or use in commerce of the PMN substance.

6 Another option which is available at Focus (as well as subsequent points in the assessment process) is to enter the chemical into the "Followup" program which would consider the need for promulgation of a "significant new use rule" under TSCA section 5(a)(2) or an information reporting rule under section 8(a). Chemicals controlled under section 5(a)(2) are subject to the same 90-day notification requirement as for new chemicals, except that the need to report is triggered by the development of one or more significant new uses not outlined in the original premanufacture notification submitted to EPA. These new uses are then examined to determine if they "may" or "will" present an unreasonable risk under section 5. Section 8(a) reporting rules, on the other hand, only require the submission of certain information and do not trigger automatic review under section 5.

7 It should be noted that the approaches employed in EPA's applications of SAR differ to a substantial degree from the approaches which are typically associated with the use of quantitative structure activity relationships (QSARs) and other computational techniques to predict the biological chemistry of xenobiotic substances. Examples of these approaches are Hansch analysis, molecular and quantum mechanics, pattern recognition, and so on (see Golberg (1983) for a general treatment of these topics). The chief constraint on the use of these approaches by the EPA at present is that the problem confronting EPA differs from the earlier formal applications of these techniques (for example, in the pharmaceutical industry) in two important ways. First, the desired goal (prediction of adverse health effects) is not a single endpoint but depends on multiple interactive paths and the mechanisms involved are often not well understood. Second, there is little experimental data available or easily obtainable not only relative to health effects of the PMN chemicals but also relative to all but the simplest physical chemical properties. Further, the chemicals confronting EPA are often not the simple extension of a family of similar chemicals where a great deal of data exist for other family members (as is often the case in pharmaceutical applications of these techniques).

8 Examples of available substructure and nomenclature search systems include SANSS (Structure and Nomenclature Search System) in the NIH/EPA Chemical Information System, CAS-ONLINE available from Chemical Abstracts Service, and DARC, a French system available from Questel.

<sup>9</sup>A "functionally similar" chemical is one which, although it differs substructurally, can be considered a functional equivalent of the PMN chemical. Examples of functional equivalents, depending on the specifics of the case, might include acceptance of an aromatic amine substituent in lieu of an aromatic nitro (based on the expectation of biotransformation) or a chloro (but generally not a fluoro) in lieu of a bromo substituent (based on the concepts of isosterism; see Burger, 1970 and Mathison et al., 1976).

<sup>10</sup>Definitions of terms used in this section are as follows:  
PMN universe - the full set of PMN chemicals submitted to EPA under TSCA section 5; sampling universe - the subset of the PMN universe remaining after certain practical exclusions have been made; sample - the one hundred (100) PMN chemicals selected from the sampling universe (specimens of these chemicals will undergo the laboratory testing described in the paper); specimen - physical sample of a PMN chemical that will be obtained from the manufacturer for use in testing.

<sup>11</sup>NRC (1984) in Appendix E of its report describes what it terms "a plausible approach -- based on economic theory -- to the assignment of costs to errors in classification" of chemical toxicity (e.g., identifying toxic chemicals as being nontoxic). The reader is referred to the cited document for details of the analysis undertaken. In brief, the NRC concluded from its analysis that "the social cost of underregulating a chemical is much greater than that of overregulation."

<sup>12</sup>15 U.S.C. 2604(h)(3) states that for chemicals not listed on the TSCA inventory small quantities can be manufactured or processed solely for purposes of scientific experimentation or chemical research.

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period will be for 28 days. (3) Section 2.B. Procedure. Animals will be dosed 7 days per week. (4) Section 2.B. Clinical examinations. (a) Hematology will include only hematocrit and hemoglobin concentration. (b) Clinical biochemistry will be done based on target organs defined by the acute study or by EPA's assessment of the PMN chemical's toxicity. (c) Urinalysis will not be done. Also follow recommendations made in HG-Neurotoxicity-Functional Observational Battery, (EPA, 1983e). (5) Section 2.B. Pathology. Gross necropsy to include weighing of ovaries in females; the organs taken for histopathologic examination will be extended to include the testes/ovaries and lungs. As part of the histopathology, follow recommendations made in HG-Neurotoxicity-Neuropathology (EPA, 1983f), but limited to examination of 6 animals in the highest dose group with observations followed to lower doses

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