"New Chemicals" and the Toxic Substances Control Act

2. "New Chemicals" and the Toxic Substances Control Act

After more than 5 years of consideration and debate during three terms of Congress, the Toxic Substances Control Act (TSCA) was passed by Congress on September 28, 1976, and signed into law by President Ford on October 11,1976. TSCA states that it is Federal policy that: 1) chemical manufacturers and processors are responsible for developing data about health and environmental effects of their products, 2) that there be adequate statutory authority to regulate chemicals posing an unreasonable risk to health or the environment, and 3) that regulatory efforts not unduly impede innovation.

An important facet of TSCA (and the Resource Conservation and Recovery Act, which provides for the regulation of chemical disposal) is that the law directs regulatory emphasis at hazardous substances wherever they may occur. Other environmental protection laws are directed at regulating exposures through specific media, such as air and water.

TSCA is generally directed at chemical substances (TSCA sec. 2), and section 3 defines a "chemical substance" as any organic or inorganic substance of a particular molecular identity including any substance which results in whole or in part from a chemical reaction *or* that occurs in nature as well as any element or uncombined radical. [Note: Throughout this report the terms "chemical" and "substance" are used interchangeably to mean "chemical substance."]

Certain substances are excluded from regulation under TSCA:

- mixtures;
- pesticides, regulated under the Federal Insecticide, Fungicide and Rodenticide Act, when they are used as pesticides;
- tobacco and tobacco products;
- nuclear materials, which are regulated under the Atomic Energy Act;
- food and food products which are regulated under the Federal Food, Drug and Cosmetic Act; and
- pistols, firearms, revolvers, shells, and cartridges.

Section 5 of TSCA is directed at preventing human and environmental exposure to new substances that will present or may present an unreasonable risk to human health or the environment and requires that the Environmental Protection Agency (EPA) be notified before new chemicals are introduced into commerce. The requirement for premanufacture notice (PMN) reflects the conclusion that human health and the environment may be better protected at less cost when a toxic chemical is regulated before it has become established in commerce:

> The most desirable time to determine health and environmental effects of a substance, and to take action to protect against any potential adverse effects, occurs before commercial production begins. Not only is human and environmental harm avoided or alleviated, but the cost of any regulatory actions in terms of loss of jobs and capital investment is minimized. (TSCA Legislative History, p. 678, quoted in OTS, **1982).**

REGULATION OF NEW CHEMICALS

Premanufacture notification allows EPA to make regulatory decisions about "new" chemicals. The category of new chemicals was established by TSCA section 8(b), which directs the Administrator of EPA to compile an "Inventory of Chemical Substances" of all chemicals subject to the provisions of TSCA that are manufactured or imported into the United States. The Inventory

was published on June 30, 1979, and all chemicals that did not appear on that list and which are not exempted from TSCA, are, by law, new.

Section 5 of TSCA stipulates that any person who intends to manufacture a substance that is not listed on the inventory and that is not excluded from TSCA must notify EPA of his or her intention 90 days before manufacture is to begin. Manufacture of small amounts of a chemical for research and development purposes to determine its usefulness and properties is, of course, permitted.

To initiate the EPA review of the new chemical, the company submits a PMN that is to contain information about chemical identity, proposed uses of the chemical, the expected production volumes of the chemical for various uses, expected byproducts, estimates of the numbers of people likely to be exposed in manufacture of the chemical, and methods for disposal.

> The notice . . . shall include—
>
> (A) insofar as known to the person submitting the notice or insofar as reasonably ascertainable, the information described in subparagraphs (A), (B), (C) (D), (F), and (G) of section 8(a)(2), and
>
> (B) in such form and manner as the Administrator may prescribe, any test data in the possession or control of the person giving such notice which are related to the effect of any manufacture, processing, distribution in commerce, use, or disposal of such substance or any article containing such substance, or of any combination of such activities, on health or the environment, and
>
> (C) a description of any other data concerning the environmental and health effects of such substance, insofar as known to the person making the notice or insofar as reasonably ascertainable. (TSCA sec. 5(d)(1)(a))

The subparagraphs of section 8(a)(2) referred to in section 5(d)(1)(a) read as follow:

> (A) The common or trade name, the chemical identity, and molecular structure of each chemical substance or mixture for which such a report is required.
>
> (B) The categories or proposed categories of use of each such substance or mixture.
>
> (C) The total amount of each substance and mixture manufactured or processed, reasonable estimates of the total amount to be manufactured or processed, the amount manufactured or processed for each of its categories of use, and reasonable estimates of the amount to be manufactured or processed for each of its categories of use or proposed categories of use.
>
> (D) A description of the byproducts resulting from the manufacture, processing, use or disposal of each such substance or mixture.
>
> (F) The number of individuals exposed, and reasonable estimates of the number who will be exposed, to such substance or mixture in their places of employment and the duration of such exposure.
>
> (G) ., . the manner or method of its [such substance or mixture] disposal . . . (TSCA sec. 8(a)(2)).

ACTIONS AVAILABLE TO EPA FOLLOWING PMN REVIEWS

The Administrator of EPA is charged with reviewing the information in the PMN within 90 days after receipt of the notice, and the agency can extend that review period for a maximum of 90 additional days (TSCA sec. 5(c)). The review of a PMN can result in any one of at least four actions by the agency.

(1) If the data in the PMN and expert opinion within the agency do not lead to the conclusion that an unreasonable risk is associated with the substance, manufacture can begin without restriction. Importantly, if EPA takes no action and the Agency is notified that manufacture of the substance described on the notice has begun, the name of the substance is placed on the Inventory of Chemical Substances. Unless the substance is the subject of a Significant New Use Rule (SNUR), this action transfers the substance from the "new" category, subject to section 5 of TSCA, to the "existing" category. [A "SNURed" chemical (see (2) immediately below) remains subject to section 5 requirements.] The testing and regulation of existing chemicals are the subject of other sections

of TSCA. Those sections are not discussed in this report.

(2) If EPA decides that the manufacture and use of the substance as described in the PMN are not associated with unreasonable risk, but, that a potential new use of the substance might be associated with unreasonable risk, EPA can commence a separate rulemaking to restrict the manufacture or distribution of the substance for uses not specified in the PMN. Under such a rule, manufacture can commence for the particular uses named in the PMN, but if the company that submitted the PMN or any other company decides to manufacture the substance for a "significant new use," EPA must be informed. The Agency then can require additional information about the substance (TSCA, sec. 5(a)(1)(B)).

The use of this authority is illustrated by the example of a chemical developed for use in commercial cleaning compounds. EPA was satisfied that its use by professional cleaning people would not be associated with an unreasonable risk, but the Agency was concerned that its use by consumers might result in such a risk. EPA took no action against the manufacture of the substance for commercial uses but drafted a "consent 5(e) order" (see (3) immediately below) that requires the reporting of additional information about toxicity before the substance is manufactured for a new use. The submitter consented to the order and agreed not to contest it in court so that manufacture for commercial uses could begin. At the same time, EPA announced that it would write a SNUR that requires that the Agency be notified before the substance is manufactured for use in consumer products. Therefore, the name of the substance is placed on the Inventory of Chemical Substances but flagged so that any subsequent manufacturer will know it is subject to pending regulation. According to EPA officials, future 5(e) orders of any kind will generally be linked to SNURS unless the submitter withdraws the PMN in the face of the 5(e) order.

(3) Section 5(e) of TSCA authorizes EPA to issue an administrative order regulating a new substance pending development of additional information by the submitter. To issue a 5(e) order, EPA must make two findings: First, the information available to EPA is insufficient to permit the evaluation of any risk that maybe associated with the new substance, and, second, either the new substance may present an unreasonable risk to health and the environment or the new substance will be produced in substantial quantities, resulting in significant exposure.

> (1)(A) If the Administrator **determines that**
>
> **(i) the information available to the Administrator is insufficient to permit a reasoned evaluation of the health and environmental effects of a chemical substance with respect to which notice** [PMN] is required . . . ; and
>
> (ii) (I) in the absence of sufficient information to permit the Administrator to make such an evaluation, the manufacture, processing, distribution in commerce, use, or disposal of such substance, or any combination of such activities, may present an unreasonable risk of injury to health or the environment, or
>
> (11) such substance is or will be produced in substantial quantities, and such substance either enters or may reasonably be anticipated to enter the environment in substantial quantities or there is or may be significant or substantial human exposure to the substance,
>
> the Administrator may issue a proposed order . . . to prohibit or limit the manufacture, processing, distribution in commerce, use, or disposal of such substances or to prohibit or limit any combination of activities (TSCA, sec. 5(e)).

In practice, 5(e) orders require that the PMN submitter develop specific items of information to assuage EPA's concern about the substance. The order can either prohibit or restrict manufacture during the period required for the development of additional information.

(4) Finally, EPA may decide from examination of the PMN that the manufacture, processing, distribution, use, or disposal of the substance "presents or will present an unreasonable risk of injury to health or environment" (TSCA sec. 5(f)). In those cases, EPA can regulate the substance.

Briefly, then, EPA can make any one of four decisions after inspecting a PMN:

1. The substance described on the PMN can be manufactured without restriction.

2. The substance can be manufactured for the uses described on the PMN, but the Agency can require that it be notified if manufacture for a significant new use is considered (TSCA sec. 5(a)(2)).
3. The manufacture, processing, distribution, use, or disposal of the new substance can be regulated pending the development of additional information about the substance (TSCA sec. 5(e)). In these cases, the Administrator must conclude that a decision about unreasonable risk cannot be made because of missing information.
4. The manufacture, processing, distribution, use, or disposal of the new substance can be regulated because it presents or will present an unreasonable risk (TSCA sec. 5(f)). In these cases, the Administrator decides that the available information is sufficient to decide that regulation is required.

PUBLIC NOTICE OF NEW CHEMICALS CONSIDERED FOR MANUFACTURE

TSCA section 5 (d)(2) provides that the Administrator is to publish a notice of receiving a PMN in the *Federal Register* within 5 business days after receipt of the notice. The published notice is to: 1) identify the chemical substance, 2) list the uses or intended uses, and 3) describe the results of any tests that were required by EPA rules under the provisions of TSCA section 5(b). (To date, no PMN containing EPA-required test results has been submitted.)

To protect confidential business information (CBI) from **public disclosure,** the submitter may designate those information items in a PMN that, were they to become public, would harm the submitter's business. Frequently, submitters have designated the chemical name as CBI. In those cases, the submitter, as part of the PMN, can use EPA guidelines and propose up to three "generic names" for listing in the *Federal Register.*

PMN REPORTING REQUIREMENTS

As required by TSCA section 5 (d)(1) all PMNs shall contain sufficient information to identify the new chemical, and to describe its projected uses and production volume, the number of workers likely to be exposed to it, its byproducts, and methods for its disposal. Those information items are specifically identified in the Act. In addition, TSCA section 5 lists some general classes of information that are to be reported on the PMN. The general reporting requirements say that any available information about the substance's physical and chemical properties and effects on health and the environment are to be included.

EPA has wrestled with the problems of specifying the form for PMNs and exactly what information should be submitted. In general, initial plans favored the submission of more detailed information, and subsequent modifications have pulled back to more general reporting requirements (see 44 F.R. 2242, Jan. 10, 1979; 44 F.R. 28564, May 15, 1979; 44 F.R. 59764, Oct. 16, 1979; 45 F.R. 74378, Nov. 7, 1980)

Currently, the EPA Office of Toxic Substances (OTS) is considering a proposal that PMNs will be required to contain only the items of information—chemical identity, proposed categories of use, estimates of production volumes, description of byproducts, estimates of the number of individuals exposed in their places of employment, and disposal methods—specified in TSCA section 5(d)(l)(a) and other "information that is essential for the review of most PMN's" (OTS, 1982). The other essential information is not described in *Priorities for OTS Operation,* but the point is made that even without having asked for additional information on the PMN itself, EPA will be able to telephone the submitter to ask for additional information as needed to review the

PMN. EPA states that in most cases, submitters have been forthcoming with such information when requested (OTS, 1982).

EPA also intends to require that all PMNs be submitted on a specified, simplified form (OTS, 1982). Currently, a PMN can be submitted on a form proposed by EPA, or on a form prepared by the Chemical Manufacturers Association, or on forms devised by individual companies.

EPA MANAGEMENT OF PMN REVIEW

Upon receipt of a PMN, EPA initiates a review that, with some exceptions, must be completed within 90 days. During the review period, EPA examines the PMN, and may request additional information from the submitter. If EPA does not find that the new substance presents or may present an unreasonable risk, EPA takes no action and the company submitting the PMN can begin manufacture when the 90-day period is completed. The submitter can request that the "clock be stopped" during the 90-day period if the company needs more time to develop information. If EPA agrees to the request, the agency waits until the company has obtained the desired information and then restarts the clock. Section 5(C) of TSCA authorizes EPA to extend the review period an additional 90 days for good cause.

PMN review is divided into 2 stages, an initial "screening" review and a detailed review. During the initial screening period, employees of EPA qualified by education and experience for the tasks, review the PMN for:

1. completeness, i.e., having the specific information required by TSCA;
2. correctness of chemical identity;
3. possibilities of occupational, environmental, and consumer exposures;
4. potential for human health effects;
5. potential for environmental effects; and
6. probable accuracy of projections of market size, new markets, and production volumes.

If an EPA reviewer thinks that the company might have additional information or that additional information is essential for the review, EPA can call the submitter. According to EPA officials and to some chemical company officials who reviewed the first draft of this OTA background paper, companies generally respond to such requests and supply the information.

When the requested information is unavailable or the company does not produce it, EPA employees can take one of several actions. They can make reasonable worst case estimates about the missing information, or they can negotiate with the company and reach an agreement that the company will run tests and supply data to EPA. If the company refuses to carry out necessary tests, EPA can write an order, as described by TSCA section 5(e), limiting or prohibiting manufacture pending development of appropriate data.

In general, each individual reviewer's report is reviewed by other, senior EPA scientists at a series of meetings. These meetings discuss the chemical described in the PMN, the information submitted, what conjectures can reasonably be made based on similarities to other chemicals, and appropriate strategies to search the literature for information about similar chemicals. Appendix A reproduces the items that may be discussed at the Evaluation Meeting which is held near the end of the initial screening period. Information about these items can be made available in the PMN or it can be estimated by EPA. Test-generated data are more reliable than estimates, but, there may be many instances when estimates are necessary.

The process of PMN review changed in May 1982 (as is described below). However, for most of the PMNs examined by OTA, the major decision was made at the "disposition meeting. " These meetings, held at day 45, considered the reviewers' comments and the reports of the earlier meetings, and discussed outstanding matters. The meetings produced one of four decisions:

1. no further review was necessary,
2. the chemical was referred to another EPA office or to another agency for action because OTS had identified an exposure that might

be of concern to another office or agency but was not of concern to OTS, or
3. the PMN was referred for detailed review, or
4. the decision was made to initiate some follow-up action, such as the writing of an SNUR.

If the first or second decision was reached, a final disposition report was written, the submitter was notified that manufacture could begin at the end of the 90-day review period, and the PMN file was closed out. If the third or fourth decision was reached, the PMN was sent to other groups within OTS for detailed review or other action.

Somewhat less than 10 percent of PMNs (7 percent of those examined by OTA) are sent to detailed review. Detailed review involves other individuals, frequently contractors to EPA, taking longer, harder looks at PMNs. During the detailed review, EPA can also telephone the submitter and request additional information. The EPA's *PMN Review Process Manual (OTS,* 1981) describes the review process in detail, and Arthur and Garrett (1982) provide a useful diagram of the process.

The review process was characterized by several EPA employees as reviews of reviews of reviews. There was agreement that the available information was thoroughly analyzed and that reasonable use was made of information about related chemicals. However, some EPA employees expressed concern about the adequacy of the data received on the PMNs and whether calls for additional information should have been made more often.

During the evolution of the PMN review process at EPA, some chemicals were identified as members of chemical classes that cause no or little concern about health or environmental effects. EPA scientists could, in the case of those chemicals, decide to drop them from further consideration at any time during the review period. In May 1982, the PMN review process was changed to accommodate EPA's conclusion that decisions about some chemicals could be made earlier in the review process. Since that time, a "focus meeting" has been held at about 15 days after PMN receipt. This meeting centers on identifying health and/or ecological concerns and assessing the accuracy of the estimates made of possible exposure to and release of the new chemical. The result of the focus meeting maybe a decision that the PMN describes a chemical of little or no concern, and such substances are dropped from further review.

OTA made no attempt to determine how the new meeting affected PMN review. EPA staff reported, however, that the meeting has been beneficial, speeded up the process, and conserved resources for the more difficult-to-review PMNs.

PROPOSED EXEMPTIONS TO THE PMN REPORTING REQUIREMENTS

TSCA section 5(h)(4) permits the Administrator of EPA to exempt substances from the PMN reporting requirements. The first exemption was granted on November 3, 1981, for chemicals used in or for instant photographic film articles (40 F.R. 54585). A manufacturer of those chemicals had petitioned for the exemption because of industry desire to introduce chemicals quickly in order to capitalize on newly opened-up markets. The 90-day PMN review period, according to the petition, would sometimes cause introduction of a new film to be delayed to the extent that a holiday market was missed. The exemption imposes requirements on the manufacture and use of the chemicals to restrict exposures.

On August 4, 1982, EPA proposed more general exemptions directed at:

1. site-limited intermediate chemicals,
2. chemicals manufactured in quantities of 10,000 kg (22,000 lb) or less annually, and
3. polymers.

The proposed exemptions for site-limited intermediates and low-volume substances were published in one notice (47 F.R. 33896), and the one for polymers was published separately (47 F.R. 33924).

EPA, in proposing these exemptions, responded to industry petitions that were based on two dif-

ferent lines of reasoning. Industry advanced the ideas: 1) that low-volume chemicals and site-limited intermediates are "characterized by limited exposure," and 2) that polymers "represent a class of substances that have intrinsically low levels of biological activity" (OTS, 1982).

Following some provisions of the industry petition, EPA proposed a policy that PMNs describing low-volume chemicals and site-limited intermediates that are not excluded from the exemption (see table 1) should be subject to an abbreviated EPA review. Agreeing with the idea that some polymers have inherently low toxicity, EPA decided that a finding of no unreasonable risk for those polymers would not depend on conditions of use, and that it would not be necessary for the Agency to review the specific properties or uses of certain polymers before they were manufactured (OTS, 1982). For certain other polymers, the Agency proposes a short review period (see table 2).

The proposed exemption for low-volume chemicals is divided into two parts. The first deals with substances made in amounts of 1,000 kg or less annually; the second with substances made in amounts of 10,000 kg or less annually. Any substance made in quantities of 1,000 kg or less would be granted an exemption unless under the conditions of use, the:

> . . . substance or a reasonably anticipated metabolite or environmental transformation product may cause . . . . serious chronic effects, including carcinogenic and teratogenic effects . . . . serious acute effects [lethal or sublethal] . . . . [or] . . . . significant environmental effects . . . under anticipated conditions of manufacture, processing, distribution **in commerce, use, or disposal.**

Table 1 .—Proposed Low-Volume and Site-Limited Intermediate Exemption Provisions

Exemption category*	Imports eligible?	Qualified expert review?	Exclusions (automatic)	Exclusions (under conditions of use)	Subsequent exemption notice required	Other manufacturers eligible for exemption?
Low volume (<1,000 kg)	Yes	No	None	Serious acute or chronic effects; significant environmental effects.	Before use or site of manufacture changes.	No
Low volume (<10,000 kg)	Yes	Yes	Carcinogenic or teratogenic effects. Acutely toxic effects.	Serious acute or chronic effects; significant environmental effects.	Before use or site of manufacture changes.	No
Site-limited intermediates	No	Yes	Carcinogenic or teratogenic effects.	Serious acute or chronic effects; significant environmental effects.	Before volume increases or site of manufacture changes.	Yes

*Some new chemical substances may be eligible for more than one exemption, Manufacturers and importers may apply for any exemption for which they are eligible.

SOURCE: Environmental Protection Agency; 47 F.R. 33897.

Table 2.—Proposed Polymer Exemption Provisions

Polymers for which no review is required	Polymers that qualify for a 14-day reveiw	Polymers excluded from exemption
1. Polymers manufactured from monomers listed by EPA. 2. Polymers of average molecular weights greater than 20,000. 3. Polymers that have limited and defined numbers of low molecular weight components.	1. Polymers of greater than 1,000 molecular weight.	1. Water soluble polymers. 2. Polymers containing less than 32 percent carbon. 3. Polymers containing more than specified percentages of certain elements. 4. Polymers produced by living or once-living organisms or cells ("biopolymers"). 5. Polymers containing halogens or cyano groups. 6. Polymers containing chemically reactive groups. 7. Polymers that are designed to degrade, decompose, or depolymerize.

SOURCE: Office of Technology Assessment from Environmental Protection Agency; 47 F.R. 33924.

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Chemicals suspected to have carcinogenic or teratogenic potential are to be automatically excluded from the proposed exemptions for site-limited intermediates and substances to be made in amounts between 1,000 and 10,000 kg annually. In addition, substances with potential acutely toxic effects are to be excluded from the 1,000 to 10,000 kg annually low-volume exemption. To be excluded from both the two proposed low-volume exemptions and the proposed site-limited intermediate exemption are any substances which, under conditions of use, potentially may cause serious acute or chronic health effects or significant environmental effects (table 1).

The reporting requirements for substances made in amounts between 1,000 and 10,000 kg annually or for use as site-limited intermediates include a stipulation that a "qualified expert" review all available data about the substance. The qualified expert, an employee of the submitting company or a consultant hired by the company, after his or her review, must conclude that the chemical meets the terms of the exemption.

To allow EPA to make a determination about the likelihood that a substance for which an exemption is requested will not cause an undesirable human health or environmental effect, the manufacture must submit a notice to the Agency 14 days before commencement of manufacture that states which exemption is being sought. In addition, for substances to be manufactured or imported in amounts of 1,000 kg or less annually, the notice is to contain sufficient information to identify the chemical and describe its use and site of manufacture. EPA, on the basis of toxicity data or by reason of structural analogies between the substance proposed for exemption and known toxic substances, could declare the chemical ineligible for exemption.

For substances to be made or imported at between 1,000 and 10,000 kg annually and for site-limited intermediates, the notice is to contain information about chemical identity, description of uses (for low-volume chemicals), production volume (for site-limited intermediates), and site of manufacture. EPA can declare any substance ineligible for exemption if the notice fails to meet the exemption requirements. Substances that are granted exemptions are not eligible for listing on the Inventory of Chemical Substances and remain subject to PMN requirements.

As is shown in table 1, only the first company to submit an exemption for low-volume production will be eligible for exemption. If, subsequently, another submission is made for a chemical that has received a low-volume exemption, a complete PMN and review will be required. A trade association that reviewed the first draft of this report objected to this provision of the proposed exemption. They argue that any number of manufacturers should be eligible for low-volume exemption from PMN reporting requirements on a chemical. Any number of manufacturers can receive a site-limited exemption to manufacture a substance.

The proposed polymer exemption distinguishes between polymers for which no review is required, those for which a 14-day review is required, and those excluded from exemption. Table 2 displays some aspects of the polymer exemption.

Polymers exempted from any review will require only that EPA receive an exemption notice at the time of the start of manufacture. Such substances will not be entered on the Inventory of Chemical Substances because they have not undergone PMN review. The exempted polymers will become subject to section 5 PMN requirements if manufactured outside the terms of the exemption.

For polymers subject to 14--day review, a PMN must be submitted to EPA that identifies the manufacturer, the site of manufacture, and the polymer, and provides information about the molecular weight of the polymer and the amount of low-molecular weight material in the polymer preparation, projections of expected production volumes and uses, and any test data. Furthermore, the submitter must certify that the substance is a polymer and that it meets the conditions for exemption.

In the event that EPA does not notify the submitter otherwise, manufacture of the polymer can begin at the end of the shortened review period. Manufacturers are to notify EPA when manufacture commences, and, at that time, a polymer that has completed the 14-day review and gone into

production will be placed on the Inventory of Chemical Substances.

Certain classes of polymers (table 2) are excluded from the proposed exemption rule. In general, EPA excluded those classes because the agency has not had sufficient experience with them to accept that they are of low potential hazard.

The low-volume, site-limited intermediate, and polymer exemptions are still in the proposed stage. Objections to the proposed exemptions focus on the undeniable fact that less information would be received by EPA about the exempted substances and that EPA's review period would be shortened. EPA justified its decisions on the basis that the proposal exemptions are sufficient to guard against unreasonable risk. However, several comments have been received arguing against the exemptions because they are seen as weakening the PMN process to the point that protection against unreasonable risks is being lessened. On the other hand, industry sees the proposed exemptions as having ample safeguards and argue that the procedure should be further simplified to minimize burdens.

Several reviewers of the first draft of this background paper objected to the proposed exemptions. The exemption categories are seen as being too broad. The absence of a requirement that the qualified expert submit the data considered in reaching a decision to certify a substance as qualified for exemption is viewed as preventing EPA from carrying out its duty to review test data before a chemical is manufactured. Furthermore, some reviewers expressed concern that polymer preparations may be contaminated with hazardous chemicals and that EPA's general decision that some polymers are inherently less hazardous is an unjustified overstatement.

RISK ASSESSMENT

Two factors are of importance in estimating the risk that may be posed by a substance. The first is to determine any deleterious effect that the substance may cause to human health or the environment. In this background paper, the word "hazard" will be used to describe such effects. The second factor is "exposure."

Exposure is a complicated factor; determining it for risk assessments considering human health involves estimating the number of people who may come in contact with the substance, the duration of the contact, the route(s) of adsorption, the amount of substance which may be encountered by people, and, especially for workers, whether or not they employ personal protection equipment to reduce the contact. For environmental risk assessments, exposure estimates must consider the number and kinds of organisms that might come into contact with the substance and the distribution of the substance in different parts of the environment. An additional complicating factor in considering exposures is the persistence of the substance, which may vary in different parts of the environment.

Human risk is estimated from knowledge of the health hazard of a substance and the number of people who are likely to be exposed to it at particular exposure levels (9). Environmental risk is estimated from knowledge of the environmental hazard of a substance and the number of organisms or fraction of the environment expected to come into contact with the substance at expected exposure levels.

Low levels of either hazard or exposure reduce the amount of concern expressed about a substance. For instance, a very hazardous toxic substance might be used in manufacturing. Although its toxicity is well known, the chemical is also contained in sealed reaction vessels and there is little or no human or environmental exposure. While there is some lingering concern in case an accident releases the chemical, safeguards to contain the accidental release or inactivate the chemical can reduce those worries also. Limited exposure, then, reduces concern about risks.

At the other extreme are substances to which exposure is widespread but which have extremely low toxicities. For instance, polyester fibers in

clothing, to which almost everyone is exposed, cause no worry for the population in general because of very low (if any) toxicity.

EPA, or any other risk assessor, needs information about both hazard and exposure. If either hazard or exposure is very low, the need for the other kind of information maybe reduced. However, always, both components of risk must be considered. This background paper reports the frequency with which PMNs contained information useful in making risk assessments.

EPA has to estimate effects when toxicity data are not included in the PMN. The technique for making those estimates and some difficulties with it are described in the next section.

STRUCTURAL ACTIVITY RELATIONSHIP ANALYSIS AND ITS USE IN PMN REVIEW

Only about half of PMNs report any toxicity data (see ch. 6), and although about 96 percent report at least one physical-chemical datum in addition to those specified in TSCA, reporting of such data is spotty (see ch. 5). EPA, in the absence of those data, must estimate either toxicity or physical-chemicals properties. A complex of activities—examining the chemical structure of the new substance, deciding which parts of the structure may be important in biological systems, comparing the structure to related structures described in the chemical literature, and making projections about the toxicity or chemical behavior of the new substance—is involved in making estimates when data are lacking. All of these activities are grouped under the rubric of Structural Activity Relationship (SAR) analysis.

The underpinnings of SAR analyses are many observations that certain chemical structures and subunits are associated with toxic properties and other structures and subunits are not. At the same time, it is well known that some substances which are quite closely related differ significantly in toxicity. A well-known example is the comparison of 2-acetylaminofluorine to 4-acetylaminofluorine. These two substances differ in the location of a small chemical sidechain; the first is a carcinogen; the second is not. The very different toxic properties of these two similar chemicals points to the difficulties of using SAR (9).

No one claims that SAR is developed or refined to the point that no toxicity testing is necessary. However, arguments do arise about when its use is appropriate, when it leads or may lead to incorrect predictions about toxicity. Ideally, criteria for when it is and is not appropriate would be available, but they have not been developed. The considerable amount of professional opinion and considered judgment that are involved in the use of SAR analysis is illustrated in EPA's proposed low-volume chemical and site-limited intermediate exemptions.

> Factors that will be considered in evaluating structural similarity include the molecular size, shape, charge distribution, and weight, and the position, size, and chemical characteristics of functional groups or other substituents. These factors are judged in terms of their effect on such parameters as chemical reactivity, stemochemically governed interaction with enzymes, absorbability and distribution, metabolism, and excretion from an organism. (Other factors and parameters may be important in specific cases.) The greater the number of such factors that are identical or nearly identical between two substances, the closer the structural similarity.
>
> The absolute degree of structural similarity, however, is not the important determinant of the *significance of structural similarity* . . . . the significance of structural similarity to a human or animal carcinogen or teratogen would be judged with reference to the probability of eliciting carcinogenic or teratogenic effects. Therefore, all available information concerning possible mechanisms of action of a carcinogen or teratogen will be relevant to an assessment of the significant [sic] of structural similarities between that substance and a new chemical substance. Moreover, information indicating that certain groups on the carcinogen or teratogen are or maybe critical for toxicologic activity has to be considered before determining whether the new molecule has significant

structural similarity to a referent chemical. Structural similarities at toxicologically significant sites or a molecule are of greater importance than similarities at other sites.

In a number of cases, neither the mechanism of action nor structural requirements for activity of a referent toxic substance is known, even though its toxicity has been clearly established. In such instances, attention is usually drawn to chemically or biologically active groups as potential sites of action. Structural similarity at these sites would reasonably be accorded higher significance than similarity at less reactive sites.

It follows from this summary statement that *a determination of significant structural similarity is often dependent on the kinds and amount of toxicological information available for the referent chemical.* Because this information will vary for each new substance, the Agency is unable to prescribe definitive criteria against which structural similarity can be measured. The determination whether there is significant structural similarity will be based primarily on whether there is an identifiable or plausible mechansim [sic] of toxicity that can be shared by the referent chemical and the new substance; or, lacking information or hypotheses on mechanism, whether substructures known or expected to be required for activity of the referent chemical are present in the new **substance (47 F.R. 33900). (Emphasis added** in paragraphs 3 and 4).

An acknowledged shortcoming of SAR analyses is that it can say nothing about an entirely "new" structure. However, EPA officials point out that the vast majority of substances submitted on PMNs are derivatives of known chemicals and that SAR is useful and sufficient to make decisions about those.

It would be possible to compare PMNs that describe novel chemicals to those that describe "me too" chemicals with an eye to determining if more data, especially toxicity data, were submitted on substances for which SAR is more likely inappropriate. Such an analysis was beyond the resources of the study described in this background paper.

Questions can be asked about what criteria EPA used to decide that SAR was sufficient for making estimates of toxicity. OTA did not attempt to answer that question, but it is clear from data presented in this paper that in many cases no toxicity data were presented on the PMNs. In those cases, if EPA was concerned about toxicity, the Agency would have to rely on SAR. It may be that EPA was too willing to use SAR analysis when what was desirable or actually necessary was more information about the chemical. To determine whether or not EPA received necessary information about particular chemicals would require a study different from the one described here (see ch. 9).