Chapter 1

THE PREMANUFACTURE NOTIFICATION (PMN) REVIEW PROCESS

1.1 Introduction

Prior to the promulgation of the Toxic Substances Control Act (TSCA) in 1976 (TSCA 1976), there was no statutory requirement that required either risk assessment of new chemical substances prior to their commercial introduction or testing of substances suspected of being harmful. Unlike other federal statutes that regulate risk *after* a chemical is in commerce, TSCA requires the Environmental Protection Agency (EPA) to assess and regulate risks to human health and the environment *before* a new chemical substance is introduced into commerce. Section 5 of TSCA requires manufacturers and importers to notify the Agency before manufacturing or importing a new chemical substance.[1] EPA then performs a risk assessment[2] on the new chemical substance to determine if an unreasonable risk may or will be presented by any aspect of the new substance. Finally, EPA must make risk management decisions and take action to control any unreasonable risks posed by new chemical substances.

TSCA implies that EPA will develop a review process for evaluating chemicals before they enter the marketplace. Other Acts, such as the Federal Food, Drug, and Cosmetic Act (FFDCA 1982) and the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA 1972), have led to the development of similar processes within the FDA's New Drug Application Program and EPA's Pesticide Registration Program, respectively.

TSCA, however, departs from FDCA and FIFRA in several significant ways in its treatment of new substances. First, under TSCA, the Agency only receives the data that are available (if any) and must then determine whether there may be an unreasonable risk associated with the chemical. Second, TSCA does not require toxicity testing of a new chemical substance prior to submission of a Premanufacture Notification (PMN) to EPA. Third, under

1. As discussed in the Appendix, these provisions apply to substances that are either manufactured within the U.S. or imported into the U.S. In the following discussion, the words manufacture or manufacturer include import or importer.

2. Risk assessment is the characterization of the potential for adverse health or ecological effects resulting from exposure to a chemical substance. Risk management is the weighing of policy alternatives and selecting the most appropriate regulatory (or non-regulatory) action after integration of risk assessment with social and economic considerations. Risk, in either case, is the probability that a substance will produce harm under specified conditions, and is a function of the intrinsic toxicity of a substance and the expected or known exposure to the substance. In practical situations, the critical factor is not the intrinsic toxicity of a substance, but the risk associated with its use.

TSCA, EPA is allowed only 90 days to review each substance (extendable to 180 days under certain conditions; see Appendix).

Currently, the EPA receives approximately 2,500 PMNs annually. The Agency must assess the risks posed by each of these new substances, regardless of the quantity or quality of data submitted or available. Charged with the difficult task of rapidly forecasting the environmental behavior and toxicity of chemical substances for which very little or nothing is known, EPA has developed the **PMN Review Process**. This process utilizes several general approaches to fill in data gaps so that the Agency can make rapid risk assessment and risk management decisions for new chemicals as prescribed by TSCA.

The PMN review process is used for "standard" PMNs as well as PMN exemption notifications (Appendix; USEPA 1986a; USEPA 1995b; USEPA 1995c). In this chapter, the terms "PMN submission" or "PMN" refer to all new substance submissions, unless one type of submission is mentioned explicitly. The types of submissions and their respective review periods are shown in Table 1-1.

Numerous acronyms are used to describe Divisions or Branches within the Office of Pollution Prevention and Toxics (OPPT) as well as to identify scheduled meetings and types of scientific reviews. Table 1-2 contains a list of frequently-used acronyms. This list is current as of December 1996. OPPT is scheduled to be reorganized in 1997 and some of these acronyms will change. The PMN review process, however, will remain essentially the same.

1.2 The PMN Review Process

The PMN Review Process consists of four distinct, successive technical phases: the chemistry review phase, the hazard (toxicity) evaluation phase, the exposure evaluation phase and the risk assessment/risk management phase. These phases are structured to “drop” substances of low-risk from review and to focus more sharply on, and explore more deeply, those substances of greater risk as the review progresses. Thus, the resource-intensive efforts of the later review phases are conserved by eliminating many PMN chemicals from consideration early in the process and by focusing only on those specific aspects of a few PMN substances for which there is the greatest concern. It is important to note that although a chemical substance may drop from review because of low risk, the 90-day review period still applies.

The PMN Review Process is designed to accommodate the large number of PMNs received, to assess the risks posed by each substance adequately within the strict timeframe prescribed by TSCA (whether or not toxicity data are available), and to maximize the efficiency of staff resources. Figure 1-1 provides an overview of the process as it exists today. Although some changes have taken place over the years, the process illustrated in Figure 1-1 is quite similar to the original PMN review process that began in 1979.

Table 1-3 contains historical information on the amount of test data

Table 1-1. Types of Submissions and Their Designators

Submission Type	Review Period	Designator	Reference: TSCA Section
PMN and Exemption Submissions:			
Standard Premanufacture Notification (PMN)	90 days	P	5(a)(1)
Low Volume Exemption (LVE)	30 days	L	5(h)(4)
Low Release and Exposure Exemption (LoRex)	30 days	X	5(h)(4)
Test Market Exemption (TME)	45 days	T	5(h)(1)
Polymer Exemption[1]	None	Formerly Y	5(h)(4)
Non-PMN Submissions:			
Correction Case[2,]	varies	C	N/A
Enforcement Case[3]	varies	I	N/A

[1] Polymers meeting the conditions of the Agency's most recent Polymer Exemption Rule no longer need to be submitted to the Agency (USEPA 1995a). See text for details.

[2] Those correction cases that go through the PMN review process arise from requests by industry to revise a previous PMN chemical name. Inventory corrections, which are requests to correct chemical identity in initial Inventory reporting forms, do not go through the PMN review process.

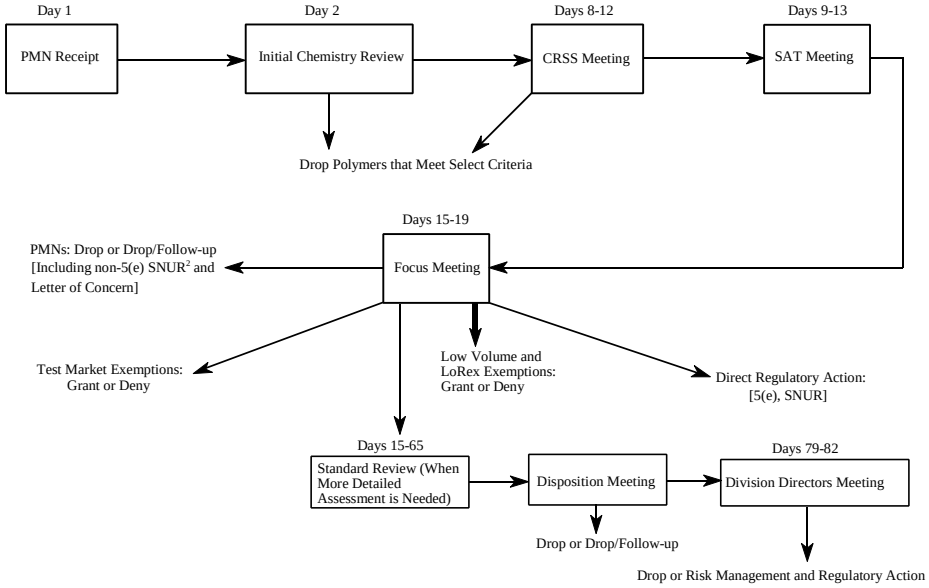
[3] Enforcement cases arise from EPA investigations into potential TSCA violations.

Table 1-2. Acronym List: Organizational and Meeting Acronyms

Organizational Acronyms*:	
Office of Pollution Prevention and Toxics	OPPT
Economics, Exposure, and Technology Division	EETD
Industrial Chemistry Branch	ICB
Chemical Engineering Branch	CEB
Exposure Assessment Branch	EAB
Regulatory Impacts Branch	RIB
Health and Environmental Review Division	HERD
Health Effects Branch	HEB
Environmental Effects Branch	EEB
Information Management Division	IMD
TSCA Information Management Branch	TIMB
Confidential Business Information Center	CBIC
Chemical Control Division	CCD
New Chemicals Branch	NCB
Chemical Screening and Risk Assessment Division	CSRAD
Analysis and Information Management Branch	AIMB
Meeting Acronyms:	
Chemical Review and Search Strategy	CRSS
Structure-Activity Team	SAT

*This list is current as of December 1996. OPPT is scheduled to be reorganized in 1997 and some of these acronyms will change.

Figure 1-1.
Office of Pollution Prevention and Toxics New Chemical (PMN) Review Process[1]



[1] See Appendix for additional information on EPA's authority under TSCA.
[2] SNUR stands for Significant New Use Rule.

Table 1-3. Test Data Submitted with PMNs (1979-1985)[1,2]

Type of Data	Percent of PMNs Containing the Specified Data		
	All	Non-Polymers	Polymers
Toxicologic data (some)	44	55	28
Acute Toxicity (oral)	38	50	22
Acute Toxicity (dermal)	21	27	13
Acute Skin/Eye Irritation	34	45	21
Mutagenicity	13	18	6
Sensitization	8	12	5
Other	8	11	3
Ecotoxicological data (some)	9	11	5
Acute Toxicity (vertebrate)	6	9	3
Acute Toxicity (invertebrate)	3	3	2
Environmental fate data (some)	9	11	5
Biodegradation	6	8	2
Log P	3	5	1
No Test Data	54	41	70

[1] These data are based on the receipt of approximately 5,500 PMNs. Current trends in test data submissions are similar. See text for additional details and references.

[2] Source: DiCarlo et al. 1986.

submitted with PMNs; although the information is several years old, the amount of data submitted has not changed significantly. From Table 1-3, it is apparent that over half of all submitted PMNs have not contained any hazard or fate test data. More recent studies show that: less than 5% of PMN submissions contain ecotoxicity data (Zeeman et al. 1993); less than 4% contain at least one measured physicochemical property value (Lynch et al. 1991); and less than 1% contain biodegradation data (Boethling and Sabljic 1989).

For the vast majority of PMN substances, the Agency is unable to reach a decision based on the submitted data alone. The Agency utilizes a number of technical approaches to overcome the lack of data during risk assessment. These approaches include, for example, chemistry review, analysis of structure-activity relationships (SARs), analysis of quantitative structure-activity relationships (QSARs), and the use of physicochemical properties to assess the likelihood of absorption in exposed individuals; the various approaches are discussed in greater detail in this chapter and in Chapter 2. The remainder of this chapter discusses the PMN Review Process, including the purpose and function of each phase, with particular focus on the technical approaches used by the Agency to assess the risks of new chemical substances. Other Agency publications are available to assist the reader in understanding the general PMN review process (USEPA 1986a) and in filing a PMN (USEPA 1991).[3]

1.2.1 Receipt of the PMN (Day 1)

PMN submissions are received at the Confidential Business Information Center (CBIC) where they are time- and date-stamped. Here, appropriate security management of any submissions containing TSCA Confidential Business Information (CBI) is initiated. The TSCA Information Management Branch (TIMB) performs an administrative review of each submission to verify that all of the required information, other than specific chemical information, is present in the PMN. This review includes submitter and chemical information, generic chemical name and use (if chemical name and use information are claimed as CBI), projected production volume, and the presence of any submitted health or environmental hazard studies in the sanitized version (i.e., the version that does not contain CBI). The submissions must also contain the English translations for any submitted studies originally written in a foreign language. Next, TIMB checks the user tracking sheets received from EPA's Financial Management Division to confirm that the appropriate fees have been paid.

The submission is then forwarded to the Industrial Chemistry Branch (ICB) of the Exposure, Economics, and Technology Division (EETD) where chemists check the adequacy of the submitted chemical name, molecular formula, and chemical structure diagram to describe the new substance. As of the effective date (May 30, 1995) of the Revisions to PMN Regulations (USEPA 1995c), EPA requires the submission of a correct Chemical Abstracts (CA) name that

3. These, and other useful documents for PMN submitters, are available through the TSCA Assistance Information Service at (202) 554-1404.

is consistent with listings of chemical names for similar substances already on the TSCA Inventory. A correct molecular formula and chemical structure diagram, where appropriate, are also required.

If the name is determined by EPA to be inadequate or incorrect, the Agency will declare the notice incomplete unless the submitter used Method 1 (USEPA 1995c) to determine chemical identification and submitted exactly the same substance information to EPA and the Chemical Abstracts Service (CAS) Inventory Expert Service. Only in this situation will EPA allow the PMN review period to continue while the problem is resolved. If the submitter did not use the CAS Inventory Expert Service (which solely constitutes Method 1) the Agency will not begin the review period until the problem is resolved by the submitter. (See USEPA 1995c for details.)

If no problems are identified during the administrative and nomenclature prescreening reviews, the first day of the 90-day clock[4] for PMN review is the day that the PMN submission was received at EPA Headquarters. If very minor problems are identified that would not constitute an incomplete notice, and the information is believed to be readily available, the submitter is contacted for this information by telephone. If the notice is incomplete, the submitter is given a list of the problems in writing so that the submitter will know what is needed to complete the notice and start the review period. If the submitter has not responded to EPA's request for additional information within 30 days, EPA terminates the notice and returns the PMN user fee. When all required additional information is received from the submitter, the first day of the review period is assigned as the day EPA receives this information.

Following the resolution of any minor problems with administrative information and chemical identification, the CBIC staff assign a case number to the PMN. Case numbers are assigned in sequential order using a one-letter designator to indicate the type of submission (see Table 1-1). The CBIC staff assign document control numbers and log each submission (and copy) into a computerized document tracking system designed for TSCA CBI documents. Using established procedures to protect CBI (USEPA 1993), the CBIC staff forward copies of each case to technical staff in EETD and the Health and Environmental Review Division (HERD) as well as to program management staff in the Chemical Control Division (CCD) for their respective reviews.

1.3 Chemistry Review Phase (Days 2-12)

The first technical phase of PMN review by EPA scientists is the **chemistry review phase**, which is performed by the Industrial Chemistry Branch (ICB). This phase establishes a chemistry profile for each new substance and establishes the essential foundation for the review by other OPPT

4. The phrase "90-day clock" refers to standard PMN submissions. In the interest of brevity, the reader should note that this phrase will be used for the amount of time in which the Agency must complete its review; the actual time for exemption notices is less than 90 days, as indicated in Table 1-1.

scientists in subsequent phases of PMN review. The chemistry review phase has four components: initial review, preparation of the Chemistry Report, Inventory review, and discussion at the Chemical Review and Search Strategy (CRSS)[5] meeting.

1.3.1 Initial Chemistry Review (Day 2)

The initial chemistry review is a rapid assessment by ICB chemists of each new chemical submission. The first step is to establish the technical completeness of the submission. The chemists check the reported Chemical Abstracts (CA) name, molecular formula, and chemical structure against the reactants and feedstocks used in its manufacture to determine quickly whether the PMN substance is identified correctly, as well as consistently, and check the generic chemical name (if provided) to verify that it is appropriate.

If the submission is an exemption notice, the chemist checks for compliance with the exemption guidelines.[6] For all submissions, an in-house electronic database is searched to establish if an identical substance has been submitted previously.[7] This check for previous exemptions is a rapid screening process, not to be confused with the definitive determination performed during the Inventory review (see below).

Based on its experience during the review of thousands of new chemical substances, EPA has identified a group of polymers (see below) that it believes poses no unreasonable risk of harm to human health or the environment. When a PMN substance in initial chemistry review falls within this group, the ICB chemist labels the case a "pre-CRSS drop" and the Agency performs no further review. As a general practice, the Agency does not notify the submitter that a PMN submission has been dropped from further review; by law, manufacture of a new substance cannot commence before the normal review period has expired, even for PMN cases that have been dropped from further Agency review.

For a polymer to be considered a pre-CRSS drop, it must satisfy all six of the following criteria:

(1) It must belong to one of twelve (12) acceptable polymer classes: polyesters, polyamides and polyimides, polyacrylates, polyurethanes and polyureas, polyolefins, aromatic polysulfones, polyethers, polysiloxanes, polyketones, aromatic polythioethers, polymeric hydrocarbons, and phenol-formaldehyde copolymers;

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5. The CRSS meeting is the first meeting of the PMN review process.

6. Since the effective date of the Agency's revised Polymer Exemption Rule (USEPA 1995a), no notifications have been required for exempt polymers. Manufacturers must, however, follow the Agency's requirements for all polymers exempt under this rule.

7. In a change from the previous low volume exemption regulation, more than one low volume exemption may now be granted for any substance (USEPA 1995b), but the Agency will assess the risk of the total production volume if there is more than one exemption notification for the same substance.

(2) The levels of oligomer present in the polymer must be less than or equal to (a) 10 weight percent of polymer molecules with molecular weight less than 500 daltons and (b) 25 weight percent of polymer molecules with molecular weight less than 1,000 daltons;

(3) It must have no more than the level of ionic character permitted by the polymer exemption rule (generally a functional group equivalent weight for ionic groups greater than or equal to 5,000);

(4) It must have (a) no reactive functional groups, (b) only reactive functional groups specifically excluded based on OPPT's risk assessment experience (e.g., blocked isocyanates), or (c) a reactive functional group equivalent weight no less than a defined threshold (e.g., for pendant methacrylates, the equivalent weight threshold is 5,000);

(5) The lowest number-average molecular weight of the polymer must be less than 65,000 daltons but greater than 1,000 daltons; and

(6) the polymer must not swell in water.

These criteria have been developed for use by EPA, although they can by useful to submitters interested in developing low risk polymers. These criteria should not be confused with the criteria stated in the Polymer Exemption Rule (USEPA 1995a), which specifically exempt certain polymers from PMN submission. (The above criteria were used, however, in the development of the Polymer Exemption Rule).

It has been the Agency's experience that polymers meeting these criteria have a low risk for causing adverse environmental and human health effects. Both the group of acceptable polymer classes and the reactive functional group criteria are being updated and expanded as OPPT's experience in risk identification and assessment continues to grow. The actual figure varies from time to time, but, in general, many of the PMNs for polymers meet these criteria and are dropped from further review. (Many of these polymers also qualify for exemption and need not be reported at all.)

Another important function of the initial chemistry review is to identify PMN cases for which pollution prevention opportunities may exist. For example, ICB has developed a PMN screening methodology known as the Synthetic Method Assessment for Reduction Techniques (SMART). The purpose of the SMART review is to identify pollution prevention opportunities (e.g., alternative syntheses, in-process recycling, etc.) and to encourage the PMN submitters to take advantage of these opportunities, if possible, during production of their new chemical substances. The SMART review of PMN cases takes place simultaneously with the chemistry review. PMN cases that are judged appropriate candidates for SMART review are assigned to staff chemists with expertise in identifying pollution prevention opportunities as they relate to the manufacture of the substance (see Chapter 3 and USEPA 1995e).

The next step of the initial chemistry review is to assign each PMN case (except those already dropped) to a chemist for preparation of a Chemistry Report. Generally, each PMN is assigned to a staff member with particular expertise in that chemical class. For example, a submission for a new dye would be assigned to an organic chemist with experience reviewing this class of substances. Substances submitted simultaneously that are closely related or that comprise a synthetic pathway are typically assigned as a group to an individual chemist for review.[8]

At this stage, the senior chemist also assigns each PMN case for presentation at a specific CRSS meeting. The CRSS meetings are held twice a week, on Monday and Thursday mornings. A routine CRSS meeting has between 10 and 30 PMN cases; frequently, some of the cases are grouped for review and are presented together. This twice-weekly bundling of cases for review greatly increases the efficiency of the PMN review process. Unless any unforeseen problems delay the review of individual cases, the cases bundled for review at this point will go through the review process together.

1.3.2 Inventory Review (Days 3-11)

The Inventory review is an extremely important component of the PMN review process, from both legal and technical standpoints. The Inventory review, performed by chemists within ICB, has two major functions. The first is to establish a complete and accurate chemical name for the new substance. The chemist compares the chemical structure, molecular formula, the reactants, and the reaction scheme for consistency with the CAS name submitted in the PMN; if a CAS Registry Number is provided, the chemist verifies it as well. The name must be consistent with CAS nomenclature policies and with how similar substances have been named previously for the TSCA Inventory. If inconsistencies are found, the chemist declares the notice incomplete, and review of the notice is terminated, unless the submitter used Method 1 to develop the name (See USEPA 1995c for details).

The second function of the Inventory review is to determine definitively that the new chemical substance is not (or is) on the TSCA Chemical Substance Inventory. For this search, the Agency uses the continually updated computer database of the Inventory, known as the Master confidential and non-confidential listings. The Agency maintains a separate list of low volume and LoREX exemptions on the Master Inventory File, in light of the special status of exempt substances.

If the Inventory review establishes that a PMN substance is currently on the TSCA Inventory or the intended use of the substance is a non-TSCA use (e.g., pesticide, pharmaceutical, pharmaceutical

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8. PMNs for closely-related new chemical substances submitted at the same time by one manufacturer are frequently grouped into what is called a consolidated submission. Each new substance gets a unique case number, however. A consolidated submission must have prior approval by the EPA. See USEPA 1991.

intermediate), the substance is excluded from PMN reporting.[9] If the review establishes that the same manufacturer had submitted the identical substance in an earlier PMN and that this submission was not withdrawn, the new notice is declared not valid. In either circumstance, Agency staff terminate the review and notify the submitter.

1.3.3 Preparation of the Chemistry Report (Days 3-11)

It is essential that all of the chemical aspects of PMN substances are thoroughly explored and understood, because the Agency's hazard and risk assessments are based largely on the chemistry of these substances. The chemistry information is summarized in the Chemistry Report, prepared for each PMN. In preparing the Chemistry Report, the chemist verifies the chemical identity information, researches the chemistry of the PMN substance, and examines and/or estimates the physicochemical properties that are critical for Agency risk assessment.[10]

Chemists frequently contact the PMN submitter to clarify information submitted or to discuss an apparent error. Most such problems are resolved over the telephone (at the submitter's discretion and with confidentiality preserved, as appropriate), allowing the PMN review to continue on its normal schedule. The manufacturer is required, however, to submit correction pages for the Agency's records. EPA may request a suspension of the 90-day clock from the submitter if obtaining the necessary information from the submitter is expected to be delayed. Examples of frequent chemistry problems with PMN submissions are given in Table 1-4 (helpful advice regarding these issues is also included). For answers to questions about procedural, technical, or regulatory requirements prior to submitting a PMN, submitters are invited to telephone a PMN Prenotice Coordinator at (202) 260-1745, (202) 260-3937, or (202) 260-8994.

OPPT utilizes an electronic database on its own local area network (LAN) that captures and rapidly disseminates information on the PMN case to the various staff participating in the PMN review process. This database, as well as the LAN, is designed to protect CBI data. A portion of this electronic database contains the Chemistry Report data.

In establishing the chemical structure, EPA recognizes two classes of chemical substances (USEPA 1986b; USEPA 1991). Class 1 substances are single compounds composed of molecules with particular atoms arranged in a definite, known structure. Class 2 substances typically have

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9. If the substance is already on the Inventory, the submitter is free to manufacture it, subject to any SNUR, section 4 test rule, or other rule that the Agency may have promulgated for that substance.

10. Many of EPA's risk assessments of PMN substances are based on the physicochemical properties of these substances. A detailed discussion of the use of physicochemical properties during risk assessment of PMN substances is provided in Chapter 2.

Table 1-4. Technical Problems Frequently Encountered in PMN Submissions

Page of PMN Form	Description of Problem
4	**Chemical Identity Problems** Chemical name and structure do not agree because: (1) degree of specificity is different in name vs. structure, (e.g., the name indicates no specific isomer, but the structure is specific for a particular isomer); (2) submitter incorrectly drew the structure (i.e., the number of bonds or atoms is incorrect; the location of bonds or atoms is incorrect); (3) submitter did not draw a representative or partial structure of a complex/variable/multi-component PMN substance (e.g., the appropriate form of a sulfur dye: leuco or oxidized). CAS Registry Number (CASRN) and chemical name or structure do not agree because: (1) submitter made a typographical error, or (2) submitter is trying to cover a choice of alternative counterions with one PMN (e.g., using either Na or Li or Mg), or (3) submitter is trying inappropriately to cover multiple, class 1 chemicals with one PMN. The EPA allows a single PMN to cover multi-components if submitter is making only one product. For multi-component submissions, each unique substance should be drawn within a single PMN. CASRN and reactant name(s) do not agree, for the same reasons. Chemical name and molecular formula do not agree, for the same reasons. Reporting two or more substances as a mixture when they should be considered collectively as a Class 2 substance.
5	**Molecular weight values** The lowest number-average (NAVG) molecular weight is supposed to be measured for the complete polymer mixture from a series of reactions or an

Table 1-4. Technical Problems Frequently Encountered in PMN Submissions (continued)

Page of PMN Form	Description of Problem
5	**Molecular weight values (continued)**
	average of multiple analyses of a particular reaction; often it is submitted as the lowest peak in an individual run.[1]
	Although submitters are not required to report values for typical number-average molecular weights for their polymers, this would be useful, especially if the typical and lowest molecular weights are far apart.
	For polymers that cannot be analyzed by GPC (these polymers typically are high molecular weight and are solvent-insoluble), the molecular weight (in grams/mole) can be estimated using Avagadro's number (6.02×10^{23}) multiplied by the mass of a typical particle.
	Molecular weight values given as "greater than" some number are not helpful unless the base number is fairly close to the actual molecular weight. For example, MW > 10,000 is often listed; it might be more accurate, for example, to list MW > 30,000 or > 100,000 or > 1,000,000.
5	**Monomer composition of polymers**
	If the submitter does not know the identity of one or more monomers because the identity is the proprietary information of a supplier, a letter of support from the supplier of the proprietary monomer(s) is required to complete the chemical identity information. The notice submitter must ensure that the supplier sends the letter of support directly to EPA, referencing the PMN submitter and the PMN user fee number. Often, these letters are missing.
5	**Structural diagram of polymers**
	The structural diagram for polymers often fails to show at least the most likely bond types (i.e., the chemical bonds of the polymer) expected to be present, or a representative arrangement of monomers and other reactants in the polymer. Submitters are expected to provide as much structural information as known to or reasonably ascertainable by them.

[1] See Chapter 2 for methodology and discussion.

Table 1-4. Technical Problems Frequently Encountered in PMN Submissions (continued)

Page of PMN Form	Description of Problem
6	**Impurities and byproducts** Unreacted feedstocks and reactants are not listed when they should be. The description of impurities and byproducts/coproducts is incomplete.
6	**Generic names** Submitted generic names often are much more general than they should be, and are sometimes improperly deceiving. The degree of masking of specific parts of a name should be minimal, just enough to hide true proprietary details. (For guidance, see USEPA 1986c.)
6	**Synonyms and generic names** Both of these need to be consistent with the chemical structure. For example, since polyethylene terephthalate is an aromatic polyester, it should not be described as an aliphatic or olefinic polyester.
7	**Use information** At least one use must be reported that is covered under TSCA. For example, a substance used for coatings on eyeglasses would be excluded from TSCA reporting, as it is part of a medical device covered under another statute, but the same substance used also for telescope lens coatings would be subject to reporting. For substances with both TSCA and non-TSCA uses, submitters need to specify the percentage of each use. The production volume to be reported is the total amount manufactured for all uses. If the use is given as "chemical intermediate," it would be useful to know the ultimate use of the final product. The ultimate use may determine whether the intermediate is even subject to TSCA. Further, unreacted chemical intermediate remaining in the final product may present risk issues.

Table 1-4. Technical Problems Frequently Encountered in PMN Submissions (continued)

Page of PMN Form	Description of Problem
8	**Process description** Weights of reactants and other starting materials charged and of product formed are often missing. A simple diagram showing only the reaction vessel and a list of reactants and other starting materials doesn't reflect critical intermediate steps and separations. For example, a simple process flow diagram for polyurethane condensation polymers may show an alcohol in the reagent list as if the alcohol were capping the polymer; however, it could be a solvent in the formulated product. Sometimes the diagram shows that both the free acid and its salt are formed and isolated, but the PMN reports only one of these. Both may be separately subject to reporting under TSCA. Submitters who are planning to import a chemical(s), but contemplating domestic manufacture should provide a prospective manufacturing process diagram. They should know and describe how the substance is made or how they plan to make it. A diagram of the processing or formulation of the PMN substance after import should not be substituted for the manufacturing process diagram. Releases of non-PMN substances, such as solvents, from the chemical reaction should be indicated. Mass or weight balance information would be helpful to tie in with pollution prevention information on page 11.
13	**Physical and Chemical Properties** The physical form of the neat substance would be very helpful and often is not stated. Physicochemical properties should be measured and reported for the neat substance, whenever possible. If data are available for mixtures, solutions,

Table 1-4. Technical Problems Frequently Encountered in PMN Submissions (concluded)

Page of PMN Form	Description of Problem
13	**Physical and Chemical Properties (continued)**

or formulations containing the PMN substance, the percent of the individual components should be specified. (Note that MSDS sheets, by law, reflect the formulated product, whereas the PMN physicochemical property sheet should reflect the neat substance.)

Upon occasion, physicochemical properties that exist in the literature are inconsistent with those measured by the submitter.

Physicochemical properties are used by Agency toxicologists; toxicologists usually consider water solubility or vapor pressure to be significant at lower levels than do submitter chemists. For example, vapor pressures given in PMNs as "<0.1 torr" are often significant for Agency reviews and should be measured more exactly. Further, estimated values expected to be less than 0.01 torr, for example, should be reported as <0.01 torr and not simply <0.1 torr. The terms "negligible" and "soluble" are not useful.

For all submitted test data, the Agency requires submission of copies of the actual data; a summary of the data is not considered to meet this requirement.

variable or unknown compositions or are composed of complex combinations of different molecules and, hence, do not meet the criteria for Class 1 substances.

For Class 1 substances, there is only one molecular entity to review. For Class 2 substances, however, the chemist usually identifies a representative molecule(s) for review purposes. For example, a PMN substance may be the reaction product of an alcohol with a fatty acid feedstock having a carbon chain length ranging from 2 to 18 atoms. The various esters in this reaction product will differ somewhat in their physicochemical properties and will likely differ in potential health hazard, ecological hazard, and/or exposure. The chemist is responsible for deciding how this substance is best represented for Agency review.

Once a Class 2 substance is placed on the TSCA Inventory, the manufacturer may have some limited compositional freedom in the make-up of the substance. Given this freedom, the Agency concentrates its review on the composition with the greatest potential for harm to health or the environment (i.e., the worst case). Typically, the chemist chooses the component that is the lowest molecular weight, the most water soluble, the most volatile, or the most prevalent to represent the whole Class 2 substance, although all reasonable components are identified during the chemistry review. Thus, the review is representative of a very complex substance, but focuses on the worst-case scenarios.

The chemist next considers the synthesis of the PMN substance. He or she reviews the feedstocks to establish that they are identified correctly, that the PMN substance can be synthesized from them, and that they are individually listed on the TSCA Inventory.[11] This aspect of the chemistry review is critical. One of the most frequent errors in PMN submissions is that the named PMN substances cannot be synthesized from the listed feedstocks; either the feedstocks or the PMN substances are not identified correctly. For example, a straight-chain octyl group is frequently listed in PMNs, whereas a 2-ethylhexyl group is the actual feedstock moiety. Although each group contains eight carbons and there are not large differences in physicochemical properties, there may be significant differences in toxicity. The Agency anticipates that the most recent PMN rule revision (USEPA 1995c) will decrease the number of problems in this area through the requirement of CAS nomenclature for naming PMN substances. Regardless of the effect of the rule, however, careful review will remain an important function of Agency chemists.

Chemists also review the chemical synthesis to identify (or confirm) impurities or byproducts that may be present in the PMN substance. If present in substantial quantities, impurities may pose even greater risks than those of the PMN substance itself.

Chemists review the uses, production volumes, and manufacturing methods of the PMN substance. They determine whether the chemical nature of the PMN substance is consistent with its intended use and also identify other potential commercial and

11. This is a quick check of the Inventory; more definitive searches of the Inventory are done as required.

consumer uses to be included in Agency assessments of potential exposure to the PMN substance from these other uses.[12]

During the chemistry review of a PMN substance, chemists frequently identify closely-related or congeneric substances for which physicochemical and toxicity data are available. These structural analogs are used as surrogates for risk assessment of the PMN substance. EPA chemists also identify previous PMN cases with chemical structures analogous to the case under review (structural analogs). This allows EPA staff to compare the current assessments with earlier ones, promoting consistency and aiding in relative risk comparisons.

Chemists also identify "use analogs," which are other substances that have been or are known to be used for the same purpose as the intended use of the PMN substance. Use analogs allow the Agency to compare the risk of the PMN substance to that of other commercial substances intended for the same use.

Those physicochemical properties of the PMN substance that are important to risk assessment are also determined during the chemistry review. These typically include molecular weight, physical state, melting point, boiling point, water solubility, vapor pressure, and octanol/water partition coefficient. Chemists develop a value for each of these properties for every PMN in the review process at this point; they may also add values for other properties as warranted by the specific PMN substance. Chemists confirm submitted values (if provided), locate experimental values from the literature, or derive estimated values using appropriate techniques. Chapter 2 provides a detailed discussion of physicochemical properties, their measurement or estimation, and their subsequent use in risk assessment.

Most PMNs contain few physicochemical data. Consequently, the majority of physicochemical properties used for risk assessment of PMN substances are obtained by EPA scientists, usually by estimation. Any chemical estimation technique possesses some degree of uncertainty. In the absence of data, it is the practice of the Agency to select the estimation method that, within reasonable limits, maximizes the exposure or hazard potential. The Agency's aim is to estimate physicochemical properties to result in somewhat higher exposure and risk, so that a margin of safety results. Therefore, actual exposures and risks will not be under-estimated due to lack of data. For this reason, it is in the submitter's best interest to provide reliable experimental values in the PMN, if these can be measured. Even accurately measured (reliable) values for close analogs of a PMN substance are likely to be helpful for accurate estimation of exposure and risk. A more detailed discussion of the importance of accurate physicochemical property data in the risk assessment of PMN substances is provided in Chapter 2.

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12. The exposure to a chemical substance that has more than one use can vary substantially from one use to the next. Thus, depending upon use, the overall risk of such a chemical can vary substantially. If there are known uses (i.e., in the case of an imported substance, commercial uses outside of the U.S.) or potential new uses that would be of concern for unreasonable risk, the Agency may choose to develop a SNUR. See Appendix.

For polymers, EPA chemists review additional data, including the number-average molecular weight of the polymer, how it was determined, and what percentages of the molecules in the polymer have a molecular mass of less than 500 daltons and 1,000 daltons (USEPA 1995d). This is a result of the Agency's findings that lower weight oligomers may pose a greater degree of risk than their corresponding higher weight polymers, all else being equal. Finally, chemists determine the equivalent weight of any reactive functional group(s) and charged species.

In rare cases, the chemist may determine, during the more thorough chemistry review, that a polymer fulfills the requirements for a pre-CRSS drop (even though the initial chemistry review did not reach that conclusion). When this occurs, the Agency drops the PMN from further review.

1.3.4 Chemical Review and Search Strategy (CRSS) Meeting (Days 8-12)

As stated earlier, the Agency's ability to assess the potential hazards and risks of a given PMN substance is based largely on the chemistry of the substance. The chemistry of each PMN substance, summarized in the form of a Chemistry Report, is presented at the CRSS meeting. The CRSS meeting is thus an extremely important meeting within the PMN process: it is at this meeting that the chemistry needed for subsequent hazard and risk assessments is discussed and evaluated. The CRSS meeting is chaired by one of the senior chemists in ICB and attended by approximately 20 Ph.D.-level scientists. The key participants are ICB chemists, but representatives of most other groups involved in the PMN review process also attend. Typically, these include toxicologists, chemical engineers, and chemists from other branches in OPPT.

The CRSS chairman follows a defined agenda to initiate discussion of each new chemical submission that is in active review at that point. (Pre-CRSS drops, invalid, delayed, withdrawn, or incomplete submissions are not discussed.) Cases that previously had been delayed while the submitter resolved problems are presented first. Second are low volume cases.[13] Finally, all test market exemptions and regular PMN and SNUN cases are discussed in the order in which they were received at EPA headquarters. Occasionally, corrections to PMN or exemption notices are discussed at CRSS meetings, as are enforcement cases. (Those enforcement cases discussed at CRSS meetings are usually PMN submissions for substances already in commerce in violation of TSCA.)

The chemist who performed the review presents the PMN case at the CRSS meeting rapidly, but comprehensively, using standardized visual aids to facilitate understanding. He or she starts with the case number (which indicates the submission type), chemical name, manufacturer, production volume, and method of manufacture, then continues with specific uses of the substance, focusing on the structure and functional group(s) that impart the characteristics of the PMN

13. Polymer exemption cases had been discussed here as well; however, under the revised polymer exemption rule, the Agency no longer reviews polymer exemption notifications.

substance. Next, the chemist discusses the values of the physicochemical properties, along with the methods used for their estimation or, in the case of measured values, the literature sources and measurement methods used. These values are closely scrutinized by meeting attendees, as they form a basis for subsequent risk assessments. The chemist compares and contrasts any structure or use analogs from previous PMN cases to the new submission.

Chemists also scrutinize PMN submissions for pollution prevention opportunities. This is discussed in detail in Chapter 3. When applicable, the chemist will discuss known or potential alternative syntheses that appear to offer greater pollution prevention opportunities than the synthesis intended to be used by the PMN submitter. If a Synthetic Method Assessment for Reduction Techniques (SMART) review (see Chapter 3, section 2.2) was undertaken, the chemist presents these results, concentrating on any less polluting alternative syntheses that he or she may have identified.

Finally, the chemist initiates a discussion of any unique, interesting, or important information regarding the new chemical substance. These additional comments may range from the curious (e.g., an unexpected shade of red displayed by a new dye) to the serious (e.g., it appears that the synthesis will form a particularly toxic byproduct that was not identified in the PMN), and may include information needed by others in the PMN review process. The chemist may discuss other potential uses of the new substances (based on use data of analogs or the substance itself) and the anticipated production volumes.

Following the Chemistry Report presentation, another ICB chemist presents the proper chemical name for the PMN substance; he or she also states whether it is present on the TSCA Inventory. This chemist further identifies any feedstocks or other reagents that are not on the Inventory. If the PMN substance is declared to be on the TSCA Inventory, all review stops, as the chemical is excluded from reporting.

Typically, during the presentation of a case, attending staff members ask questions and provide comments in informal, round-table peer review. These discussions draw on the combined experience (both academic and industrial) and scientific expertise of all participants to evaluate the chemistry of the PMN substance. Attendees also suggest ways to resolve any problems that have arisen. If, following all this discussion, the CRSS meeting participants feel they do not have sufficient information to be comfortable with the technical quality and reliability of the chemistry for the PMN substance, they will delay further Agency review of the case until additional information can be gathered. The vast majority of cases, however, proceed to the next step.

After the case is presented, ensuing discussions are completed, and a consensus is reached, the meeting chairman records the status of each case using one or more identifiers (shown in Table 1-5). The case number, the chemist responsible for the case, and the identifier(s) are entered into the CRSS meeting notes. These notes are physically posted in a central location and on the CBI LAN. The CRSS notes are used by subsequent reviewers for scheduling purposes.

Table 1-5. Notations Used For CRSS Meeting Notes

Notation	Description
BT	**B**io**t**echnology Case: The PMN substance is a biotechnology case.
CP	**C**onsolidation **P**roblem: The different substances contained in a consolidated submission are not sufficiently similar in nature or use.
DE	**De**layed: Indicates that the case could not be discussed at its initially-scheduled CRSS meeting and will be delayed to the next meeting. Typically due to missing, ambiguous, inconsistent, or incorrect information that could not be obtained, clarified, or corrected prior to the meeting. The review period clock (between 30 and 90 days) does not stop for delayed cases.
DR	**Dr**opped: Indicates a polymer that was dropped from further review, i.e., a pre-CRSS drop or a drop decision made during the CRSS Meeting.
ER	**E**xcluded from **R**eporting: Indicates a substance that is specifically excluded from TSCA § 5 reporting requirements (i.e., the chemical substance is listed on the TSCA Inventory, is not subject to TSCA reporting, or does not meet the definition of "chemical substance" under TSCA).
EL	**El**igible: The new chemical meets the requirements for exemption. Only substances submitted as PMN exemptions may be declared eligible.
IC	**In**c**c**omplete: The submission does not contain mandated information.
ID	Chemical **Id**entity: The correct identity of the new chemical substance is not accurately described or cannot be ascertained.
MC	**M**ulti-**c**omponent case: A reaction product combination reported in one submission (one PMN case number) that is represented as a mixture under TSCA Inventory policy.
MX	**Mix**ture: The substance is a mixture of chemical substances and thus is excluded as a whole entity under TSCA; the individual substances are, however, subject to PMN notification if they are not already on the Inventory.
NE	**N**ot **E**ligible: The PMN substance is not eligible for the type of exemption filed.
NV	**N**ot **V**alid: The submission is identical to an earlier one submitted by the same manufacturer. (Previously, only one low volume exemption was allowed per substance and any subsequent exemption requests were declared not valid; see the revised exemption, USEPA 1995b.)
NX	**N**ot E**x**posure-based: The substance is a polymer produced at greater than 100,000 kg/yr that does not meet certain criteria for inhalation toxicity. It is exempted from a human and environmental exposure review.
SP	**S**us**p**ended: Review of the substance is suspended at the submitter's request, although this process is usually initiated by EPA phoning the submitter; the review clock stops.
SR	**S**uspension **R**equested: A significant problem affecting the review of the case was found; the suspension request is transmitted to the CCD manager who contacts the submitter to request a suspension.
UF	**U**ser **F**ee: A problem with the fee payment must be resolved before the review (and the review clock) can be started.
WD	**W**ith**d**rawn: The submitter withdrew the submission.
YX	E**x**posure-based: The new chemical substance is produced at greater than 100,000 kg/yr, is not a polymer (unless it meets certain criteria for inhalation toxicity) and is, therefore, subject to a section 5(e) exposure review.

Following the CRSS meeting, the chemist who presented a specific case makes any necessary changes to his or her Chemistry Report and files the report electronically on the CBI LAN and in hard copy in the CBIC. Subsequent reviewers at EPA use this report as a source of validated chemical information for the next steps in the PMN process: hazard identification and risk assessment. The report is especially critical to the hazard determinations performed by the Structure-Activity Team (SAT); correct structure, presence of impurities, and physicochemical properties identified during the chemistry review are key to the accuracy of the SARs used by the Agency to predict human and environmental hazard, especially in the absence of toxicological test data.

1.4 Hazard Evaluation

The second phase of the PMN review process is the **hazard evaluation phase.** The term "hazard," in the vernacular of PMN review, is synonymous with toxicity. The purpose of this phase, as the name implies, is the identification of possible hazards (toxic properties) of PMN substances to human health and the environment; this phase includes analyses of the likelihood of absorption and metabolism in humans, human toxicity, toxicity to environmental organisms, and environmental fate. During this phase, OPPT convenes a team of scientists who specialize in organic chemistry, biochemistry, medicinal chemistry, pharmacokinetics, metabolism, toxicology, genetics, oncology, environmental toxicology, and environmental fate. It is the responsibility of this multidisciplinary team to assess the potential hazards and risks of each new substance within the narrow time constraints of TSCA, using the sparse data available for most of the substances. During the hazard identification phase, these EPA scientists strive to elucidate the probable human toxicity, environmental fate, and environmental hazards posed by each new chemical substance. The hazard identification phase begins at approximately the same time as the Inventory review and preparation of the chemistry report and continues after the CRSS meeting.

1.4.1 Human and Ecological Hazard Identification (Days 2-12)

For any case that is not a pre-CRSS drop, scientific staff from the EAB, the Health Effects Branch (HEB), and the Environmental Effects Branch (EEB) of HERD initiate reviews in the areas of environmental fate, human toxicity, and ecological effects, respectively, at approximately the same time as the Chemistry Report is being prepared by the ICB. The first step is to evaluate submitted test data and to search the scientific literature for published information on the PMN substance. As previously stated, however, PMNs seldom contain enough measured toxicity data to perform a complete hazard assessment (see Table 1-3). In addition, because PMN substances are "new" substances, there are seldom any data available on them in the scientific literature.

The paucity of human, animal, and aquatic toxicity data for most PMN substances has led OPPT scientists to use several different approaches for hazard identification. These approaches include: consideration of the likelihood of absorption from the lung, gastrointestinal tract, and

skin; consideration of the expected products of metabolism and their toxicity; structure-activity relationships (SARs); and consideration of the presence of structural groups or substituents that are known to bestow toxicity. SARs are the comparison of the substance under review with structurally analogous substances for which data are available.[14] In SARs, a series of structurally similar chemicals for which a measured toxicological or environmental endpoint (the "activity") is available is used as a basis for qualitative estimation of the same endpoint for an untested chemical of the same structural class. The underlying assumption in using SARs is that the toxicological properties of substances belonging to the same chemical class are related or attributable to the general structure (or some particular portion thereof) of the class. Logically, any substance that has the same general structure is likely to have the same toxicological properties. Using SARs, for example, one can be alerted to the possibility of a new, untested chemical sharing the same toxic effect(s) with structurally similar chemicals that are known to produce the effect(s). On the other hand, SARs can be used to mitigate a health concern for a substance if an analog is identified with data showing that the analog is nontoxic.

HEB scientists qualitatively estimate human acute and chronic toxicity of PMN substances, including: oncogenicity; mutagenicity; developmental toxicity; neurotoxicity; reproductive toxicity; and systemic toxicity, irritability, and sensitization. Again, the Agency's findings of the likelihood of these effects occurring in humans are seldom based on measured animal data on the PMN substance. Rather, they are usually based on structural comparison of the PMN substance with closely-related substances for which toxicity data are available (SARs). To use SARs during PMN review, OPPT scientists try to identify structural analogs of PMN substances from the literature or from in-house sources, including PMN structural databases, TSCA section 8(e) toxicity databases, and other in-house substructure-searchable databases of substances for which toxicity data are available.

Subtle differences in molecular structure within a congeneric series of substances can greatly change the relative toxicity. Knowledge of the biochemical mechanisms of toxicity can help to explain why such structural differences affect toxicity. OPPT scientists utilize their knowledge of toxic mechanisms, whenever possible, to improve the predictive quality of SARs. In cases where analogs closely related to the PMN substance are equally good but vary greatly in toxicity and for which mechanistic data on the chemical class are unknown to EPA, it is the general practice of EPA to assume that the PMN substance is as toxic as the most toxic analog. If, however, mechanistic data are available and such data lead OPPT scientists to believe that the PMN substance is less toxic than other analogs, then EPA will assume that the PMN substance is less toxic. Although not required under TSCA, it

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14. For most chemical substances, toxicity data are almost always derived from animal studies. It is the policy of the EPA to assume that chemicals that are capable of causing toxic effects in animals will cause the same toxic effects in humans.

would be extremely helpful if PMN submitters would provide analogs of the PMN substance for which toxicity data are available in their PMN submissions, particularly if mechanistic data for the chemical class are known to the submitter. Such information would greatly enhance EPA's ability to make more accurate hazard assessments of PMN substances and lessen the likelihood that OPPT scientists will over-estimate the toxicity of PMN substances.

HEB scientists also estimate the probable human pharmacokinetics of the PMN substance, evaluating absorption, distribution and redistribution, metabolism (biotransformation), and excretion of the substance. Special attention is given to the possible formation of toxic metabolites. (The role of pharmacokinetics in predicting health hazards is illustrated in Table 1-6 and described further in DiCarlo 1986.) Estimation of absorption is a particularly important component of hazard identification in that a PMN substance may appear toxic (based on SARs), but it may have other characteristics that will lead HEB scientists to believe that the substance will not be significantly absorbed through the gastrointestinal tract, skin, or lungs of humans. A human toxicity concern for a PMN substance derived by SARs may be mitigated by EPA's belief that the substance will be poorly absorbed.

Although SARs are useful in estimating toxicity, the likelihood of absorption of a PMN substance through the skin, lung, and gastrointestinal tract may not be inferred easily from the structure without careful consideration of the physicochemical properties of the substance. The relationship between the physicochemical properties of a substance and its absorption is discussed in greater detail in Chapter 2. OPPT scientists use physicochemical properties extensively to predict the likelihood of absorption of a PMN substance.

Another approach used by EPA to identify the likely toxicity of PMN substances is quantitative structure-activity relationships (QSARs), which combine physicochemical properties with SARs. In QSARs, a particular biological (toxicological) or environmental property of a series of structurally analogous chemicals is mathematically correlated with one or more physicochemical properties of the chemicals using a regression equation. The goal of QSAR is to delineate a particular property or activity more precisely than is possible by intuition or SAR alone. Using QSARs, one can predict, for example, the acute toxicity (LD_{50}) value of an untested substance directly from a physicochemical property of that substance.

EEB scientists use QSARs to estimate chronic and acute toxicity values for fish (vertebrates), daphnids (invertebrates), and algae (plants) (USEPA 1994). Based on these values, EEB scientists determine a concentration of concern, the minimum concentration at which Agency scientists have concern about harm to these aquatic species. These QSARs most frequently utilize octanol/water partition coefficient as the physicochemical descriptor of toxicity. Some other physicochemical properties used by EEB scientists in QSARs include melting point, dissociation constant, and water solubility.

Table 1-6. The Role of Pharmacokinetics in Predicting Health Hazards

Metabolic Process	Role in Human Health Risk Assessment
Absorption	If a substance is not absorbed, its toxic expression is limited to topical effects such as skin and eye irritation, and to unfavorable effects on nose, mouth, respiratory tract, and gastrointestinal tract membranes. Qualitative estimation of the rate and extent of absorption is based on lipophilicity and water solubility. The susceptibility of the substance to (and the likely products of) degradation by microorganisms in the gastrointestinal tract is important for assessing absorption following oral exposure.
Distribution/Redistribution	Tissue distribution and redistribution determine the potential for a substance to reach a site where toxicity can be expressed. These assessments require knowledge of blood flow rates, the octanol/water partition coefficient, and the dissociation constant of the PMN substance.
Biotransformation	The rate of degradation as well as the nature and reactivity of the metabolites are required for this assessment. Although the body frequently uses biotransformation to detoxify absorbed xenobiotics, in some cases toxic metabolites are created.
Excretion	If a compound is absorbed, its capability to express a biological effect is generally limited by the amount of time it remains in the body. Thus, a rapid rate of excretion will limit the potential for an adverse effect.

1.4.2 Environmental Fate

The environmental fate of PMN substances is assessed by EAB scientists. Environmental fate is a very important component of hazard identification; it predicts where a chemical will partition in the environment, which is useful in determining environmental and human exposure and, ultimately, long-term health and environmental effects of a substance. Information on the partitioning and environmental lifetime of a substance is important in determining levels, routes, and the likelihood of both human and environmental exposure. Environmental fate assessment includes the consideration of: relative rates of environmental biodegradation, hydrolysis, and photolysis; adsorption to soils and sediments; treatability (generally in publicly-owned treatment works (POTWs)); and half-lives in the atmosphere, surface waters, soils, and sediments.

Because fewer than 10% of submitted PMNs contain environmental fate data, EAB scientists typically must estimate the environmental fate of new substances. EAB scientists estimate the environmental fate of a new chemical substance utilizing the substance's water solubility, octanol/water partition coefficient, soil adsorption coefficient, vapor pressure, Henry's Law constant, absorption spectra, and bioconcentration factor (BCF). Utilizing the physicochemical properties obtained not only from the Chemistry Report, but also from their own preliminary review, EAB scientists estimate the potential for a substance to adsorb onto soils and sediments, pass into streams, rivers, and groundwaters, and to volatilize into the atmosphere. EAB scientists also estimate the environmental lifetime of a PMN substance by determining the percentage of the substance removed by wastewater treatment plants and the speed of hydrolysis, primary and ultimate biodegradation, and destruction by sunlight (photolysis) or atmospheric oxidants.

It is readily apparent from the preceding paragraphs of this section that physicochemical properties play an important role in estimating the likelihood of human exposure and absorption, environmental fate, ecological toxicity, and thus, risk of chemical substances. A more comprehensive discussion of physicochemical properties, including their measurement, estimation, and use in estimating absorption, environmental fate, QSARs, and exposure is provided in Chapter 2. It is important to stress here, however, that when PMN submitters do not submit accurately-measured physicochemical property data to EPA, OPPT scientists will estimate such data if they are unavailable from the literature or other sources. The estimated values may not always be accurate and may vary greatly from one estimation method to another because of the limitations of the estimation methods. As a general practice during physicochemical property estimation, OPPT scientists will use those estimated values that indicate significant exposure, absorption, or toxicity. The importance of OPPT possessing, and consequently utilizing, accurately-measured physicochemical property data for hazard identification cannot be overstated.

1.4.3 Structure-Activity Team Meeting (Days 9-13)

Because of the strict time constraints imposed by TSCA for PMN review, the OPPT scientists involved with assessing the potential hazards posed by PMN substances must have their hazard and environmental fate evaluations completed by the time the PMN substances are to be discussed at the designated SAT meetings. For most PMN substances, this allows only two weeks or less for the chemistry review, environmental fate, *and* hazard evaluation by OPPT scientists.

The SAT is a multidisciplinary team composed of approximately twenty OPPT scientists who specialize in disciplines that include organic chemistry, biochemistry, medicinal chemistry, pharmacokinetics, general toxicology, neurotoxicology, reproductive and developmental toxicology, genetics, oncology, aquatic toxicology, and environmental fate. These scientists are the same scientists who perform the hazard identification for PMN substances. The purpose of the SAT meeting is for these scientists to make a critical judgement on the likely hazard(s) posed by each PMN substance to human health and the environment, so that subsequent risk assessments and risk management decisions regarding these substances can be made.

The SAT meetings are held twice a week, on Tuesday and Friday mornings. In general, the PMN cases discussed at the CRSS meeting the day before (Monday or Thursday, respectively) are discussed at the SAT meeting. Exceptions are those cases for which technical problems at CRSS delay the review or those cases dropped from review at CRSS. Each PMN substance is discussed separately, and each SAT member individually discusses his or her findings and opinions, as well as the scientific basis for those opinions.

The discussion of a PMN submission begins with a summary of the chemistry of the substance by the CRSS chairperson, including: synthesis; byproducts or products from side reactions that may be present as a result of the synthesis; intended use; and physicochemical properties. The environmental fate specialist then summarizes the potential for the substance to adsorb onto soils and sediments, pass into streams, rivers and groundwater, and volatilize into the atmosphere; the percentage removed by wastewater treatment plants; rates of hydrolysis; primary and ultimate biodegradation; and destruction by sunlight (photolysis) or atmospheric oxidants. Following the environmental fate discussion, the pharmacokinetic specialist discusses the extent to which the substance is expected to be absorbed through the skin, lung, and gastrointestinal tract and the expected metabolites of the substance following absorption. The other SAT members then individually discuss their findings and judgements regarding the case being presented. The discussion may include, for example, the toxicity of analogs, previous related PMN cases, the significance of functional groups, and toxic mechanisms. These discussions culminate in deliberations that lead to establishing separate, overall ratings of the level of concern for human health effects and for ecological effects of each PMN substance using the following scale: low, low to moderate, moderate, moderate to high, or high.

1.5 Exposure Evaluation (Days 13-15)

The third phase of PMN review involves **exposure evaluation.** Following the SAT meeting, other OPPT scientists and engineers estimate the degree of human exposure (occupational and general population) and environmental exposure for those PMN substances that receive a SAT score of at least "low to moderate" for either health or ecological effects. Like hazard identification, exposure evaluation is a critical component of risk assessment; it consists of establishing the likelihood and magnitude of occupational, consumer, general population, and environmental exposure of a substance through careful consideration of the substances's physicochemical properties, expected environmental releases, known commercial or consumer use(s), potential commercial or consumer use(s) (identified during the chemistry review), and environmental fate.

Substances that receive "low" SAT scores for both human health and environmental effects may also undergo an exposure analysis if their production volumes are greater than 100,000 kg per year, because high production volumes such as these may lead to significant exposure and risk. Substances that receive “low” SAT scores for both human health and environmental effects and that have production volumes below 100,000 kg per year are generally not reviewed further.

The initial part of an exposure review of a PMN substance is performed by the Chemical Engineering Branch (CEB) of EETD, two to four days prior to the Focus meeting where the substance will be discussed. CEB engineers utilize the physicochemical properties of the PMN substance, most notably vapor pressure and molecular weight, to establish the importance of both dermal and inhalation exposure. For example, volatile substances and powder are typically evaluated for their potential for inhalation exposure.

CEB relies on the process flow and unit operations to identify potential release and exposure points. Using physicochemical property data and identified release and exposure points, CEB evaluates the potential for occupational exposure and for releases to the environment expected to result from manufacturing, processing, and commercial or industrial use of the substance. In addition, CEB may apply exposure and release data available on chemical substances analogous to the PMN substance, that are produced or used in similar circumstances as the PMN substance, to further evaluate occupational exposure and environmental release.

Using models that take into account the physicochemical properties of the PMN substance as well as unit operations, number of workers performing each operation, and industry-specific worksheets to fill remaining gaps, CEB engineers estimate the number of workers potentially exposed, their activities, their duration of exposure, and potential dose rates.

Emissions to the environment are obtained by evaluating data contained in the PMN and industry-specific worksheets to establish the potential for releases from manufacture, processing, and use of the PMN substance. Releases may be process-related, such as equipment vents and container residual. For example, losses to

waste by a component of a photoresist pattern are expected to be relatively high (since most of a photoresist washes away during the developing stage), whereas those from a site-limited synthetic intermediate are expected to be relatively low. The physicochemical properties of the PMN substance may also be important at this stage; for example, water solubility is sometimes used along with information in the PMN to estimate potential releases to water, and vapor pressure could be used to estimate emissions to air.

EAB staff then receive data generated by CEB staff, allowing them to estimate levels of consumer and general population exposure as well as the resulting environmental concentrations that arise from emissions. For example, a component of a new spray coating designed for the household market might be expected to have higher levels of consumer exposure (through inhalation) during use than a new additive for motor oil (through dermal contact). To estimate exposure to the general population, EAB scientists consider the level of emissions into each environmental medium and the expected rate of removal. For releases to water, EAB will consider the percentage removed in a POTW (using the actual facility expected to receive that waste as indicated in the submission), the rates of biological and chemical degradation, and the degree of partitioning between water and sediment. For releases to air, EAB uses the rates of oxidation and photolysis to determine probable fence-line concentrations at the manufacturing facility. EAB uses the rates of biodegradation, volatilization, and percolation through soils to derive the concentration of the PMN substance in groundwater following its release to land (including landfills). The concentrations derived through this process are then compared to the ecological concentrations of concern developed prior to the SAT meeting to establish the potential for ecological effects that may result from environmental emissions. Estimations of yearly human intake from drinking water and fish consumption (if bioaccumulation is expected) are used to evaluate the potential for health effects.

As in hazard identification, physicochemical properties play a very important role in estimating occupational, population, and environmental exposure to PMN substances. The quality of these exposure estimates is obviously dependent on the accuracy of the physicochemical property data. Measured data are always preferred over estimated data because estimation methods, even the very good ones, do not take into account all of the intra- and intermolecular interactions responsible for given physicochemical properties. Estimated physicochemical properties, therefore, generally contain errors, which may vary widely. Estimated physicochemical properties that contain significant errors obviously affect the reliability of the exposure and hazard estimates derived from them. In cases where physicochemical property data are not available to EPA, the Agency estimates such data using several methods. It is the policy of the Agency to use those estimated values which lead to greater hazard and greater exposure. It behooves PMN submitters, therefore, to submit accurately measured physicochemical properties whenever possible.

An economist from the Regulatory Impacts Branch (RIB) assesses the validity of the production volume data submitted in the PMN by comparing the reported values to the historical median for similar chemical substances.

1.6 Risk Assessment/Risk Management Phase (Days 15-82)

The fourth phase of the PMN review process is the **risk assessment/risk management phase.** As stated earlier in this chapter, risk is the probability that a substance will produce harm under specified conditions. Risk is a function of the inherent toxicity (hazard) of a substance and the expected or known exposure to the substance. Risk assessment is the *characterization* of the potential for adverse health or ecological effects resulting from exposure to a chemical substance.

Risk management refers to the way in which the risks posed by a chemical substance are minimized. This involves the weighing of policy alternatives and selecting the most appropriate regulatory (or non-regulatory) action after integration of risk assessment with social and economic considerations. It is in the risk assessment/risk management phase of PMN review that the results of the hazard and exposure evaluation phases are used to assess the risk of PMN substances and make the necessary decisions to manage any unreasonable risks that may be posed by PMN substances.

1.6.1 Focus Meeting (Days 15-19)

The general purpose of the Focus meeting is to allow EPA staff and management to discuss the hazard and exposure evaluations of PMN substances and to make risk assessment and risk management decisions. More specifically, the purposes of the Focus meeting are to: (1) characterize (assess) the risks posed by each PMN substance; (2) decide which PMN substances will not present an unreasonable risk and drop them from further review; (3) identify the PMN substances that may present an unreasonable risk but for which risk management decisions can be made without additional review; and (4) identify the PMN substances that may present an unreasonable risk but require additional review for risk characterization.

Focus meetings are held twice weekly, on Monday and Thursday afternoons. Focus meetings are chaired by representatives from CCD; they are attended by the chairpersons of the CRSS and SAT meetings, and representatives from the groups that performed the economic analysis, environmental fate, and exposure assessments.

The discussion of a PMN substance at the Focus meeting begins with a summary by the CRSS chairperson of its chemistry, intended use, potential uses identified by EPA, and any remarkable attributes of the substance, as claimed by the submitter or identified by EPA. Next, the SAT chairperson summarizes the human health and ecological hazards identified by the SAT. This is followed by a summary of the occupational, population, and environmental exposures expected to occur from the intended or potential uses of the PMN substances by the people who made these

estimates. A RIB economist will discuss the validity of the production volume estimates.

From the information presented, the Focus meeting participants assess and characterize the risks posed by the PMN substance to human health and the environment, and carefully consider these risks along with the expected or potential societal benefits of the substance. Often, EPA may identify significant risks of a PMN substance that also has significant benefits to society (e.g., the PMN substance will supplant an existing chemical substance that poses a greater risk). In such instances, it is the practice of EPA to balance these factors in making risk management decisions regarding the PMN substance. It is the policy of EPA's PMN Review Program to encourage creative thinking by chemical manufacturers and producers to design and produce efficacious substances, and not make risk management decisions (e.g., over-regulation) that stifle creativity. Almost 90 percent of the PMNs submitted to the EPA complete the review process without being restricted or regulated in any way (USEPA 1995f).

There are eleven possible outcomes for a PMN substance at the Focus meeting (Table 1-7). These range from dropping a regular PMN from further review (or granting an exemption) to pursuing a regulatory ban on the production, use, or disposal of the new substance. Approximately 80% of all PMN submissions are dropped between pre-CRSS and the end of the Focus meeting.

Some of the remaining 20% fall into one of approximately 46 Chemical Categories (USEPA 1996b) that have been identified to date by the New Chemicals Program. These categories were developed as an administrative aid to facilitate reviews by grouping chemicals into categories with similar hazard concerns and testing requirements. For each Category, the Agency has developed a standard regulatory response, often involving a section 5(e) order to limit chemical production (and, thus, exposure) pending a certain pertinent test. This categorical approach is continually evolving as EPA's experience increases.

For PMNs outside of the Categories that the Focus group characterizes as possessing significant risks, the chairman of the Focus meeting will recommend a specific regulatory response to mitigate the concerns of the Agency's risk assessment. For example, the meeting chairman may decide to pursue regulation under an exposure-based section 5(e) order if a high production volume substance has high predicted levels of worker, consumer, and environmental exposure and a long environmental lifetime. For another substance that is expected to be released to the environment in moderate amounts and is similar in structure to a substance of known chronic aquatic toxicity, the chairman may decide to pursue a risk-based section 5(e) order. Finally, the chairman may decide to drop from further review a substance expected to be released to the environment in moderate amounts yet expected to have a very short environmental lifetime.

For low volume exemptions and LoRex exemptions, the Focus meeting usually serves as the final regulatory decision meeting because of the short review period for these exemptions.

Table 1-7. Possible Outcomes of the Focus Meeting

Outcome	Description
Grant	A PMN exemption is granted.
Deny	A PMN exemption is denied; the submitter is free to submit the substance as a regular PMN.
Drop	A regular PMN case is dropped from further review.
Standard Review	Further review of the substance is required before a regulatory decision can be made; this review is often targeted to answering one or more specific questions.
Letter of Concern	A concern for harm to health or the environment exists for the substance although the risk is relatively low due to low production, exposure, or release. After the meeting, the Agency will send a letter to the manufacturer explaining the expected risk and suggested (i.e., voluntary) controls to reduce human and environmental exposure. Letters of concern may be appropriate for routine PMNs, exemption cases, enforcement cases, or corrections.
Non-5(e) SNUR (Significant New Use Rule)	EPA will begin to draft a non-5(e) SNUR, which prohibits manufacture of the substance for any use other than that contained in a regular PMN submission; manufacturers who wish to use a substance for such a prohibited use must submit a Significant New Use Notification (SNUN) to the Agency. Non-5(e) SNURs are used for those PMNs in which the intended use is judged not to be an unreasonable risk, whereas uses other than the intended use may lead to unreasonable risk.
5(e) SNUR	In conjunction with a 5(e) order, EPA will begin to draft a SNUR to restrict the uses of a routine PMN substance. This is often necessary because 5(e) orders apply only to the original submitter, whereas SNURs apply to all manufacturers of that specific substance.
5(e) Consent Order	EPA will begin to negotiate with the submitter to prepare a written agreement under section 5(e) that specifies testing required to determine the risk of a routine PMN substance. The negotiated 5(e) order will restrict the production, distribution, use, or disposal of the substance until EPA has received and acted upon the required test data. Consent orders are used for those regular PMNs whose intended use, manufacture, processing, etc. may lead to an unreasonable risk unless certain conditions are met to reduce exposure.
5(e) Exposure-Based Authority	This is not a risk-based finding. The Agency begins to prepare a 5(e) order requiring testing based on exposure only.
Unilateral 5(e) Order	The Agency begins to prepare a unilateral order restricting a PMN substance under section 5(e) until specified tests have been carried out.
5(f) Order	The Agency begins to prepare an action to initiate a order under section 5(f) restricting or banning a PMN substance because unreasonable risk has been established.

If a question concerning a PMN arises that cannot be answered during the meeting, but may be answered quickly with further investigation, the chairman may delay a regulatory decision until the next Focus meeting. If more substantial questions remain or if closer examination of the chemical is deemed necessary, the chairman may put the PMN into Standard Review (see section 1.6.2, below).

If a Focus meeting decision on a PMN is to pursue regulation, the Program Manager for a PMN case (from CCD staff) will contact the manufacturer and describe the reasons for the Agency's concern as well as the regulatory controls that EPA intends to impose.[15] Often, the manufacturer may disagree with the Agency's concern, and may ask the Agency to suspend the review period to allow the manufacturer time to conduct the appropriate tests[16] that the manufacturer feels will mitigate the EPA's concern and lead the Agency to reverse its regulatory controls. The Agency will then use these measured data in preference to estimated data or worst-case assumptions. In some cases, the real data mitigate the risk sufficiently and the Agency drops the case (or grants the exemption, as appropriate) without the manufacturer having to contend with the potential effects of EPA regulation on the substance's marketability. Discussions of the Agency's regulatory mandate are available elsewhere (Appendix; USEPA 1986a).

1.6.2 Standard Review (Days 15-65)

If it is decided at the Focus meeting that a PMN substance may present significant risk(s), but either the hazard or exposure information identified prior to the meeting is inadequate to characterize the risk fully at the Focus meeting, a more detailed review may be necessary for adequate risk characterization, and the PMN submission will be put into Standard Review. The purpose of a Standard Review is to explore further the potential or known hazards and exposures posed by a PMN substance, so that an adequate risk assessment may be made. Currently, approximately 5% of all PMN submissions go into Standard Review.

All of the scientists and other PMN review personnel who have participated in the regular review of the PMN substance before the Focus meeting typically participate in the Standard Review. In Standard Reviews, individual detailed reports on the chemistry, environmental fate and exposure, worker and consumer exposure, and health and ecological effects of the PMN substance are prepared. Considerable effort is devoted to identifying related analogs, performing comprehensive literature searches on these analogs, and retrieving and analyzing toxicity data on these analogs.

In addition, RIB staff perform an economic assessment of the PMN substance

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15. The detailed regulatory process itself is outside the scope of this document and the reader is referred to other documents for further information (USEPA 1986a).

16. EPA is developing final test guidelines; for status, contact the TSCA Assistance Information service at (202) 554-1404 or access the guidelines on the Internet at http://fedbbs.access.gpo.gov/epa01.htm See also USEPA 1996a.

that includes comparing the PMN substance to other commercial products that are used for the same purposes. The economic analysis identifies alternative uses (if any) of the PMN substance, evaluates the markets for the PMN substance and their potential for growth, and estimates the selling price of the substance. The economist may also perform specialized financial studies to evaluate claims in the PMN including market limitations due to cost of the PMN substance and the feasibility of process and input modifications.

These detailed, individual reports are used by a designated technical integrator to prepare a single report that summarizes the findings of the Standard Review. In addition to summarizing the findings of the review team, the technical integrator writes a risk characterization of the PMN chemical, including recommendations for testing. The information contained in this report is then used by the review team and the senior risk assessors of OPPT to make a more complete risk characterization and to decide on the most appropriate risk management option(s). These findings are then presented at the Division Directors' meeting for a risk management decision. For PMN substances that go into Standard Review, the Division Directors' meeting is the final phase of the PMN review process and takes place between days 79 and 82. This meeting is attended by the Directors of the seven divisions participating in the PMN review process and is chaired by the Director of CCD, or his designee. It is the role of the Division Directors at this meeting to discuss the risk assessment findings and to make risk management decisions.

Following the Division Directors' meeting, the PMN program manager takes the necessary steps to implement the risk management decision.

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List of Selected Readings for Chapter 1

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