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Chemistry Assistance Manual for Premanufacture Notification Submitters

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PREFACE

Since the passage of the Toxic Substances Control Act (TSCA) in 1976, the Environmental Protection Agency (EPA) has received and reviewed nearly 30,000 Premanufacture Notifications (PMNs) for new chemical substances. During this period, the Agency has developed both a review process to estimate the risk attributable to a new chemical substance and a decision process to determine whether an unreasonable risk may occur if the substance is commercialized.

The information included in the PMN submissions constitutes the basis of the Agency's risk assessments. Careful consideration is given to all submitted physicochemical, environmental, and health-related data. If the PMN does not contain chemical properties or other information needed for assessment, the Agency scientists often must estimate the missing values. This leads to less accurate risk assessments than might be desirable, and may lead to regulation of substances that would not have been regulated if data had been available.

The purpose of this book is to assist submitters in the technical aspects of PMN preparation. EPA's hope is that, with this information, submitters will be able to develop more physicochemical property data and other technical information for their new substances so that the Agency's ability to perform accurate risk assessments will increase. Chapter 1 provides a discussion of the PMN review process, emphasizing its scientific aspects. Chapter 2, the heart of the book, reviews the most important physicochemical properties, including methods for measurement and estimation, and describes how EPA uses these properties to assess the risks of PMN substances. Chapter 3 discusses the Agency's pollution prevention program as it relates to the PMN program, emphasizing factors that submitters should consider in the development of new chemical substances and in their preparation of PMNs. Both references and a list of selected reading materials containing additional information are included at the end of each chapter. Also included is an Appendix, which provides an historical overview of the factors and events leading to the passage of TSCA, a summary of the premanufacture provisions of TSCA, and a review of the Agency's implementation of TSCA.

This book is intended primarily for people in the chemical industry who are involved with the design and development of new chemical substances, and the submission of PMNs. This book is also intended for a broader audience of other individuals such as technical managers, risk assessors, and risk managers who are involved with evaluating chemical substances for potential risks. We feel that the information contained in this book will help these individuals make better risk assessment and risk management decisions.

Stephen C. DeVito, Ph.D.
Carol A. Farris, Ph.D.

Exposure, Economics, and Technology Division
Office of Pollution Prevention and Toxics U.S.
Environmental Protection Agency
Washington, DC 20460

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Frank S. Amato
(Eastman Kodak Company,
Rochester, NY)
Kent E. Anapolle, Ph.D.
Paul T. Anastas, Ph.D.
Charles M. Auer
Robert S. Boethling, Ph.D.
Anna C. Coutlakis
Mary E. Cushmac, Ph.D.
Gregory L. Fritz, Ph.D.
Roger L. Garrett, Ph.D.
Steven M. Hassur, Ph.D.
Carol L. Hetfield
Rebecca A. Jones
Leonard Keifer, Ph.D
Raymond J. Kent, Ph.D.
Doyoung Lee, Ph.D
Robert J. Lenahan.
C-T. Daniel Lin, Ph.D.
Robert L. Lipnick, Ph.D.
Gregory J. Macek
Nhan T. Nguyen
Breeda M. Reilly
William A. Silagi
Jay Tunkel, Ph.D.
(Syracuse Research Corporation,
Syracuse, NY)
Caroline D. Weeks, Ph.D.
Tracy C. Williamson, Ph.D.
Maurice G. Zeeman, Ph.D.

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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.

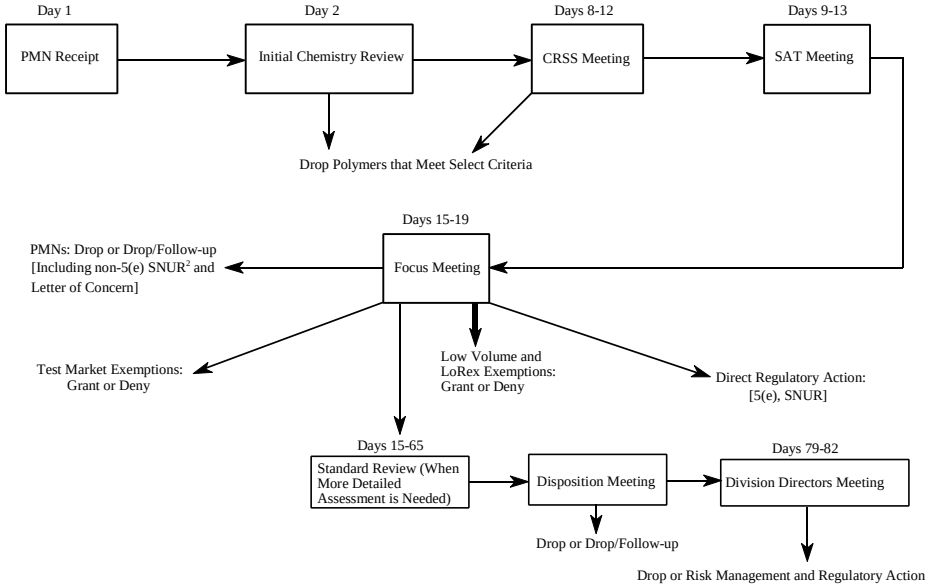
[3] Enforcement cases arise from EPA investigations into potential TSCA violations.

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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Chapter 2

CHEMICAL INFORMATION NEEDED FOR RISK ASSESSMENT

2.1 Introduction

EPA requests various types of chemical information from companies submitting PMNs, including information on the physicochemical properties, synthesis, purity, and use of PMN substances. EPA receives approximately 2,000 PMN submissions annually and many of these do not contain all of the information necessary for a good screening-level risk assessment of the PMN substance (some contain no useful information other than the chemical name and structure). PMN submitters are required to provide certain information whereas other information is optional. This optional information is, nonetheless, important in EPA's review of chemicals, and its inclusion in PMN submissions improves the basis for EPA's evaluation and facilitates the review process. Such information can also be very helpful in avoiding misunderstandings leading to additional but unnecessary EPA review.

Chapter 1 addressed the process that EPA uses in its evaluation of PMN substances. The present chapter (Chapter 2) discusses the chemical information considered by EPA in its review process, how this information is used, and EPA's strategy when pertinent information is omitted from PMN submissions. The chemical information requested in a PMN submission is very important because it forms the underlying basis for risk assessment and risk management decisions made during the PMN review process.

The first section of this chapter discusses each of the different types of chemical information that EPA uses in its evaluation of PMN substances and the importance of this information to risk assessment. Definitions of physicochemical properties are included, and methods of measuring or estimating properties are described. EPA depends very heavily upon physicochemical properties of chemical substances for estimating their transport, environmental fate, exposure, and toxicity to mammalian and aquatic species. The use of this information in risk assessment is presented briefly graphically and is discussed.

The final section of this chapter describes EPA's methods for obtaining or estimating values for physicochemical properties essential in the review of PMN substances, but often not included in PMN submissions. Although accurately-derived empirical data are preferred over estimated data, if such data are not provided in a PMN submission, EPA will first search the literature for data on the PMN chemical, then search for data on analogous substances, and, finally, estimate the required data. Data sources and methods used by EPA in this process include reference books, on-line databases, and computer estimation programs.

This chapter is intended to provide submitters with an understanding of the basis for EPA's requests for certain chemical information. The solicited information is important in EPA's review of PMN chemicals. In all cases, EPA prefers accurate empirical data. If such data are not provided by the submitter and EPA is unable to find data on the PMN chemical, it is EPA's policy to make conservative assumptions and use credible worst case scenarios in its evaluations. Worst case scenarios may, in some cases, lead to overestimating the exposure and risk of a chemical. By providing as much physicochemical property data as possible in PMN submissions, submitters can aid EPA in assessing exposure and risk more accurately.

2.2 Important Chemical Information

To many people, properties such as physical state, melting point, boiling point, vapor pressure, water solubility, lipophilicity (octanol/water partition coefficient), molecular weight, etc., seem to have little to do with toxicity and environmental fate, although the relevance of some of these properties to exposure assessment may be clear. The main purpose of this chapter is to show how these and other physicochemical properties are used extensively by EPA for risk assessment of new chemical substances during PMN review.

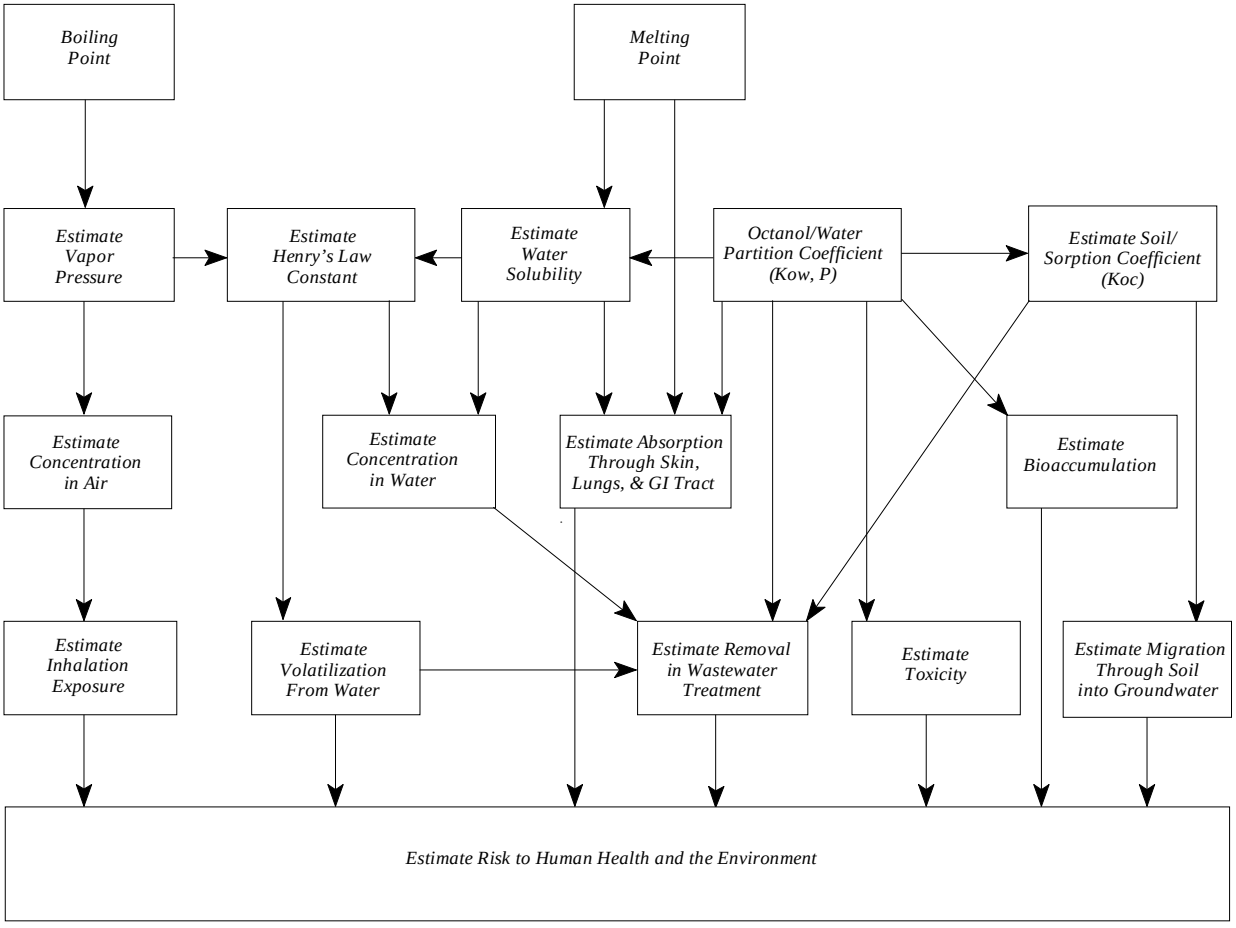
Other factors such as intended use, other uses, and synthesis as they relate to risk assessment are also discussed. The intent is not to describe all aspects of risk assessment and associated physicochemical properties. Comprehensive treatises on risk assessment, physicochemical properties, and their measurement, estimation, and use in predicting environmental fate, exposure, toxicity, and pharmacologic response are listed under the Suggested Readings heading at the end of this chapter.

Figure 2-1 illustrates the physicochemical properties most commonly used during risk assessment of PMNs. The important lesson to be learned in this chapter is that essentially all forms of risk assessment of new chemical substances are largely dependent upon physicochemical properties. When measured physicochemical properties of chemicals are not available, they must be estimated. Although many reliable estimation methods are available, in any estimation a certain degree of error is always present. Thus, estimation of physicochemical properties should never supplant actual measurement. This section discusses the chemical data that are most important to EPA in reviewing PMNs and how EPA uses these data in risk assessments.

2.2.1 Melting Point

Melting is the change from the highly ordered arrangement of molecules within a crystalline lattice to the more random arrangement that characterizes a liquid. Melting occurs when a temperature is reached at which the thermal energy of the molecules is great enough to overcome the intracrystalline forces that hold them in position in the lattice. As a solid becomes a liquid, heat is absorbed, and the heat content (enthalpy) increases. In other words, the enthalpy of a substance in the liquid state is greater than the enthalpy of the same

Figure 2-1. Important Physicochemical Properties, Their Interrelationships, and Their Uses in Risk Assessment



substance in the solid state. The entropy (a measure of the degree of molecular disorder) also increases as substances change from solid to liquid.

Melting point is an important property used by EPA in the evaluation of PMN substances. The melting point of a pure substance is characteristic of that substance. Melting point, therefore, can be used in the identification of an unknown substance (theoretically, a substance has a single melting point value; however, several substances can coincidentally have the same melting point). The melting point also provides information about the purity of a substance. A sharp melting point or narrow melting range is a good indication that the substance is pure. A fairly wide melting point range generally indicates the presence of impurities. Some substances may decompose or sublime rather than melt. Decomposition and sublimation are also characteristic properties and, hence, are useful for identification purposes.

Melting point is a function of the crystal lattice of a solid, which in turn is dictated primarily by three factors: molecular forces, molecular symmetry, and the conformational degrees of freedom of a molecule (Dearden 1991). Most ionic substances have very high melting points because the forces that hold the ions together are extremely strong. For organic substances, the most important force influencing melting point is intermolecular hydrogen bonding. A substance that has less intermolecular hydrogen bonding and more intramolecular hydrogen bonding will have a lower melting point than a structural isomer of the same substance that has more intermolecular and less intramolecular hydrogen bonding. Melting point also tends to increase with molecular size, simply because the molecular surface area available for contact with other molecules increases, thus increasing the intermolecular forces (Dearden 1991).

Melting point can provide information about the water solubility of non-ionic organic substances. Both melting point and water solubility of non-ionic organics are affected by the strength of the intermolecular forces in the substance. If the intermolecular forces are very strong in a solid, the melting point is likely to be high and the solvation of the individual molecules by water is likely to be low. The melting point of a non-ionic solid, therefore, may be used as an indicator of water solubility. The water solubility of a non-ionic solid depends largely on the temperature of the water, the melting point, and the molar heat of fusion of the solid (Yalkowsky and Banerjee 1992). Abramowitz and Yalkowsky (1990) have reported the use of melting point with total molecular surface for the accurate, quantitative estimation of water solubility for a series of PCBs. Melting point has also been used with K_{ow} (i.e., octanol/water partition coefficient) for an accurate, quantitative estimate of water solubility of liquid or crystalline organic non-electrolytes (Yalkowsky et al. 1979, 1980). Melting point may also be used with other physicochemical properties to derive quantitative estimates of water solubility for non-ionic solids; some of these methods have been summarized by Yalkowsky and Banerjee (1992).

Because the melting point can provide an indication of a substance's water solubility, it can also serve as a tool for

estimating the distribution of the substance in aqueous media. If a chemical substance is poorly soluble in water, its concentration in aqueous media may be too low for significant exposure; however, if a substance is highly soluble in water, its concentration in aqueous media is higher, thus increasing exposure potential. In general, high-melting non-ionic solids are likely to have low water solubility and exposure, whereas low-melting, non-ionic solids are likely to have higher water solubility and exposure.

For non-ionic organic substances, melting point can provide an indication of the likelihood of human exposure to a chemical via absorption through the skin, lungs, or gastrointestinal tract. In general, low-melting substances are more likely to be absorbed than substances that melt at higher temperatures, because, for a substance to diffuse through biological membranes, the molecules must be in their greatest state of molecular disaggregation (i.e., in solution). Non-ionic substances that melt at lower temperatures have less energy within their crystalline lattice, are more water soluble, and will be absorbed more readily than compounds that melt at higher temperatures. Substances that are liquids at ambient temperature are generally much better absorbed than solids (USEPA 1992).

Although reasonably accurate methods for the quantitative estimation of melting point have been reported for certain classes of substances (Abramowitz and Yalkowsky 1990; Dearden 1992), estimation of melting point is generally very difficult because the property depends upon a significant number of complex interactions including crystal packing and symmetry, molecular size, and hydrogen bonding (Yalkowsky et al. 1980; Yalkowsky and Banerjee 1992). While melting point may be roughly estimated by analogy with other chemicals that have similar structures, it is well known that even subtle changes within a homologous series of compounds can greatly affect melting point. Accurate estimation of a substance's melting point by comparison to similar substances, therefore, is not always feasible. Melting point is easily measurable for most organic substances (Shriner et al. 1980).

EPA chemists routinely estimate melting points if submitters do not provide them, but measured values are preferable. There is little justification for a PMN submitter to omit melting points for solids since melting point is easy and inexpensive to measure; in many cases, the submitter's analytical laboratory will have measured melting points during research and development activities. These data are considered health and safety data and must be submitted with the PMN. For known substances, the melting point is often available in the scientific literature, but literature values, of course, have no bearing on the purity of the submitter's chemical. Submitters should so indicate when they use literature values in PMN submissions.

When reviewing a PMN substance for which the melting point has been omitted by the submitter, EPA chemists search the literature for an empirical (measured) value. If an empirical melting point is not available, it is the general policy of EPA to estimate a more conservative, relatively low melting point in its risk assessment for that substance. As a consequence, EPA may conclude that the substance may be absorbed more readily through the skin, lung, or

gastrointestinal tract than is actually the case and, thus, may predict that the substance will be toxic to humans. Likewise, in the absence of data, EPA will make the assumption that the substance has relatively high water solubility and may be toxic to aquatic life. These reasonable worst-case estimation scenarios can be avoided or mitigated if the submitter provides EPA with empirical melting points.

2.2.2 Octanol/Water Partition Coefficient (K_{ow}, P)

A partition coefficient describes the equilibrium ratio of the molar concentrations of a chemical substance (the solute) in a system containing two immiscible liquids (the solvents). The partition coefficient is not simply a comparison of the solubility of a substance in one immiscible solvent with that in another such solvent. The most common partition coefficient is the octanol/water partition coefficient, expressed as either K_{ow} or P, in which the two immiscible solvents are *n*-octanol and water. The equation for K_{ow} (or P) is:

$$K_{ow} \quad \frac{[chemical\ substance]\ in\ n\ octanol}{[chemical\ substance]\ in\ water}$$

where concentrations are in moles/liter.

For purposes of simplification, K_{ow} is usually reported as its common logarithm (log K_{ow} or log P). A large log K_{ow} value for a chemical (relative to other substances), indicates that the chemical has a greater affinity for the *n*-octanol phase and, hence, is more hydrophobic (lipophilic). A low or negative log K_{ow} value indicates that a chemical has a greater affinity for the water phase, and hence, is more hydrophilic. A chemical substance with a log K_{ow} of 1 has ten times the affinity for *n*-octanol that it has for water, whereas a chemical substance with a log K_{ow} of -1 has ten times the affinity for water that it has for *n*-octanol.
A chemical substance with a log K_{ow} of 0 has equal affinity for *n*-octanol and water. Substances containing polar substituents (e.g., -OH, -SH, $-NH_2$, etc.) tend to have lower log K_{ow} values than substances that lack such substituents.

For practically any given non-ionic organic substance, it is possible to use the octanol/water partition coefficient to estimate other physicochemical properties and, in many cases, the distribution of the chemical within a living system or the environment. This is why octanol/water partition coefficients are extremely helpful and are used extensively during risk assessment of chemical substances. Specifically, octanol/water partition coefficients are often used by EPA and others to estimate water solubility, soil and sediment adsorption, biological absorption (following oral, inhalation, or dermal exposure), bioaccumulation, and toxicity.

A primary reason for the versatility of the octanol/water partition coefficient in risk assessment is that it serves as a model for the distribution of a chemical substance within both biological and non-biological systems. Biological membranes and systems (e.g., organs, cell membranes, capillaries, blood-brain barrier, skin, intestines) typically contain various combinations of lipid and aqueous components. For a chemical substance to gain entry into and distribute throughout a biological system, it must have a certain amount of both lipid and water solubility. The octanol and water phases of an octanol/water system are representative of

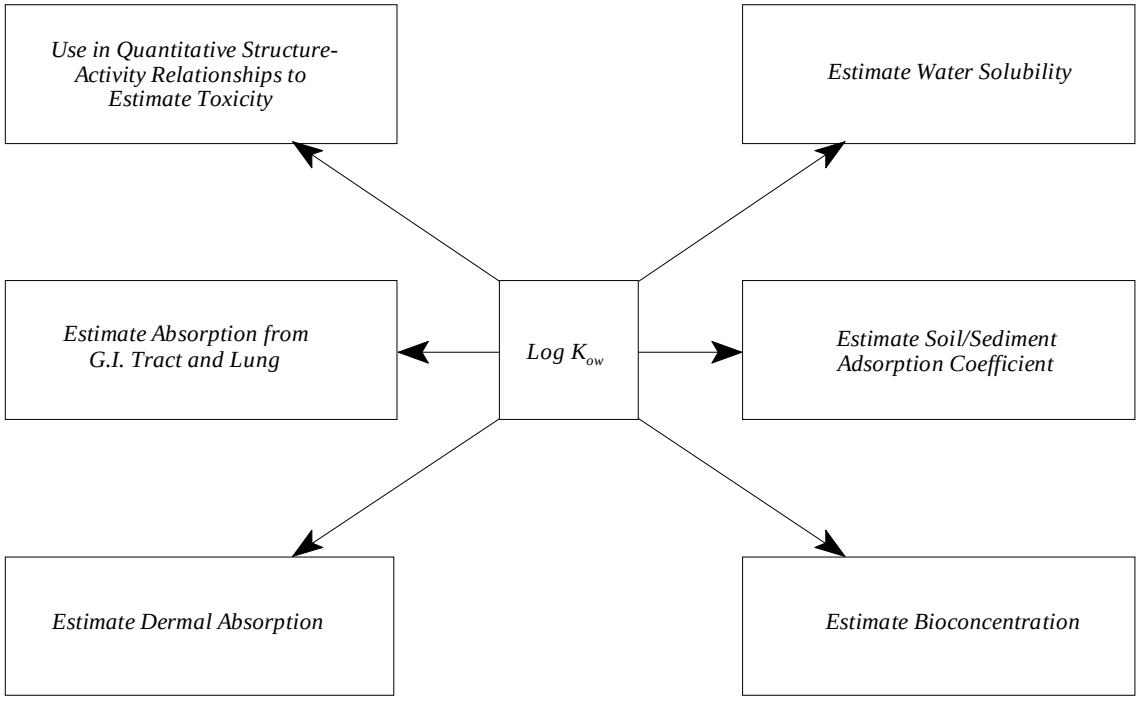
the lipid and aqueous components of biological systems, respectively. Thus, the octanol/water partition coefficient is an important property influencing the biological activity of a chemical substance (Hansch and Dunn 1972; Hansch and Clayton 1973). For this reason, the octanol/water partition coefficient is used extensively by EPA and others in the quantitative prediction of toxicity (Blum and Speece 1990; Karcher and Devillers 1990; Hermens and Opperhuizen 1991; Grogan et al. 1992) and environmental fate (Lu and Metcalf 1975; Kenaga and Goring 1980; Swann et al. 1983). Pharmaceutical companies use the octanol/water partition coefficient for the quantitative prediction of pharmacological activity of many chemical substances (Martin 1978; Yalkowsky et al. 1980). Figure 2-2 illustrates the usefulness of log K_{ow}. Suggested readings, including the use of octanol/water partition coefficient in estimating bioavailability, toxicity, and pharmacological activity, are provided at the end of this chapter.

Substances with high (> 5) log K_{ow} values are so hydrophobic that they partition very poorly into the aqueous components of biological systems, remain within the lipid components and are generally poorly absorbed following acute exposure. Chemical substances with high log K_{ow} values, although poorly absorbed, are more likely to bioaccumulate into fat tissue, whereas compounds with lower log K_{ow} values generally do not bioaccumulate because of their lower affinity for lipids (Lyman et al. 1982; Noegrohati and Hammers 1992). Substances with high log K_{ow} values that exist in the environment at sub-toxic levels may bioconcentrate to toxic levels within aquatic organisms, following sufficient exposure duration to achieve steady state partitioning. The ability of a very hydrophobic chemical to produce toxic effects may be limited by high melting point, resulting in both insufficient water and lipid solubility to reach toxic levels at the site of action within the aquatic organism (USEPA 1985). Generally, chemicals with good lipid and water solubilities are likely to be absorbed from all routes of exposure, including the skin (Shah 1990).

Substances with high log K_{ow} values tend to adsorb more readily to organic matter in soils or sediments because of their low affinity for water. Compounds with lower log K_{ow} values are not as likely to adsorb to soils or sediments because they will be more prone to partition into any surrounding water. Log K_{ow} is often used, in fact, by EPA to estimate quantitative soil/sediment adsorption coefficients, K_{oc} (Lyman et al. 1982) and qualitative removal of a substance during wastewater treatment.

Because the octanol/water partition coefficient is an equilibrium ratio of the molar concentrations of a chemical substance in *n*-octanol and water, it is often useful in estimating water solubility. Water solubility is often a difficult property to estimate; however, regression equations for the quantitative estimation of water solubility using log K_{ow} have been reported for organic chemical substances from several classes (Yalkowsky et al. 1979; Yalkowsky et al. 1980; Yalkowsky and Valvani 1980; Yalkowsky and Valvani 1979; and Yalkowsky and Banerjee 1992; Bowman and Sans 1983; Isnard and Lambert 1989; Kenaga and Goring 1980). As a general rule of thumb with non-ionic organic substances, the higher the log K_{ow}

Figure 2-2. Use of Octanol-Water Partition Coefficient (Log K_{ow}) in Risk Assessment



value, the lower the water solubility. Estimation of water solubility is discussed in more detail later in this chapter. The EPA is currently developing guidelines for the selection of measured or estimated K_{ow} data. These will provide additional guidance to PMN submitters.

Measuring log K_{ow}

Several methods of measuring octanol/water partition coefficient are described in EPA's Test Guidelines (USEPA 1996), and newer methods continue to appear in the literature. Each of these methods has advantages and disadvantages; one must be very careful to select the best method for a particular chemical in order to obtain an accurate value. It is very important to state the method of measurement along with each log K_{ow} value, so that the reliability of the value is apparent.

The classical method for measuring log K_{ow} is the "shake-flask" method. In this method, the test chemical is mixed with an appropriate *n*-octanol/water mixture and shaken for some given period during which equilibrium between both phases is achieved. It is important for the *n*-octanol and water phases to be mutually saturated prior to shaking with the test chemical. After the phases separate, the concentrations of the test chemical in the octanol and aqueous phases are determined. The aqueous phase often needs to be centrifuged to remove any small octanol droplets.

The shake-flask method is widely used to measure the K_{ow} accurately for many chemicals. This method is not appropriate, however, for substances with high partition coefficients (log $K_{ow} > 4.5$). The shake-flask method is also inappropriate for (1) polycyclic aromatic substances lacking polar substituents, (2) halogenated hydrocarbons, and (3) large, non-polar chemicals, because large volumes of the aqueous phase are required for analysis and, in addition, the aqueous phase becomes contaminated with micro-emulsions formed during shaking. Although it may be possible to prevent or remove the emulsions formed during the shake-flask procedure, literature data for K_{ow} measured by this technique indicate that in many cases, the formation of emulsions has influenced the observed K_{ow} values. This may account for the high variance among literature values for rather hydrophobic chemicals whose K_{ow} values were determined by independent investigators using this method (Hansch and Leo 1979; Kenaga and Goring 1980).

Brooke and co-workers (1986) have described a "slow-stir" method for measuring octanol/water partition coefficients for hydrophobic chemicals. This method is similar to the shake-flask method, but differs in that the octanol and water phases are equilibrated under conditions of slow stirring rather than vigorous shaking. By careful stirring and rigid temperature control, the formation of emulsions can be prevented, and accurate partition coefficients can be obtained relatively easily for very hydrophobic substances. De Bruijn and co-workers (1989) found that for substances with log K_{ow} values ranging from 0.9 to 4.5, experimental data obtained by the slow-stir method were in good agreement with literature values based on the shake-flask method. For substances having log K_{ow} values of 4.5 and higher, there was reasonable agreement between data obtained using the slow-stir method and data obtained

using either reversed-phase high performance liquid chromatography (HPLC) or the generator column method. Thus, the slow-stir method appears to be very useful for measuring log K_{ow} for hydrophobic as well as hydrophilic substances. In addition, the method is easy to use, relatively fast, and does not require expensive equipment. Detailed discussions of the slow-stir method in determining K_{ow} are available (Brooke et al. 1986; de Bruijn et al. 1989).

Another very versatile method for measuring log K_{ow} is the generator column method (USEPA 1985). In this method, a generator column is used to partition the test substance between the octanol and water phases. The column is packed with a solid support and is saturated with a fixed concentration of the test substance in *n*-octanol. The test substance is eluted from the octanol-saturated generator column with water. The aqueous solution exiting the column represents the equilibrium concentration of the test substance that has partitioned from the octanol phase into the water phase. The primary advantage of the generator column method over the shake-flask method is that the former completely avoids the formation of micro-emulsions. Therefore, this method is particularly useful for measuring K_{ow} for substances having log K_{ow} values over 4.5 (Doucette and Andren 1987, 1988; Shiu et al. 1988), as well as for substances having log K_{ow} values less than 4.5. A disadvantage of the generator column method is that it requires sophisticated equipment. A detailed description of the generator column method is presented in USEPA 1985.

EPA encourages PMN submitters to provide accurately-measured log K_{ow} data in PMN submissions. For certain types of chemical substances, however, it is not necessary to do so. Substances that contain several aromatic rings, lack polar substituents, or are polyhalogenated most likely have log K_{ow} values greater than 7. Similarly, chemicals that contain long-chained (10 or more carbons) alkyl substituents with few polar groups (e.g., fatty acids) are also likely to have log K_{ow} values above 7. Such substances are so clearly hydrophobic that it is not necessary to have an accurately-measured K_{ow} value for risk assessment purposes. In addition, it is generally not necessary to measure K_{ow} values for substances that have strong surfactant properties. Measuring K_{ow} for surfactants (particularly ionic surfactants) is usually difficult because the surfactant causes the octanol and water phases to become miscible, preventing partitioning between the two solvents. EPA does not generally recommend measuring log K_{ow} for polymers or PMN substances that lack definite structure (class 2 substances). For most substances, especially class 1 compounds (i.e., those with defined structures), measured K_{ow} values are very helpful for properly and fairly characterizing risk potential. It is also helpful to provide EPA with the method used for measuring K_{ow}. Table 2-1 summarizes the methods used for measuring octanol/water partition coefficient.

Estimating log K_{ow}

Recognizing the importance of log K_{ow} in predicting absorption, biological

Table 2-1. Methods of Measuring Octanol/Water Partition Coefficient (K_{ow})

Method	Advantages	Disadvantages	References
Shake-Flask	Easy to use. Reliable for substances that have log K_{ow} values < 4.5. Doesn't require expensive equipment.	Generally not useful for measuring K_{ow} values for substances having log K_{ow} values > 4.5; shaking may form micro-emulsions, which lead to inaccurate measurement.	USEPA (1985); Kenaga and Goring (1980).
Slow-Stir	Easy to use. Relatively fast, doesn't require expensive equipment. Reliable for essentially all substances.	Requires careful stirring and close temperature control to avoid formation of micro-emulsions.	Brooke et al. (1986); de Bruijn et al. (1989).
Generator Column	Reliable for essentially all substances. Avoids formation of micro-emulsions.	Requires expensive equipment.	USEPA (1985); Doucette and Andren (1987, 1988); Shiu et al. (1988).

properties, and environmental fate, scientists over the years have measured and recorded log K_{ow} values for thousands of substances, largely from the shake-flask method. These empirical data sets have served as a basis for developing techniques to estimate log K_{ow}. Numerous methods for estimating log K_{ow} accurately for many different classes of substances are now available. Some of these methods have recently been reviewed (Leo 1993; van de Waterbeemd and Mannhold 1996). Most of the log K_{ow} estimation methods are based upon one or more of the following approaches:

- fragment or substituent additivity (Hansch and Leo 1979; Leo 1990);
- correlations with capacity factors on reversed-phase HPLC (Lins et al. 1982; Brent et al. 1983; Garst 1984; Garst and Wilson 1984; USEPA 1985; Dunn et al. 1986; Minick et al. 1988; Yamagami et al. 1990);
- correlations with descriptors for molecular volume or shape such as molecular weight, molar refraction, parachor, molar volume, total molecular surface area and total molecular volume (Dunn et al. 1986; Doucette and Andren 1987; de Bruijn and Hermans 1990); and
- correlations with molar volume, solvatochromic (thermodynamic) parameters, or charge transfer interactions (Kamlet et al. 1988; Saski et al. 1991; Dunn et al. 1991; Moriguchi et al. 1992; Da et al. 1992).

A major problem in estimating log K_{ow} is that most methods work well for certain classes of substances, but not for other classes. Typically, originators of these estimation methods are quick to point out the shortcomings of other methods, but not the limitations of their own methods. Before using any method for estimating log K_{ow}, the user should become familiar with the theoretical basis of the method, its applicability, and its limitations. Estimation methods that have not been validated (i.e., tested against accurately-measured log K_{ow} values) should not be used. The remainder of this section briefly discusses the methods above for estimating log K_{ow} and attempts to provide some guidance with respect to their use. Table 2-2 summarizes the advantages and disadvantages of the methods. A detailed description of each estimation method is beyond the scope of this text; however, a comprehensive listing of references describing various estimation methods of log K_{ow} is provided in the Suggested Readings section at the end of this chapter.

The foremost method used in estimating log K_{ow} is that of Hansch and Leo (1979). This method uses empirically-derived fragment constants and structural factors to calculate log K_{ow} from a structure. Estimates are made from addition of fragment constants and structural factors, which are compiled for thousands of structural fragments and atoms stored in a database. The method has been validated by many investigators. A detailed description of how the method is used is available (Lyman et al. 1982). Using this method, one

Table 2-2. Methods of Estimating Octanol/Water Partition Coefficient (K_{ow})

Method	Advantages	Disadvantages	References
Fragment Constant Additivity	Calculation of log K_{ow} for many substances can be accomplished directly from structure. Available as a computer program. Known to be very accurate for substances having log K_{ow} values less than 4.5	Inaccurate for substances with log K_{ow} > 6. Cannot estimate log K_{ow} for substances containing substituents that are not in the fragment constant database (except for the Meylan and Howard method).	Hansch and Leo (1979); Meylan and Howard (1995).
Correlation of Reversed-Phase HPLC Retention Times	Known to be very accurate.	Requires a dataset of accurately-measured log K_{ow} values and HPLC retention times of substances closely related to the test substance.	Garst (1984); Garst and Wilson (1984); USEPA (1985).
Correlation of Molecular Surface Area and Volume	Very accurate for certain non-polar hydrophobic substances.	Requires a dataset of accurately-measured log K_{ow} values and HPLC retention times of substances closely related to the test substance. Only accurate for non-polar hydrophobic substances such as halogenated and nonhalogenated benzenes and biphenyls.	Yalkowski and Valvani (1976); Doucette and Andren (1988); de Bruijn and Hermens (1990); Brooke et al. (1987).
"Three Dimensional" Modeling	Calculation of log K_{ow} for many substances can be accomplished directly from structure. May be used for substances whose log K_{ow} values cannot be calculated by the fragment constant additivity method (due to missing fragment constants).	Requires knowledge of molecular modeling. Requires sophisticated computer hardware and software. Has not been thoroughly validated.	Sasaki et al. (1991); Moriguchi et al. (1992); Waller (1994).

can estimate log K_{ow} for almost any substance. If an accurately-measured value of K_{ow} is available for a structurally similar or "parent" compound, this measured value can be used to estimate the log K_{ow} of the "derivative" by adding or subtracting the appropriate fragment constant or structural factor. This approach is preferred whenever a reliable measured value of a parent compound is available because the solvent-solute interaction terms in the parent molecule are already accounted for. A major advantage of the Hansch and Leo method is that log K_{ow} values can be estimated (calculated) directly from structure alone. This method is very accurate for many classes of chemical substances, but is known to overestimate log K_{ow} for some substances with log K_{ow} values greater than about 6 (Lyman et al. 1982). A computer program (CLOGP) of the Hansch and Leo method is available.[17] A disadvantage of the method is that it cannot estimate log K_{ow} for substances that contain substituents whose fragment or structural factor contributions to log K_{ow} are unknown. Meylan and Howard (1995) have recently reported a variation of the Hansch and Leo fragment addition method for estimating K_{ow}. This variation uses atom/fragment contribution values and correction factors obtained from measured K_{ow} values of structurally diverse substances. Using the Meylan and Howard method, the K_{ow} of a substance is estimated by summing all atom/fragment contribution values and correction factors pertaining to the structure. The primary advantage of this method over the Hansch and Leo method is that it can calculate K_{ow} for substances for which K_{ow} cannot be calculated using the Hansch and Leo method. The Meylan and Howard method is easy to use, and reported to be very accurate. A computer program (LOGKOW) of the method is available.[18]

A great deal of effort has been directed towards estimating K_{ow} from retention times determined by reversed-phase HPLC . A detailed discussion of this method is available in USEPA 1985. In this technique, accurately-measured log K_{ow} values for a set of closely related substances are correlated to the reversed-phase HPLC retention times of the substances, and a regression equation is obtained. The log K_{ow} of a structurally similar substance can be estimated using its retention time and the regression equation. This method is semi-empirical since HPLC retention time must be measured.

The reversed-phase HPLC method is known to be very accurate for many chemical substances (Lins et al. 1982; Brent et al. 1983; Garst 1984; Garst and Wilson 1984; Minick et al. 1988; Yamagami et al. 1990). Obvious disadvantages of this method, however, are that it requires accurately-measured log K_{ow} values of analogous substances, sophisticated technical equipment, and a certain amount of technical expertise. Another disadvantage is that the linear regression equations cannot be extrapolated beyond the K_{ow} range for

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17. The CLOGP computer program is available through the Pomona College Medicinal Chemistry Project, Claremont, California, 91711.

18. The LOGKOW computer program is available from Syracuse Research Corporation, Environmental Science Center, Merrill Lane Syracuse, NY, 13210.

which the equations were derived. Also, log K_{ow} values for the reference chemicals are usually determined by the shake-flask method and, therefore, are not very reliable for hydrophobic substances. Leo (1990) has discussed other disadvantages to this approach. The reversed-phase HPLC method should only be used for chemicals and reference compounds whose chemical structures are similar.

Several investigators have reported exceptional correlations between log K_{ow} and molecular surface area or molecular volume for hydrophobic aromatic substances, such as halogenated benzenes and biphenyls (Yalkowsky and Valvani 1976; Doucette and Andren 1987, 1988; Brooke et al.1986, 1987; de Bruijn and Hermans 1990). Like the reversed-phase HPLC method, correlations with molecular surface area or volume require a data set of measured K_{ow} values for structurally similar substances. Molecular surface areas or molecular volumes are calculated for each chemical in the group and are then correlated with log K_{ow} to give a regression equation. Log K_{ow} of an analogous substance can then be estimated using the substance's calculated molecular surface area or volume in the regression equation. This method is not useful for estimating log K_{ow} for aromatic substances (or others) that contain polar substituents, since it does not take into account the effects that these substituents have on octanol/water partitioning.

An extension of this approach uses polarizability/dipolarity and hydrogen bonding terms in addition to molecular volume, and also has been found to predict log K_{ow} values accurately for PCBs and polycyclic aromatic hydrocarbons (Kamlet et al. 1988). Use of these descriptor terms in predicting log K_{ow} for more polar substances is presumably under investigation. A potentially serious drawback to this approach is that the descriptor terms may not always be available.

Recent advances in computer hardware and software have made estimation of log K_{ow} possible through consideration of three-dimensional intra- and intermolecular interactions (Sasaki et al. 1991; Moriguchi et al. 1992). This three-dimensional approach estimates log K_{ow} for organic substances through correlation with molecular surface area, electrostatic potential, charge transfer interactions, and other electronic and structural effects derived from three-dimensional molecular structures. Advantages to these methods are that log K_{ow} can be estimated directly from chemical structure and for substances to which Hansch and Leo's fragment constant approach has not been applicable. Although the three-dimensional methods for estimating log K_{ow} have not yet been completely validated, they appear to be very useful for rapid estimation of log K_{ow} for a wide variety of chemical substances. When in doubt regarding the applicability of a particular log K_{ow} estimation method, one should seek measured data on an analog and test the estimation. Alternatively, the analog can be used as the basis for estimation by subtracting and adding needed small fragments to obtain the PMN structure.

The octanol/water partition coefficient is very important in EPA's evaluation of PMN substances. EPA uses either measured or estimated log K_{ow} values in assessing approximately 50% of all PMN substances (which represents about 80% of

all non-polymer PMN substances). As discussed above, octanol/water partition coefficients can be used to estimate other properties (e.g., solubility, bioaccumulation, toxicity); these other properties are then used to evaluate the potential risk of a chemical to human health and the environment. The submission of accurately measured octanol/water partition coefficients allows for the reliable prediction of the effects of a chemical on human health and the environment. Accurately estimated log K_{ow} values are also useful to EPA. If an accurately measured or estimated log K_{ow} value is not provided by the submitter, then the EPA will estimate K_{ow} using one of the methods discussed previously. In cases where it is not apparent to EPA as to which estimation method will provide the most accurate log K_{ow} value, EPA will select the method that provides a log K_{ow} value that results in the highest toxicity or exposure.

2.2.3 Water Solubility

Water solubility is defined as the maximum amount of a substance in its finest state of molecular subdivision that will dissolve in a given volume of water at a given temperature and pressure. For risk assessment, EPA is most interested in the water solubility of chemical substances given at environmental temperatures (20-30 ^{o}C). Water solubility may be expressed in a number of units; EPA prefers water solubility data to be given in grams/liter (g/L). Most common organic chemicals have water solubilities that range anywhere from 0.001 g/L (1 part per million, ppm) to 100 g/L (100,000 ppm) at environmental temperatures. Solubilities for extremely hydrophobic substances (e.g., dioxins) have been measured below 1 part per billion, whereas some substances are infinitely soluble (completely miscible) in water.

Water solubility is one of the most important properties affecting bioavailability and environmental fate of chemical substances. Chemicals that are reasonably water soluble (that have low log K_{ow} values) are generally absorbed into biological systems because most of these systems contain a significant number of aqueous components. Such chemicals have relatively low adsorption coefficients for soils and sediments, and they bioconcentrate poorly, if at all, in aquatic species. Furthermore, highly water soluble substances tend to degrade more readily by processes such as photolysis, hydrolysis, and oxidation (Klopman et al. 1992). Water solubility also affects specialized transport pathways such as volatilization from solution and washout from the atmosphere by rain (Lyman et al. 1982). Water solubility, therefore, is a key element in the risk assessment of any chemical substance.

Measuring water solubility

The two most common methods for the experimental determination of water solubility are the shake-flask and generator column methods (Yalkowsky and Banerjee 1992; USEPA 1985; Lyman et al 1982). Although these methods are not technically difficult, there can be considerable variation in the water solubility measured for the same substance using the same method, but in different laboratories. These discrepancies result primarily from the large number of experimental variables that are known to affect solubility measurements. These variables include properties of the water such

as temperature, pH, presence of suspended solids, salt content, and organic content, and include properties of the chemical such as the physical state (especially particle size of solids), purity, and adsorption of the chemical onto the walls of the experimental apparatus (Kenaga and Goring 1980; Yalkowsky and Banerjee 1992). It appears that discrepancies increase as hydrophobicity increases (USEPA 1979). The shake-flask method is acceptable for determining water solubilities for substances that have log K_{ow} values of 3 or lower. Disadvantages of the shake-flask method are: (1) the method requires considerable sample handling between saturation and analysis steps; (2) colloid formation may occur as result of the shaking; and (3) the method is inaccurate for hydrophobic substances. The generator column method does not have the shortcomings of the shake-flask method and, therefore, is the preferred method for measuring water solubility. In addition, it is very rapid, precise, and is applicable to substances with water solubilities ranging from 10 parts per billion to grams per liter (Yalkowsky and Banerjee 1992; USEPA 1985). The equipment used in the generator column method, however, is more sophisticated and, hence, more expensive. PMN submitters are encouraged to provide information on the method used to measure water solubility, as well as an estimate of systematic and random errors of the reported result.

Estimating water solubility

A considerable amount of effort has been devoted to understanding the mechanism of aqueous solubility and developing methods that enable accurate estimation. A comprehensive treatise on water solubility and methods for its estimation has been published (Yalkowsky and Banerjee 1992). To summarize the contents of the text, water solubility is governed by three major factors: (1) the entropy of mixing; (2) the differences between the solute-water adhesive interaction and the sum of the solute-solute and water-water adhesive interactions; and (3) the additional intermolecular interactions associated with the lattice energy of crystalline substances (Yalkowsky and Banerjee 1992; Klopman et al. 1992). In estimating the water solubility of liquid substances, only factors 1 and 2 need to be considered, whereas in estimating the water solubility of solids, factor 3 must be included as well.

Most estimation methods for water solubility consist of regression equations that contain K_{ow} data as descriptors of factors 1 and 2 (Lyman et al. 1982; Yalkowsky and Banerjee 1992). Generally, if K_{ow} data are not available, it is difficult to estimate water solubility accurately. Some estimation methods also incorporate atomic fragment constants, and have been moderately successful for certain types of substances (Lyman et al. 1982; Wakita et al. 1986; Yalkowsky 1988; Klopman et al. 1992). Methods for estimating water solubility have been more successful for liquids than for solids. This is largely because of the difficulty in incorporating descriptors of intermolecular interactions for solid substances into the regression equations of the estimation methods. Incorporation of melting point, entropy of fusion, or enthalpy of fusion as descriptors of factor 3 has met with limited success for only certain types of compounds and, thus, has limited applicability (Lyman et al. 1982; Yalkowsky

and Banerjee 1992). In short, accurate estimation of water solubility is generally difficult, particularly for solid substances. As a general rule, non-ionic substances that are liquids at room temperature are usually more soluble than solids. Solid non-ionic substances with higher melting points or greater polarity tend to be less soluble than non-ionic solids that have lower melting points or lower polarity.

As noted earlier, when estimation of properties is difficult, EPA uses conservative values that ultimately tend to increase the Agency's overall concern for the chemical. EPA encourages the inclusion of reliably measured water solubility data in PMN submissions. By providing such information, the PMN submitter both eliminates the possibility that EPA will overestimate the water solubility of a chemical and ultimately assists EPA in making the most accurate risk assessment and risk management decisions.

It is not always necessary, however, for PMN submitters to provide EPA with measured water solubility data. For example, it is not necessary to measure the aqueous solubility of substances that are obviously very soluble, such as mineral salts of amines, metal salts of sulfonic acids, and quaternary ammonium compounds. For risk assessment purposes, EPA is not concerned with discerning the precise aqueous solubility for substances that are considerably water soluble. It is also, in general, not necessary for PMN submitters to determine water solubility for substances that are extremely water insoluble. Chemicals that are extremely hydrophobic (log K_{ow} greater than 7) are so poorly soluble that for risk assessment purposes, such substances are regarded as essentially insoluble. Finally, it is not necessary to measure water solubility for polymeric materials that are dispersible.

To decide whether water solubility should be measured, one should first determine or estimate the log K_{ow} of the substance. It is best to measure water solubility for substances whose log K_{ow} values are between -1 and 7. The generator column method is preferred for measuring water solubility for substances that have log K_{ow} values of 3 or greater. The shake-flask method is acceptable for measuring water solubility of substances having log K_{ow} values less than 3.

It is important that water solubility be determined for the substance itself, not for formulations of the substance. It is not uncommon for EPA to receive PMN submissions that include measured water solubility data for formulations of the PMN substance in co-solvents (e.g., alcohols, dimethylformamide, or dimethylsulfoxide). Such measured data are useless to EPA for risk assessment purposes.

Terms such as "insoluble" or "not very soluble" should not be used unless they are accompanied by data from attempted solubility measurements (such as "log K_{ow} is greater than 7"). A substance that is regarded as "insoluble" by a chemist may be sufficiently soluble to contribute to risk, as determined by a toxicologist or environmental fate specialist. Similarly, terms such as "soluble" or "very soluble" should not be used unless, again, they are accompanied by data from attempted solubility measurements (such as "water solubility is greater than 100 g/L").

2.2.4 Soil/Sediment Adsorption

Coefficient

The soil/sediment adsorption coefficient, K_{oc}, is a measure of the tendency of a chemical to be adsorbed onto soils or sediments. K_{oc} is defined as the ratio of the amount of chemical adsorbed per unit weight of organic carbon (oc) in soils or sediments to the concentration of the chemical in solution at equilibrium:

$$K_{oc} \quad \frac{\mu g\ adsorbed/g\ organic\ carbon}{\mu g/mL\ solution}$$

Discussions on soil and sediment adsorption are available (Karickhoff et al. 1979; Means et al. 1982). Values of K_{oc} can range from 1 to 1 x 10^7 (Lyman et al. 1982).

K_{oc} is important in the assessment of the fate and transport of chemicals in soils and sediments. A chemical with a high K_{oc} value is likely to be adsorbed to soils and sediments and thus, is likely to remain on the soil surface. In contrast, a chemical with a low K_{oc} value is not likely to be adsorbed to soils and sediments but is likely to leach through these soils and sediments and, if not degraded, may reach ground and surface waters. Chemicals that adsorb tightly to soils and sediments may accumulate in soils, but will be less prone to environmental transport in the gas phase or in solution. Chiou and co-workers (1983) reported that the extent of a chemical's insolubility in water is the primary factor affecting its adsorption to soils and determines its degree of mobility in rivers, groundwater, and runoff. Also, a substance that is tightly adsorbed to soils is less likely to be subject to other fate processes (such as volatilization, photolysis, hydrolysis, and biodegradation) than a substance that tends to partition into water.

EPA's Toxic Substances Control Act Test Guidelines (USEPA 1985) describe an experimental method for determining the adsorption coefficient K, which can be used to calculate K_{oc}. The method involves equilibrating various aqueous solutions containing different concentrations of the test chemical and a known quantity of sediment or soil. After equilibrium is reached, the distribution of the chemical between the aqueous phase and the solid phase is determined. The coefficient, K, is determined from the following equation:

$$\frac{x}{m} \quad KC^{\frac{1}{n}}$$

where

x/m = (µg of chemical absorbed)/(g soil or sediment)

C = (µg of chemical)/(mL of solution)

n = a parameter ranging from 0.7 to 1.1 (Lyman et al. 1982)

K_{oc} is determined from K and the percent of oc in the soil or sediment:

$$K_{oc} \quad \frac{K}{\%oc}\ x\ 100$$

Several methods are available for the estimation of K_{oc} from empirical relationships with other properties (Lyman et al. 1982). Octanol/water partition coefficient (K_{ow}) is often used in regression equations for the estimation of K_{oc}. Other properties used to estimate K_{oc} include water solubility, bioconcentration factor (BCF) for aquatic life, and parachor. Swann et al. (1983) found that the retention times of chemicals in reversed-phase high performance liquid chromatography (RP-HPLC) correlate well

with measured K_{oc} values. Bahnick and Doucette (1988) and Sabljic (1984, 1987) have reported the use of molecular connectivity indices for estimation of K_{oc}. Meylan and co-workers (1992) have recently reported a model for K_{oc} estimations that uses molecular connectivity indices and fragment descriptors. This last method appears to produce more accurate estimates of K_{oc} than other models, is easier to use since measured or estimated K_{ow} or water solubility values are not needed, and is more comprehensive in its applicability to a variety of structurally diverse organic compounds.

K_{oc} provides a measure of a substance's distribution between soil and water. For practical reasons, EPA does not expect PMN submitters to measure K_{oc} values for substances submitted in PMNs. In fact, EPA has, to date, never received a PMN that included a K_{oc} value; however, EPA estimates K_{oc} values for practically every PMN substance submitted to the Agency because of the importance of this property in predicting environmental partitioning and distribution. This emphasizes the need for the inclusion of certain physicochemical property data (such as water solubility and K_{ow}) in PMNs, which EPA can then use in estimating K_{oc}. K_{oc}, used with the K_{ow}, BCF, and Henry's Law constant, can predict the environmental distribution of a chemical and, thus, is a measure of environmental risk (McCall et al. 1983).

2.2.5 Henry's Law Constant

A substance that is introduced into the environment by release to air, water, or land tends to diffuse through all environmental media in the direction of establishing an equilibrium between these media. Henry's Law describes the distribution of a chemical between water and air and states that when a substance is dissolved in water, the substance will have a tendency to volatilize from the water into the air above until an equilibrium is reached. Henry's Law constant (H) can be considered an air-water partition coefficient and is defined as the concentration of the chemical substance in air relative to the concentration of the chemical substance in water:

$$H \quad \frac{[chemical\ substance]\ in\ air}{[chemical\ substance]\ in\ water}.$$

This equation is appropriate only for equilibrium conditions of dilute solutions (those typically observed in the environment). Chemicals that have high H values have a greater tendency to volatilize from solution and partition towards air, whereas relatively low H values indicate that the substances will tend to partition into water. Some groups of substances tend to partition significantly toward air despite possessing relatively low vapor pressures. These high H values are primarily the result of the poor solubility of these substances (hydrocarbons, for example) in water.

Henry's Law constant can be expressed as a ratio of the partial pressure of a substance in the vapor above a solution to the concentration of the substance in the solution:

$$H \quad \frac{equilibrium\ vapor\ pressure}{solubility}$$

where vapor pressure is in atmospheres and the solubility is in moles per cubic meter.

The vapor pressure of the pure substance, typically in units of atmospheres-

cubic meters per mole (atm-m^3/mol), is often used as an approximation of the partial pressure (Lyman et al. 1982). This approximation is valid for substances with low water solubilities. If the solubility of a substance exceeds a few percent, then the dissolved substance's vapor pressure will be lower than that of the pure substance due to its dilution by water (Mackay and Shiu 1981). The thermodynamic principles that govern the relationships between vapor pressure, water solubility, and H for solid and liquid substances have been addressed in detail by Mackay and Shiu (1981). Also included in this discussion are experimental techniques for obtaining these properties. The inverse of the H value is also used by some investigators (McCall et al. 1983); therefore, the ratio H must be defined as being either air/water or water/air. The vapor pressure term can be expressed in other units (e.g., Pascals, torr), and the solubility term can be expressed in other concentration units (e.g., grams per cubic meter) or as a mole fraction.

The H value is often calculated from data for vapor pressure and water solubility that are measured independently (see the sections on these two properties for information on obtaining experimental measurements). As mentioned, this method may not be accurate for substances with water solubilities exceeding a few percent, but it is considered to be satisfactory for less soluble substances (Mackay and Shiu 1981). A second method for determining H involves measuring the water solubility and vapor pressure of a substance in a system that is at equilibrium (Mackay and Shiu 1981). This method is typically used for substances with high water solubilities. A third method described by Mackay and Shiu (1981) is most appropriate for substances with very low solubilities and vapor pressures. The method involves measuring the relative concentration changes in one phase during an equilibrium air-water exchange process. The H value is then determined from the slope of a semilogarithmic plot of concentration versus time.

EPA often estimates H using vapor pressure and water solubility data. Several methods are also available for estimating H from molecular fragments (Bruggemann and Munzer 1988; Hine and Mookerjee 1975) and bond contribution values (Meylan and Howard 1991).

Whereas the soil adsorption coefficient (K_{oc}) provides a measure of a substance's distribution between soil and water, H provides a measure of a substance's distribution between water and air. As with K_{oc}, EPA does not expect PMN submitters to measure H values for substances submitted in PMNs. EPA, however, does estimate H values for many PMN substances submitted to the Agency to describe the volatilization of a substance from water. This further emphasizes the need for the inclusion in PMNs of certain physicochemical property data (such as water solubility and vapor pressure, or at least boiling point), which EPA can then use for estimating H. The H value, water solubility, K_{ow}, K_{oc}, and BCF are all important properties used in determining the environmental distribution pattern of a substance and in assessing its environmental risk.

2.2.6 Boiling Point

Boiling point is the temperature at

which the vapor pressure of a substance in the liquid state is equal to atmospheric pressure. A substance boils when it has absorbed enough thermal energy to overcome the attractive forces between the molecules of the substance. The heat required to overcome these forces is the latent heat of vaporization. Solid substances, of course, must first liquify (melt) before they can boil. Some solid chemicals *sublime*; they pass directly from the solid to the gaseous state without melting. Boiling points and sublimation temperatures, like melting points, are characteristic properties of pure substances and may be used for the purpose of identification. Boiling points can also provide an indication of the purity of a liquid. With the exception of azeotropes, a liquid that is a mixture of several substances will begin to boil at a temperature equal to the boiling point of its most volatile component. The temperature will then gradually increase as the vapor phase becomes more rich with the less volatile component(s), until the temperature equals the boiling point of the least volatile component.

Boiling point is an indication of the volatility of a substance. It is particularly important in EPA's assessment of PMN substances, because it can be used to estimate vapor pressure, a vital property in estimating exposure (see section on vapor pressure). Boiling points are easily measured; EPA's Toxic Substances Control Act Test Guidelines (USEPA 1985) describe five methods for measuring boiling points. These methods include: (1) determination by use of an ebulliometer, in which the substance is heated under equilibrium conditions at atmospheric pressure until it boils; (2) the dynamic method, in which the vapor recondensation temperature is measured by means of a thermocouple; (3) the distillation method, in which the liquid is distilled and the vapor recondensation temperature is measured; (4) the Siwolloboff method, which involves heating the sample in a heat bath and measuring the temperature at which bubbles escape through a capillary tube; and (5) the photocell method, in which a photocell is used with the Siwolloboff method to detect rising bubbles in the capillary tube. Boiling point should always be measured using a pure sample of the substance and should never be measured from a mixture or a solution containing the substance.

The boiling points of members of a homologous series of substances generally increase in a uniform manner with increasing molecular weight. Therefore, the boiling point of a substance may be estimated using its molecular weight, if boiling points for homologous substances are available. Boiling points measured or estimated at reduced pressure can be used to estimate boiling points at one atmosphere (760 mm Hg).

Lyman et al. (1982) discuss seven different methods for estimating boiling point. At the time of this writing, no other methods have been reported since. All of the methods discussed by Lyman are capable of estimating boiling point from structure alone. Each method has its own advantages and disadvantages with respect to applicability and, therefore, is typically used only for a particular class of substances. EPA chemists often use these methods to estimate boiling point when an experimental value is not included in PMN submissions and is not found in the literature. EPA chemists

frequently have difficulty determining which method is the most appropriate for a chemical that has multiple functional groups and falls into several different chemical categories. In such cases, EPA usually selects the estimation method that results in the lowest boiling point, consequently maximizing exposure to the PMN substance. As with estimating water solubility, boiling points of liquid substances are easier to estimate than boiling points of solids, since the latter include intermolecular, intracrystalline forces (such as crystal packing) that are very difficult to estimate (see section on water solubility).

Experimental boiling points are known for many chemicals and are easily measured. PMN submitters, therefore, should be able to provide boiling point data for many new chemical submissions, provided that the substance does not decompose rather than melt or boil. It is not necessary, however, for PMN submitters to provide EPA with measured boiling point data for every PMN substance. EPA is concerned primarily with chemicals that melt below 100 ^{o}C, since these substances are most likely to volatilize readily. High melting solids (> 150 ^{o}C) typically have very high boiling points and, therefore, do not volatilize significantly. Polymers and other structurally large substances (solid or liquid) usually have low volatilities because of their high molecular weights, and often decompose upon heating. Salts also have low volatilities because of their strong ionic forces and very high melting points. Therefore, it is not necessary (or it may not be possible) for a PMN submitter to provide EPA with boiling point data for substances that have high molecular weights or very high melting points.

2.2.7 Vapor Pressure

Vapor pressure is the pressure at which a liquid substance and its vapor are in equilibrium at a given temperature. At this equilibrium, the rate of condensation of the vapor (conversion of gaseous substance to liquid) equals the rate of vaporization of the liquid (conversion of liquid substance to vapor); the vapor phase in this equilibrium is saturated with the substance of interest. Vapor pressure is characteristic of a substance at a given temperature, and is usually expressed in units of millimeters of mercury (mm Hg, or torr), atmospheres (atm), or Pascals (Pa); EPA prefers mm Hg or torr.

Because vapor pressure is an indication of the volatility of a substance, it can be used to estimate the rate of evaporation of that substance and is very important in the exposure assessment of chemicals. EPA uses the vapor pressure and molecular weight of PMN substances to estimate their concentrations in air and assess occupational exposure and potential environmental releases. Vapor pressure is also used in assessing potential exposure to consumers from products that contain the PMN substance. In the exposure evaluation of PMN chemicals, EPA is particularly concerned with substances that have vapor pressures greater than 10^{-3} mm Hg.

Vapor pressure is also an important property in the assessment of environmental fate and transport of a chemical substance. Volatilization is an important source of material for airborne transport and may lead to the distribution of a chemical over wide areas and into bodies of water far from the site of release (USEPA 1985). Chemicals

with relatively low vapor pressure, high soil adsorptivity, or high solubility in water are less likely to vaporize and become airborne than chemicals with high vapor pressure, low water solubility, or low soil adsorptivity. Chemicals that do become airborne are unlikely: (1) to be transported in water; (2) to persist in water and soil; or (3) to biodegrade or hydrolyze. Such chemicals may undergo atmospheric oxidation and photolysis. Non-volatile chemicals, however, are of greater concern for accumulation in soil and water (USEPA 1985).

Several experimental procedures are available for measuring vapor pressure; two are described in EPA's Toxic Substances Control Act Test Guidelines (USEPA 1985). The first method, the isoteniscope technique, is a standardized procedure applicable to pure liquids with vapor pressures from approximately 0.75 to 750 mm Hg. The second method, the gas saturation procedure, involves a current of inert gas passed through or over the test material and can be used for solids or liquids with vapor pressures ranging from 7.5×10^{-8} to 7.5 mm Hg (USEPA 1985).

Lyman et al. (1982) discuss several methods for estimating vapor pressure. EPA often uses these methods when vapor pressure data for a substance are not included in a PMN and are unavailable from the literature. Theoretically derived equations are used to estimate the vapor pressures of solids, liquids, and gases from measured or estimated normal (760 mm Hg) boiling points or from boiling points obtained at reduced pressure. Vapor pressure data, either estimated or measured, are necessary to estimate other properties such as Henry's Law constant.

EPA encourages PMN submitters to provide vapor pressure data in PMNs whenever possible because of the importance of vapor pressure in determining human exposure and environmental fate. Vapor pressure data should be obtained for the pure PMN chemical and not for a formulation of the substance. A frequent problem in PMNs is that the vapor pressure data submitted were measured for the PMN substance dissolved in a solvent. In such cases, the vapor pressure data represent the solvent, *not* the PMN substance, and are, therefore, useless to EPA. If measured vapor pressure data are not supplied, then measured boiling point data may be used to estimate vapor pressure reliably. If measured boiling points are not available, estimated boiling points may also be used to estimate vapor pressure, but estimated boiling points can decrease accuracy and increase the possibility of error. As with other physicochemical properties, if EPA is uncertain about its estimated vapor pressure, it will most likely use a value that reflects a worst case scenario, leading to greater exposure.

As with boiling point, PMN submitters do not necessarily need to provide EPA with measured vapor pressure data for every PMN substance. EPA is concerned primarily with chemicals that are liquids or gases at room temperature or solids that melt below 100 ^{o}C, since these substances are most likely to volatilize readily, which can result in significant exposure during manufacture or use. High melting solids (> 150 ^{o}C) are expected to have very high boiling points (and very low vapor pressures) and, therefore, are not expected to volatilize significantly. Polymers or other high

molecular weight substances (solid or liquid) typically have low volatility because of their large size. PMN submitters do not need to provide EPA with vapor pressure data for such substances.

2.2.8 Reactivity

The reactivity of chemical substances within biological and environmental systems is crucial to EPA's risk assessment of PMN substances. Toxicity is often the result of a chemical's ability to interfere with normal biochemical processes at the cellular level. Many biochemical processes are enzyme-mediated reactions involving various organic molecules used to produce other organic molecules for a specific function that is vital to the organism. The mechanisms for these enzyme-mediated reactions are fundamentally identical to reaction mechanisms of organic chemistry. Biochemical reactions may involve, for example, nucleophilic attack, electrophilic substitution, loss of electrons (oxidation), gain of electrons (reduction), or hydrolysis.

A knowledge of organic reaction mechanisms is necessary in understanding how a xenobiotic (a chemical that is not part of a biological system or process) will behave or react with molecules that are part of a biochemical pathway. EPA chemists and toxicologists examine every PMN substance to ascertain how these substances may react following absorption into the human body. For example, PMN substances that contain electrophilic substituents, such as acid chlorides, isocyanates, anhydrides, or α,β-unsaturated carbonyls (acrylates, acrylamides, quinones), may undergo nucleophilic attack by free amino (NH_2) groups present in proteins, thus perturbing the biochemical pathway. In fact, substances containing these functional groups are often quite toxic because of their susceptibility to nucleophilic attack by biological molecules (Anders 1985; De Matteis and Lock 1987; Gregus and Klaassen 1996). EPA does not automatically assume, however, that a PMN substance is toxic just because it contains a reactive functional group. Physicochemical properties must also be considered to assess exposure and bioavailability. Poor water solubility, for example, may mitigate EPA's concerns for the toxicity of a PMN substance containing a reactive functional group, because substances with poor water solubility are expected to be poorly absorbed. This example further illustrates the importance of physicochemical properties in EPA's risk assessment of PMN substances.

EPA chemists and toxicologists consider potential reactivity in predicting the toxicity of PMN substances that contain reactive functional groups and for which few or no toxicological and physicochemical property data are provided. However, it is often difficult to predict the reactivity of a functional group, especially if, for example, the group is hindered or otherwise chemically influenced by other substituents contained within the molecule. In such cases, EPA's policy is to assume reactivity, which may lead EPA scientists to predict a health concern. EPA chemists would prefer to have more information from the PMN submitter with respect to the relative reactivity of any functional groups in a PMN substance. EPA does not expect submitters to conduct extensive laboratory experiments investigating the reactivity of functional groups. EPA believes, however, that the

opinions of the submitter's in-house chemists, with respect to chemical reactivity, would be very helpful.

2.2.9 Hydrolysis

Substances may also react in the environment to produce other substances with properties different from those of their precursors. A type of reaction of particular interest is hydrolysis, which is the decomposition of a substance upon reaction with water. Hydrolysis is often described using rate constants (the rate of disappearance of the substance) and half-lives (the time required for the concentration of the substance undergoing hydrolysis to be reduced to one-half its initial value). In addition to hydrolysis, reactions with water in the environment can include elimination of a chemical group, isomerization, and acid-base reactions. Hydrolysis is likely to be the most important reaction of organic substances in aqueous environments, although elimination reactions can also be significant (Lyman et al. 1982).

Chemicals released into the environment are likely to come into contact with water following direct release into surface water, soil, or the atmosphere. It is important to know whether a substance will hydrolyze, at what rate, and under what conditions. If a substance hydrolyzes rapidly, then the hydrolysis products may be more important than the original substance in assessing environmental fate and effects. For a substance that hydrolyzes slowly, however, both the parent substance and the hydrolysis products should be assessed.

Certain chemical groups (e.g., haloformates, acid halides, small alkoxysilanes, epoxides) are very susceptible to hydrolysis, while others hydrolyze more slowly (e.g., alkyl halides, amides, esters). Water solubility can be a limiting factor in hydrolysis. Generally, the more soluble a substance is, the faster it will hydrolyze. Substances with very low water solubility that contain hydrolyzable substituents may hydrolyze very slowly, if at all. Half-lives (the time required for the concentration of the chemical to be reduced to half its initial value) for the hydrolysis of even reasonably similar chemicals can vary widely, from seconds to years, depending primarily on water solubility, but also on pH and temperature.

EPA's Toxic Substances Control Act Test Guidelines (USEPA 1985) describe a procedure for determining hydrolysis rate constants and half-lives at several pH levels. The method involves preparing solutions of a substance of known concentrations and then determining the changes in concentrations of these solutions at various time intervals. This method is also applicable to elimination reactions. The rate constants generated by this method can be used to determine the hydrolysis rates at any pH of environmental concern.

In the absence of experimental data, EPA makes qualitative and semi-quantitative estimates of hydrolysis rates based upon chemical structure, physicochemical properties, and comparison to similar substances with known rates of hydrolysis (Mabey and Mill 1978; USEPA 1986, 1987, 1988a, 1988b). This estimation approach is most reliable when measured physicochemical properties (particularly water solubility) for the substance of interest are available, as well as measured hydrolysis

rate constants for analogous substances. Physicochemical properties for the substance and rate constants for analogous substances, however, are not always known. In such cases, EPA bases hydrolysis estimates on chemical structure and estimated physicochemical properties. In the face of uncertainty, EPA will rely on conservative assumptions (e.g., EPA will assume a slower hydrolysis if EPA has environmental concerns for the intact chemical; if EPA has concerns for the hydrolysis products, EPA will assume a faster rate of hydrolysis). EPA does not expect PMN submitters to provide measured hydrolysis data routinely along with their PMN submissions. However, providing EPA with any qualitative or quantitative information pertaining to hydrolysis would be very helpful. This information would make it possible for the EPA to make more accurate risk assessments and to avoid the use of credible worst case assumptions.

2.2.10 Spectral Data

Many PMN submitters include spectral data in their submissions, which EPA finds helpful in verifying the identity of PMN substances. Spectral data are also helpful in identifying the presence of unreacted functional groups (e.g., isocyanate) and unknown, possibly toxic byproducts (e.g., dioxins, PCBs), especially if EPA suspects that such chemical species may be present. If EPA chemists suspect that unreacted functional groups or toxic byproducts may be present, given the synthesis of a PMN chemical, but no spectral data are provided, then their presence may be assumed by EPA. In actuality, EPA chemists often use spectral data provided by PMN submitters to rule out (rather than confirm) the presence of toxic byproducts or unreacted functional groups.

The spectral data that EPA finds most useful include mass spectra (MS), infrared (IR), hydrogen (^{1}H) and carbon (^{13}C) nuclear magnetic resonance (NMR), and ultraviolet (UV). Each of these spectral techniques provides unique information and collectively this information is extremely useful for structure elucidation (Pavia et al. 1979; Silverstein et al. 1981).

Ideally, EPA would like to have spectral data on a purified sample of the PMN substance; however, spectral data on a less pure commercial grade product are also helpful. It is not necessary for PMN submitters to provide spectral data for polymers (other than the data obtained from spectral techniques used to determine molecular weight) that were synthesized from monomer species with no reactive functional groups other than those necessary for the polymerization reaction.

2.2.11 Photolysis (Direct/Indirect)

Many chemicals released into the atmosphere or surface water undergo chemical transformation through absorption of sunlight. Photolysis is the decomposition of a substance as a result of absorbing one or more quanta of sunlight radiation; it can take place in water or in air. Rate constants (measurement of the rate of disappearance of the substance) and half-lives (the time required for the concentration of the substance undergoing photolysis to be reduced to one-half its initial value) provide information on photochemical transformation in water and the atmosphere. In direct

photolysis, a substance absorbs solar radiation and undergoes a photochemical reaction. In indirect photolysis, one substance absorbs sunlight, then transfers the energy to another substance, thus initiating a chemical reaction. Absorption of light in photochemical reactions (direct and indirect) can result in intramolecular rearrangements, isomerization, homolytic and heterolytic cleavages, redox reactions, energy-transfer reactions, and reactions with water.

Photochemical processes in the atmosphere can produce reactive atoms and free radicals such as the hydroxyl radical (•OH). Chemicals that do not absorb sunlight (i.e., do not undergo direct photolysis) may undergo indirect photolysis in the atmosphere by reacting with hydroxyl radicals or with ozone (Finlayson-Pitts and Pitts 1986). The oxygen present in water may participate in direct or indirect photochemical reactions as an acceptor of energy or electrons. Decaying vegetation in water may also absorb sunlight; energy is then typically transferred to another substance, thus initiating an indirect photochemical reaction (Leifer 1988).

Photochemical reactions in the atmosphere and water are important examples of chemical transformations that should be considered when assessing the environmental fate of chemical substances. The products of photochemical reactions and their resulting effects on human health and the environment are also important considerations in chemical evaluations.

Like K_{oc}, EPA has never received a PMN submission that included photolysis rate constants. EPA estimates photolysis rate constants, however, for essentially every PMN submitted. For practical reasons, the Agency does not expect PMN submitters to provide measured photolysis data in their PMN submissions, although it would be helpful to EPA if PMN submitters at least provided UV absorption data. UV data can be used by EPA to determine if a substance will undergo direct photolysis and, if it does, the data will then be used to estimate the relative rates of the direct photolysis of the substance (USEPA 1985).

EPA, in its Toxic Substances Control Act Test Guidelines (USEPA 1985), describes test methods for determining molar absorptivity and reaction quantum yield (the fraction of absorbed light that results in a photoreaction at a fixed wavelength) for direct photolysis of a substance in an aqueous solution. The Guidelines also discuss methods for determining the rate constant and half-life of a substance in an aqueous solution or in the atmosphere, as a function of latitude and season of the year in the United States.

Photolysis of chemicals in the atmosphere and water can be estimated by various methods. Computer programs are available that calculate rate constants and half-lives for reactions with hydroxyl radicals and ozone in the atmosphere (e.g., the EPI program described in Section 2.4.4 of this chapter). Lyman et al. (1982) describe several methods for estimating atmospheric residence time, which is related to half-life. Qualitative estimates of photolysis can be made based on the types of compounds that may be subjected to photolysis and the types of reactions they may undergo. Certain types of chemical groups are known to absorb light and undergo photolysis; therefore, the rate constant and half-life for a

particular substance may be estimated qualitatively by analogy to known data on other compounds with similar structures.

2.2.12 Other Chemical Information

Use (Intended Use/Other Uses/Potential Uses). Information on the intended use(s) of a PMN substance and the percent of total production estimated for each use, both provided by the submitter, are important to EPA's review of the substance. EPA uses this information to trace a PMN chemical's life cycle and to estimate health and environmental exposures to the chemical. Use and disposal information also reveals which release scenarios are likely to be the most significant with regard to exposure to a substance, and could determine which physicochemical properties are most important during the review of the substance. In addition to evaluating the occupational exposure of workers to a chemical during its manufacture, EPA considers potential consumer exposure if the chemical is to be used in a commercial product. A substance with consumer use(s), for example, will most likely lead to a significantly greater number of exposures than a chemical with only industrial uses.

In addition to the listing of intended uses provided by the submitter, EPA identifies and evaluates other possible or potential uses of the chemical by searching the literature and EPA's in-house database of PMN submissions for structurally-analogous substances, particularly those that pose a potential risk to human health or the environment. The identification of other uses is important because anyone may market or use a PMN substance for any purpose once the substance is on the TSCA Inventory (unless the substance is restricted by a 5(e) consent order or a SNUR). If a substance is used for an entirely different purpose than originally stated in a PMN submission, then production volume, environmental releases, and human exposures could be significantly different than those estimated from the initial PMN. A new use for a substance, therefore, could pose a threat to human health and the environment. The potential for other uses, especially those involving high exposure or release, leads EPA to restrict the future uses of some PMN substances through SNURs. The manufacturer of a chemical may not always be aware of other potential uses for a substance or may not be planning to pursue other uses because of the substance's marketability or the company's interests. It would be helpful to EPA, however, if submitters would provide known potential uses of a substance even if they are not planning to pursue them.

Synthesis. EPA requests information on the synthesis of PMN substances, including data on feedstocks, solvents, catalysts, other reagents used in the synthetic process, and byproducts (chemicals produced in the synthetic process without a separate commercial intent). This information is supplemented by process and operation descriptions and is utilized during several stages of EPA's evaluation of PMN substances.

Information on the synthesis of a chemical is important in several ways. Review of the synthetic process helps EPA to verify the identity of the PMN substance. From a review of reaction conditions, EPA may also be able to predict the existence of impurities and by-products, including toxic

reaction products (e.g., PCBs, dioxins or nitrosamines), that are unknown to the submitter because, for example, such substances may be present only in very small concentrations.

EPA scientists also review the synthetic processes for selected, potentially higher-risk PMN substances with respect to pollution prevention. EPA investigates whether any modifications could feasibly be implemented in this synthesis that would limit or avert the use of hazardous substances (including solvents and all reactants) or that would reduce or prevent the production, not just of hazardous waste, but of all waste. In a few cases, EPA scientists may also identify alternative synthetic sequences that would at least reduce the production of toxic byproducts or the use of high-risk solvents and feedstocks.

Submitters may demonstrate to EPA on the Optional Pollution Prevention page of the PMN (page 11) any pollution prevention strategies that they plan to implement. Some companies provide detailed descriptions of synthetic pathways that incorporate pollution prevention (e.g., processes that give high yields and use few or no organic solvents). EPA would like to see more companies do the same. For PMN submissions that do not contain synthetic information (synthetic data are not required for imported substances), pollution prevention information voluntarily supplied by submitters can assist EPA in its review of the PMN substance. For example, if a synthetic scheme is not given for a PMN substance, EPA may be concerned about the possible existence of toxic byproducts and impurities, based on information known about the synthetic scheme of similar substances. If the submitter, however, includes pollution prevention information explaining how their synthesis has improved upon known methods, then EPA would not need to assume a worst case scenario.

Purity/Impurities. The purity of a PMN substance, as well as the identities, concentrations, and hazards of all impurities are considered in the evaluation of every PMN substance. During review, EPA investigates whether any reported physicochemical properties submitted for a PMN substance (especially melting point and boiling point) coincide with any data previously recorded in the literature. Discrepancies between literature values and the data contained in the PMN submission may be attributable to impurities. EPA will contact the submitter if it is not clear in the PMN what the identities of impurities are, especially if impurities are predicted from EPA's analysis of the synthetic process. The presence of hazardous impurities (such as dioxins, PCBs, or nitrosamines) is cause for concern and, if present at significant levels, such impurities would lead EPA to predict potential risk to human health and the environment, especially if the PMN substance is intended for consumer use.

Molecular Weight. The molecular weight of a substance is the sum of the atomic weights of all the atoms in a molecule. For a simple molecule, the molecular weight is easily determined if the structure is known. Polymers, however, are typically comprised of a variable number and sequence of monomer units that may themselves also have varying chain length and molecular weight. The molecular weight of a polymer is frequently reported as a number-average weight (the sum of the molecular weights of the molecules divided

by the number of molecules).

Very large molecules are unlikely to be absorbed and, therefore, may be of little concern to EPA unless, of course, they contain reactive functional groups. EPA consequently exempts under TSCA section 5(h)(4) certain polymers (those with number-average molecular weights greater than 1,000 and certain polyesters, for example) from some of the PMN requirements. EPA does have concerns, however, for certain polymers with average molecular weights of 10,000 daltons or greater. These concerns are largely for lung toxicity (USEPA 1995).

2.3 Use of Chemical Information in Assessment of PMN Chemicals

Each physicochemical property discussed in this chapter is important in EPA's evaluation of the potential risks posed to human health or the environment by PMN substances. Refer back to Figure 2-1, which illustrates some of the physicochemical data used, their interrelationships, and their importance in risk assessment. Because of the large volume of data that EPA uses in its evaluation of PMN substances, Figure 2-1 does not attempt to include all of the types of chemical information used or to describe all of their functions in risk assessment.

2.4 How EPA Obtains Physicochemical Information

2.4.1 General Approach

When physicochemical property data required for chemical evaluation are not reported in a PMN submission, EPA finds or estimates values for the missing data. EPA's general approach for obtaining physicochemical property data is first to search for data on the PMN substance by following a sequence of literature and database sources. If data on the PMN substance cannot be found, EPA scientists may identify close structural analogs and use the same search strategies to find property data for those analogs. EPA scientists then use professional judgment to extrapolate property values for the PMN substance from the data available for the analogs. If the required properties for structural analogs cannot be found, EPA scientists estimate the properties needed for the PMN substance using the best estimation method available to EPA (Lynch et al 1991). If properties for structural analogs are found, EPA scientists may still estimate the same properties for the PMN substance. EPA scientists then analyze and compare both sets of data to determine which set is most reasonable. A flowchart illustrating EPA's procedure for obtaining physicochemical properties is presented in Figures 2-3 and 2-4. The sources EPA uses for searches and the

Figure 2-3. Methods for Obtaining Measured Physicochemical Property Values on Exact Structures

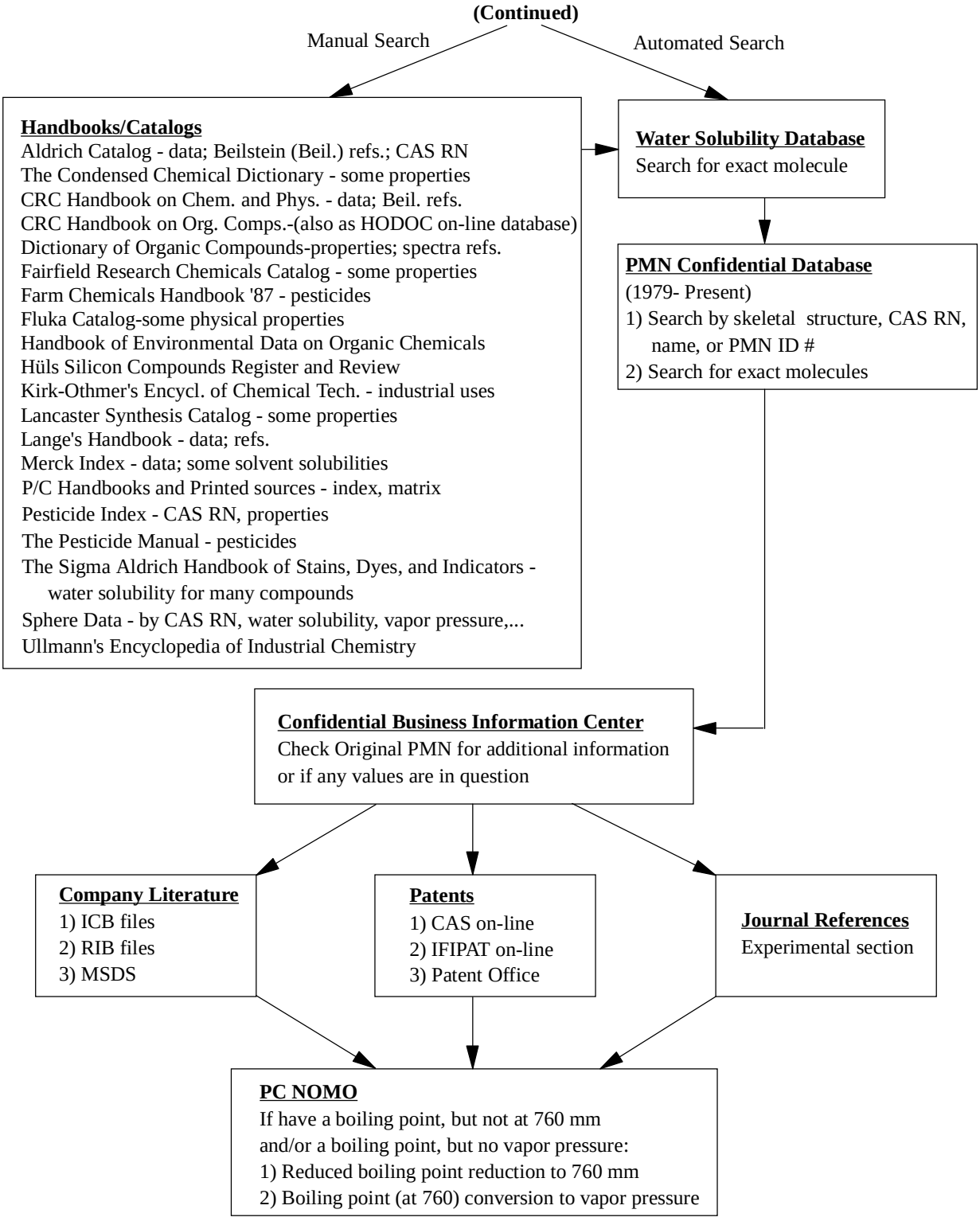


Figure 2-3. Methods for Obtaining Measured Physicochemical Property Values on Exact Structures

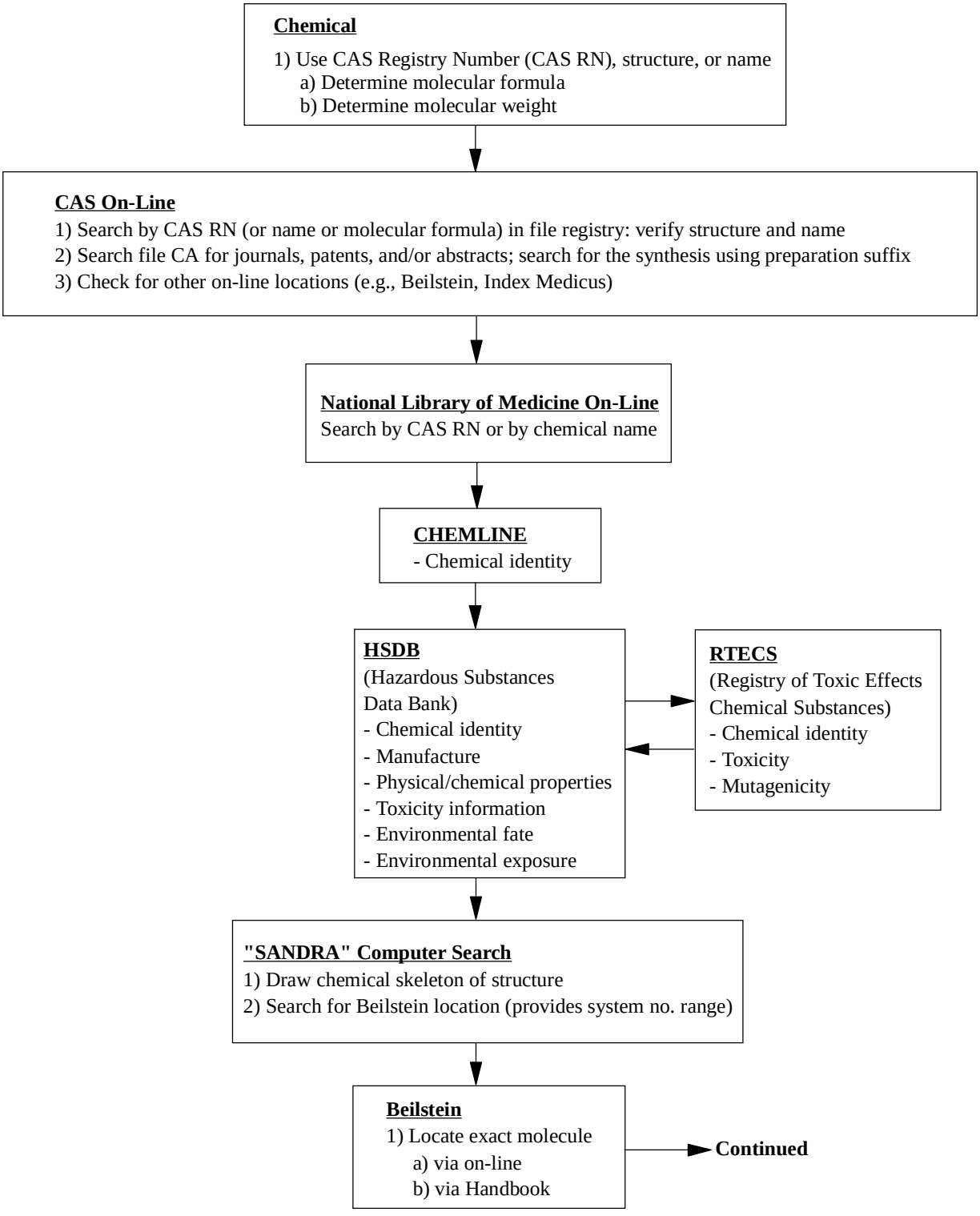
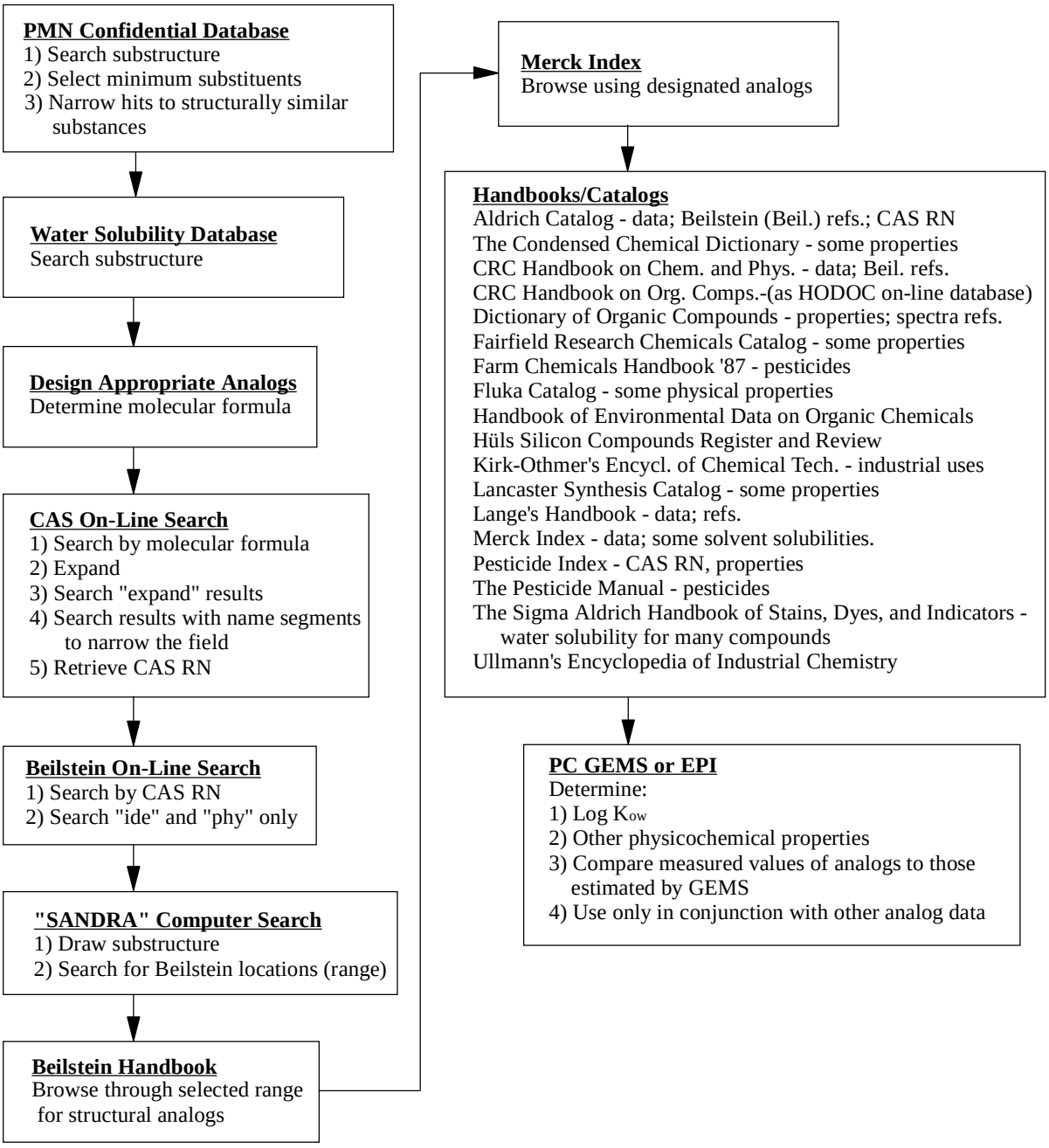


Figure 2-4. Methods for Identifying Analogs of PMN Substances and Their Physicochemical Properties



Note: Once an analog has been found, further data can be searched using Figure 2-3.

programs used for estimating property values are discussed below. Additional information on the on-line databases, reference books (e.g., Verscheuren 1983), and computer programs EPA uses to obtain property data is provided below.

2.4.2 Methods of Searching for Measured Physicochemical Properties

CAS On-line Search. The American Chemical Society's Chemical Abstracts Service (CAS) On-Line Database includes several files that can be searched for chemical information. EPA first conducts a CAS On-Line search on the Registry File by CAS Registry Number (CAS RN), chemical name, or molecular formula. The easiest search to perform uses the CAS RN, if it is available. If EPA does not have a CAS RN for the PMN substance, then an accurate chemical name or molecular formula is used for searching.

Linking a molecular formula in a search with a chemical name or name fragments can also be useful for finding the exact substance or a closely related analog. The CAS Registry File provides, among other information, the most recent CAS Registry chemical name, molecular formula, the chemical structure, other on-line sources where the substance may be found (e.g., Beilstein On-Line, discussed below), and abstracts of the literature references to that substance. This information can be used to verify any name and structural information already provided.

Information on the synthesis of a substance can be obtained by searching the Chemical Abstracts file using the CAS RN. This file provides references (usually scientific journal citations or patents) and may contain physicochemical property data (in the experimental sections of scientific papers) or potential uses.

GMELIN On-Line Database. For information on organometallic or inorganic compounds, EPA searches the Gmelin on-line database which contains the critically reviewed and evaluated data from the *Gmelin Handbook of Inorganic and Organometallic Chemistry*. Useful information includes structural data, structural images, chemical and physical properties, and bibliographic data.

National Library of Medicine (NLM) On-Line Databases. This inexpensive on-line system contains individual databases that include information on chemical identification, physicochemical properties, manufacturing processes, and uses. These databases are, therefore, useful for obtaining a variety of information on many chemicals or on analogous substances. NLM databases include the Hazardous Substance Data Bank (HSDB), the Registry of Toxic Effects of Chemical Substances (RTECS), and Chemline.

HSDB entries contain information and data on chemical identity (name, CAS RN, synonyms, molecular formula), methods of manufacture (including impurities and formulations), manufacturers, major uses, and chemical and physical properties (such as color, physical state, odor, boiling point, melting point, molecular weight, density, dissociation constant, heat of combustion, heat of vaporization, octanol/water partition coefficient, pH, solubility, spectral properties, surface tension, vapor density, and vapor pressure).

Toxicity, environmental fate, and exposure data may also be provided.

RTECS is primarily a database of toxicological data and references, including information on acute and chronic toxicity, mutagenesis, and skin and eye irritation. The database also includes chemical identity information such as chemical name, CAS RN, synonyms, molecular formula, and molecular weight.

Chemline is an interactive chemical dictionary file containing approximately one million chemical substance records. The data elements consist of CAS RN, molecular formula, synonyms, ring information, and a locator to other on-line databases that might contain further information on a compound.

Beilstein On-Line Database. The Beilstein On-Line Database is an on-line version of the Beilstein Handbook of Organic Chemistry (see below), an extensive compilation of information on organic compounds comprised of a multi-volume Home Register and five supplements. Information includes synthetic methods, measured physicochemical properties, and references. If the CAS On-Line search (described above) identifies a compound as listed in Beilstein, then a Beilstein On-Line search can be performed to provide physical data quickly, particularly if a CAS RN is known. Specific data can be selected for retrieval. References for the data are provided, but Beilstein Handbook citations are not included.

SANDRA Computer Search. SANDRA is a computer program that provides information on the general location of where a substance might be found in the Beilstein Handbook, and therefore, enables rapid searching of the handbook. If a CAS On-Line search of a substance does not list the chemical as being available from Beilstein On-Line, one can use SANDRA to draw the structure of the substance, of an analog, or of a fragment of either, and then one can search to locate the range of the structure (system number, home register page(s), and supplement volumes) within the Beilstein Handbook.

Beilstein Handbook. The Beilstein Handbook (see the discussion of Beilstein On-Line and SANDRA, above) can be searched manually using the molecular formula indexes. EPA typically uses SANDRA, as described above, to expedite the search. Physicochemical properties most commonly found in Beilstein are melting point, boiling point, density, and refractive index. Other data such as vapor pressure or water solubility are less commonly reported.

Other Handbooks/Catalogs. EPA also may search various handbooks and commercial chemical catalogs for data on PMN chemicals, although these sources are most useful if the substance in question is relatively simple or if a close structural analog is commercially marketed. Handbooks and catalogs EPA uses include the Aldrich Chemical Company Catalog Handbook of Fine Chemicals, the Merck Index, Hüls Silicon Compounds Register and Review, and the Farm Chemicals Handbook (includes data on pesticide intermediates).

Confidential PMN Database. EPA has an in-house confidential PMN database that contains chemical structures and data from chemistry reports from over 8,000 PMNs submitted since January 1993. Most

entries provide physicochemical properties that were either measured by the submitter or estimated by EPA chemists. All information in this database is regarded and treated as confidential business information (CBI), and only EPA personnel with TSCA CBI clearance have access to it.

Water Solubility Database. EPA has developed a water solubility database file that can be searched by structure. At present, this database contains over 6,000 substances with measured water solubility values (expressed as grams per liter at measured temperatures) and contains other measured physical properties for some of these substances as well. It currently contains data from the Arizona database (also known as the AQUASOL DATABASE, see Yalkowsky and Banerjee 1992), the PHYSPROP® database (available from Syracuse Research Corporation, Syracuse, NY), the Merck Index, Beilstein, and other pertinent literature and journal articles. All information is referenced within this database.

Patents. EPA periodically searches for patents that may have useful physicochemical property data, manufacturing information, and use information. The IFIPAT (IFI Patent Database) file in the STN computer network system contains records for granted U.S. chemical and chemically-related patents from 1950 to the present. Patents on some other subjects are also included. Hard copies of U.S. patents can be obtained from the Public Search Room at the U.S. Patent Office in Arlington, Virginia. The location of a patent within the Public Search Room can be found from the classification number (determined from the U.S. Patent number, which can be obtained from a CAS On-Line search).

Scientific Literature. EPA often uses articles published in scientific journals to obtain information on synthetic methods as well as physicochemical and spectral properties.

2.4.3 Methods For Estimating Physicochemical Properties From Structural Analogs

When measured physicochemical property data are unavailable for a specific PMN chemical, EPA attempts to obtain the needed data by extrapolating from measured data available for close structural analogs. EPA searches the same information sources for analogs as for specific chemicals, but the search strategy differs in that compounds that are structurally and functionally similar to the substance under consideration must either be "designed" or found using handbooks and databases.

Confidential PMN Database. EPA's confidential PMN database is searched using a skeletal drawing of the PMN substance, if the structure is not too novel or complex. More often, a fragment that contains the important structural features of the PMN substance is used in the search. The PMN database has evolved to contain numerous classes of chemicals that are structurally very similar, and all entries found that possess the same basic structural and functional features as the PMN substance can be identified and reviewed for useful information.

Designing Structural Analogs. One effective method that EPA uses for searching the enormous expanse of chemicals in the literature is to design appropriate structural analogs that may have been previously reported. By changing functional groups, alkyl chain lengths, ring sizes, or other features in a step-wise fashion, close structural analogs can be created and prioritized for searching. The molecular formula, as well as a chemical name are then determined for each analog. EPA searches CAS On-Line for these analogs, as described below, to determine whether they actually exist and, if they do, whether physicochemical property data are available.

CAS On-Line Search. Searching CAS On-Line for an analog designed for a PMN substance can be accomplished most readily by simply entering the analog's molecular formula. If a relatively small number of entries are obtained from the search, then all are retrieved and reviewed. If a large number of entries are obtained, then the search can be narrowed by using selected name segments. From this narrowed search, any entries that are suitable analogs are retrieved to obtain CAS RNs and to determine if Beilstein data are available. EPA has found that expanding on the molecular formula of pre-designed analogs is successful for finding very close structural analogs.

The Merck Index. EPA periodically uses this comprehensive, interdisciplinary encyclopedia of organic chemicals, pharmaceuticals, and biological substances to scan for new analogs or to search for designed analogs. The Merck Index is an excellent source for obtaining measured physicochemical properties for over 50,000 chemical substances.

2.4.4 Methods For Estimating Physicochemical Properties Using Computer Estimation Programs

If measured property values are unavailable or cannot be found for the PMN substance or for compounds that are structurally analogous to the PMN substance, then EPA tries to estimate the properties using appropriate estimation methods. EPA uses several computerized chemical property estimation programs, including PC-NOMOGRAPH, PC-Graphical Exposure Modeling System (PC-GEMS), Oligo 56, and Estimation Programs Interface (EPI). Values obtained from these estimation programs are scrutinized at CRSS meetings (see chapter 1) by EPA chemists, who exercise professional judgment to determine whether the values are reasonable. Some of the computer estimation programs used by EPA are discussed briefly below.

PC-NOMOGRAPH. This computer program calculates a normal boiling point (boiling point at one atmosphere pressure, 760 torr) from either a measured or estimated boiling point obtained at reduced pressure. The vapor pressure at 25°C also can be calculated from a normal or reduced boiling point. Actual boiling point-pressure nomographs (pressure-temperature alignment charts) can also be used in boiling point estimations by helping to verify the computer calculations. These charts allow the conversion of a reduced pressure boiling point to a boiling point at one atmosphere. Separate vapor pressure nomographs are available for low-boiling and high-boiling compounds.

PC-GEMS. The estimation routines in PC-GEMS represent a computerized version of well-known methods from the Handbook of Chemical Property Estimation Methods (Lyman et al. 1982). Estimation routines are available for the octanol/water partition coefficient, water solubility, soil adsorption coefficient, boiling point, vapor pressure, melting point, and Henry's Law constant.

EPI. EPI, developed by Syracuse Research Corporation, Syracuse, New York, integrates several computer programs. Programs are included for estimating: octanol-water partition coefficient; Henry's Law constant; soil adsorption coefficient; rate of hydrolysis (for substances with a hydrolyzable group); atmospheric oxidation (including half-lives for reaction with hydroxyl radicals and ozone); probability of biodegradation (based on several different models); and, removal during wastewater treatment.

OLIGO 56. Oligo 56, developed by the Mitre Corporation, McLean, Virginia, is used to estimate molecular weight and functional group equivalent weight of polymers.

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Chapter 3

POLLUTION PREVENTION AND PREMANUFACTURE NOTIFICATIONS

3.1 Introduction: Pollution Prevention

The preceding chapters describe the evolution of EPA's PMN Program and the approaches that EPA uses to characterize and understand the risks new chemical substances may pose to human health and the environment. Characterized risks are then balanced against the expected economic and societal benefits of a new chemical. TSCA empowers EPA to regulate risks associated with the manufacture, use, and disposal of a new chemical substance. Traditionally, however, the focus of the PMN Program has been on the toxicity of a new chemical substance itself and the risks associated with its use and disposal, with less emphasis on the risks from the pollution created as a result of the manufacture or use of the new substance.

Although TSCA and the other environmental statutes have had a positive impact in protecting human health and the environment, the United States still produces millions of tons of pollution annually and spends tens of billions of dollars per year controlling this pollution. EPA realizes that there may still be significant opportunities for industry to reduce or prevent pollution at the source through cost-effective changes in production, operation, use of raw materials, or chemical design. Such changes have the potential to offer industry substantial savings in reduced costs for raw material, pollution control, and liability as well as to help protect the environment and reduce risks to the environment and human health. In addition, EPA realizes that the costs of complying with regulations imposed under existing statutes are becoming prohibitive for the chemical industry and the consuming public. A more preventative way of solving the problem of pollution is needed.

In 1990, the EPA embarked on a new approach, termed "pollution prevention," to reduce the releases of toxic wastes into the environment through eliminating or minimizing creation of such wastes. At approximately the same time, the Pollution Prevention Act (PPA) was passed by Congress (PPA 1990). This act articulates the interest of Congress to have both the EPA and industry apply pollution prevention principles to their efforts to reduce toxic waste generation and subsequent discharge. The underlying philosophy of pollution prevention is fundamentally simple: the creation of pollution must be avoided whenever and wherever possible. The pollution prevention paradigm is very much like the preventative medicine paradigm. The goal of preventative medicine is to prevent illnesses from occurring rather than to find cures or treatments after illnesses have occurred, whereas the goal of pollution prevention is to prevent the creation of pollution, so as not to have to deal with the health and ecological damage it causes. The basic pollution prevention strategy, therefore, is to avoid generating waste in the first place.

Any practice that reduces the amount of any hazardous substance entering any waste stream or otherwise released into the environment (including fugitive emissions) prior to recycling (except in-process recycling), treatment or disposal is considered pollution prevention.

The PPA identifies several general approaches to preventing pollution and establishes a pollution prevention hierarchy as a national policy. The approaches, starting with the most important, are:

- pollution should be ***prevented at the source*** wherever feasible;

- pollution that cannot be prevented at the source should be ***reduced at the source*** wherever feasible;

- pollution that cannot be prevented or reduced at the source should be ***recycled in an environmentally safe manner*** wherever feasible;

- pollution that cannot be recycled should be ***treated in an environmentally safe manner*** whenever feasible;

- ***disposal or other release into the environment should be employed only as a last resort*** and should be conducted in an environmentally safe manner.

Pollution prevention has become the preferred method in the hierarchy of environmental practices and the foremost priority of the EPA (Browner 1993).

Although recycling, treatment, and disposal are clearly important components of pollution control, they are *not* included in the definition of pollution prevention because they do not represent preventative approaches to controlling pollution.

The PPA also provides the framework for creative thought and collaborations on the part of the chemical industry and the EPA to reduce pollution and exposure to toxic substances. Newer EPA programs (e.g., OPPT's Design for the Environment Program, Green Chemistry Program, and Pollution Prevention Division) devoted to pollution prevention have evolved in recent years, and many of EPA's existing programs, including the PMN Program (see below), have been or are being analyzed to determine how pollution prevention can be incorporated. In addition, many collaborations and initiatives between EPA, the chemical industry, and academia are identifying and implementing new ways of preventing pollution.

EPA's Design for the Environment (DfE) Program, for example, is a voluntary initiative that forges partnerships with stakeholder groups in an effort to incorporate environmental considerations into the decision-making of the chemical industry and to build incentives for continuous environmental improvement. EPA's 33/50 Program is another voluntary program under which EPA and the chemical industry collaborate to reduce the environmental releases of certain substances on the Toxics Release Inventory.[19]

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19. The Toxics Release (TRI) Inventory is a publicly-available compilation of chemical releases updated annually under the authority of Section 313 of the Emergency Planning and Community Right to Know Act (EPCRA 1986). More information on TRI is available from TRI User Support (phone: 202-260-1531).

These and other EPA initiatives aimed at pollution prevention have been very successful in pollution prevention and in establishing collaborations between the chemical industry, EPA, other federal agencies, and academic institutions.

A very recent EPA initiative is Green Chemistry. Green Chemistry strives to encourage the development of safer commercial substances and non-polluting commercial syntheses. Traditionally, during the commercial development of chemical substances, chemists concentrate on those chemicals that can be synthesized in the highest yield at the lowest direct cost to satisfy particular intended uses. Generally, chemists give little or no consideration to the inherent toxicity or hazardous nature of a desired chemical substance, or to alternative syntheses that neither use toxic reagents or solvents, nor produce toxic byproducts. This traditional approach to chemical design creates pollution and is clearly incompatible with achieving the pollution prevention needs of society and the goals of the Pollution Prevention Act.

EPA's Green Chemistry initiative represents a more rational approach to the design of chemicals and syntheses. Green Chemistry is based on the premise that the most desirable and efficient way of preventing pollution is to: 1) intentionally design chemicals such that they will have minimal or no toxicity, while maintaining their commercial efficacy with respect to intended use; and, 2) intentionally design synthetic pathways such that they neither utilize toxic reagents or solvents, nor produce toxic byproducts. Through the Green Chemistry initiative, the federal government, universities, and the chemical industry are forming collegial relationships (Anastas and Farris 1994; Anastas and Williamson 1996; DeVito and Garrett 1996), and the Agency hopes that these relationships will lead to the design and commercialization of less toxic chemical substances and less polluting syntheses. In fact, President Clinton has made Green Chemistry one of the highest priorities of the EPA (Clinton 1995).

3.2 Pollution Prevention Initiatives within EPA's PMN Program

Because the PMN Program characterizes the risks new chemical substances may pose to human health and the environment before they enter commerce and takes necessary action to prevent or control such risks, the PMN Program may be considered a pollution prevention program. In addition to traditional PMN review, however, the PMN Program offers other approaches to preventing pollution. These are not regulatory, but rather voluntary or collaborative on the part of EPA and the chemical industry. This section discusses two relatively recent pollution prevention initiatives that have been incorporated into the review of PMNs.

3.2.1 Optional Pollution Prevention Information (page 11 of the PMN form)

In 1991 the PMN form was modified to include a section containing "optional pollution prevention information" (page 11 of the PMN form). This was the first direct indication that pollution prevention had become an important component of PMN review. On this page, the submitter may provide information regarding its efforts to reduce or minimize pollution associated

with activities surrounding manufacturing, processing, use, and disposal of the PMN substance. PMN submitters should describe net benefits such as: 1) the extent to which the new chemical substance may be a substitute for an existing substance that poses a greater overall risk to human health or the environment; 2) a reduction in the volume of the new substance manufactured compared to a competitive existing substance, if the new and existing substances are equally toxic but more of the existing substance is required for commercial use; 3) elimination or reduction in the amount of waste materials through source prevention, source reduction, recycling, or other means; 4) low toxicity of the PMN substance; and 5) a reduction in human exposure to the PMN substance and/or a reduction in environmental release.

It is up to the discretion of the submitter to provide EPA with this information. All pollution prevention information provided in this section of the PMN is considered by EPA during PMN review, and EPA strongly encourages PMN submitters to incorporate such information in their PMNs as it helps the Agency to balance the benefits of a PMN substance against any risks it poses. This information is, of course, considered confidential by EPA if so indicated by the submitter.

Most current PMN submissions contain some optional pollution prevention information. However, most of the information currently provided by submitters deals with the benefits of the PMN substance with respect to its intended use, and *little* information is provided with respect to pollution prevention in the manufacture of the substance, even when such benefits exist. PMN submitters probably know (or should at least be able to discern) whether the manufacturing process for their PMN substance offers pollution prevention advantages over an alternative process used for a similar substance. Although ICB chemists are sometimes able to identify the advantages of such syntheses during routine PMN review, PMN submitters should compare their manufacturing processes to known alternative processes for making the same substance (or similar substances) and indicate on page 11 of the PMN form any advantages that their processes may have.

3.2.2 Synthetic Method Assessment for Reduction Techniques (SMART) Review

Simultaneous with the traditional chemistry review of PMN substances (discussed in Chapter 1), ICB chemists now perform a pollution prevention review known as the Synthetic Method Assessment for Reduction Techniques (SMART) Review for PMN substances (Farris et al. 1994). The SMART review is a non-regulatory review designed to identify PMN substances (or related substances) for which individual companies may be able to prevent pollution in an economically feasible manner. In this review ICB chemists attempt to identify potential pollution prevention opportunities based on information in the PMN and reference sources. Pollution prevention opportunities may include: using an alternative reaction pathway that is less polluting; switching to a less toxic solvent; recycling of solvents or unreacted starting reagents; or, recovery of toxic byproducts, unreacted starting

reagents, or PMN substance lost to waste streams.

The SMART review process is described briefly here; a detailed description is also available (Farris et al. 1994). The SMART review is performed as follows. During the regular chemistry review of a PMN, the chemist will also screen the PMN to determine if the submission meets the criteria for a SMART review. These criteria include: the notice must be a non-exempt Premanufacture Notice; the PMN substance must be a Class 1 substance (see Appendix, section A.3.3); the third year production volume must be greater than 10,000 kg/year; and manufacture of the PMN substance must take place within the United States. These criteria are merely guidelines; a PMN submission that does not meet these criteria may still undergo a SMART review. For example, PMN submissions for which pollution prevention opportunities are readily apparent will most likely undergo a SMART review in any case.

Each PMN submission selected for SMART review is first subjected to a preliminary assessment. The objective of the preliminary assessment is to determine the source, identity, and quantity of each waste component associated with the manufacture of the PMN substance. Sufficient information needs to be provided in PMN submissions in order for a preliminary review to be completed (much of this information is required). General information that is necessary for preliminary reviews includes: chemical name; chemical structure; process description; identity of impurities; and production volume.

Chemists also assess the types of wastes (i.e., extremely toxic, hazardous, potentially hazardous, or innocuous) produced by (or during) the manufacture or processing of the PMN substance, as well as the sources and quantities of such wastes (Farris et al. 1994). The classification of waste in terms of relative toxicity is based upon several Agency lists. ICB chemists estimate the percentages of waste substances relative to the production volume of the PMN substance. These percentages are compared to trigger levels (the quantity of a given type of waste relative to the quantity of the PMN substance produced) established by ICB chemists, to ascertain whether a particular waste component from a given manufacturing process is present in an excessive quantity. Different sets of trigger levels are used for hazardous wastes and for potentially hazardous wastes.

The outcome of the preliminary SMART assessment determines whether a detailed assessment is warranted. If the quantities of the hazardous wastes produced from the manufacture of a PMN substance do not exceed their trigger levels, ICB chemists do no further assessment. In cases where the hazardous wastes exceed their trigger levels, ICB chemists perform a more detailed assessment. The main purpose of the detailed assessment is to determine the fate of hazardous wastes. In cases where hazardous wastes are treated or will enter the environment from waste streams, stack emissions, or other sources, ICB chemists try to identify opportunities for preventing or reducing these wastes. These opportunities may include: (1) using a less toxic solvent (if the hazardous waste is a solvent used in the manufacture of a PMN substance); (2) using an alternative synthesis that utilizes

fewer or no toxic reagents or solvents, or does not generate toxic byproducts or wastes; and, (3) in cases where these two opportunities are not feasible, recycling of the waste materials. If as a result of the detailed assessment ICB chemists identify possible pollution prevention opportunities, the ICB chemist performing the assessment will inform the PMN submitter of the findings (either orally or in writing).

The purpose of such communication is to solicit the submitter's voluntary consideration to study and perhaps incorporate the pollution prevention opportunities identified by ICB. To date, several PMN submitters have responded that they will attempt to incorporate Agency suggestions into their manufacturing processes, and will inform the Agency of their success or failure. In some instances, PMN submitters have replied that the pollution prevention opportunities identified by ICB chemists may not be feasible for reasons that are apparent only to the submitter. For example, an alternative synthesis identified by an ICB chemist may already have been studied by the submitter prior to PMN submission and found to be unsuccessful for commercial synthesis of the PMN substance.

Feedback from PMN submitters is very important to ICB chemists, because PMN submitters are generally in a better position to evaluate the practicality of incorporating changes into their manufacturing processes than are ICB chemists. The Agency appreciates the additional insight from such feedback that may not be available from PMNs or other sources. Such non-regulatory communication stimulates creative collaboration between PMN submitters and the Agency in identifying feasible opportunities for preventing pollution.

3.3 Considerations in Implementing Pollution Prevention Practices Prior to Submission of PMN Substances

Pollution prevention is an overarching goal of the Agency, particularly OPPT. This chapter has briefly described two EPA pollution prevention initiatives (the Optional Pollution Prevention section of the PMN form, and the SMART review) that were designed specifically for incorporating pollution prevention into PMN review. EPA is currently pursuing additional initiatives such as: funding universities to develop new, environmentally-benign synthetic strategies for the manufacture of commercial substances; funding universities to develop synthesis software that can assist in the identification of environmentally-benign syntheses; and the Green Chemistry Challenge, which encourages, identifies, and awards innovative chemistry achievements in preventing pollution. Although these additional initiatives are not formally part of PMN review, the Agency expects they will eventually influence PMN submissions. Information on these broader pollution prevention projects may be obtained from the TSCA Assistance Information Service and the Pollution Prevention Information Clearinghouse. (See Table A-1 for addresses and phone numbers.)

The EPA realizes that PMN submitters are faced with many challenges in developing substances that must not only satisfy customer needs and remain competitive with other products, but must also comply with existing regulations.

Some PMN submitters may view EPA's recent emphasis on pollution prevention as an additional burden to product development. It is not the intent of EPA to stifle or impede the creativity of chemical producers in the development of chemical products by encouraging pollution prevention practices. In fact, the pollution prevention initiatives described in the preceding paragraphs are intended to help PMN submitters design products that are useful and safe for human health and the environment, and are manufactured safely. As safer substances and environmentally friendly syntheses replace existing toxic chemical substances and polluting syntheses, respectively, fewer regulations will be needed.

In recent years the EPA has noticed that PMN submitters are beginning to incorporate pollution prevention practices into the design and synthesis of new chemical substances. Specific examples cannot be provided here due to the confidentially of the submissions. Generally, some PMN submitters are using available toxicity data on related existing chemicals as a basis for designing new chemicals that are less toxic but equally efficacious for commercial use. In such instances PMN submitters often obtain data on the structure-activity (toxicity) relationships and biochemical (mechanistic) bases of toxicity of existing related substances, and from these data infer structural modifications that reduce toxicity without affecting use efficacy (see Chapter 2 in DeVito and Garrett 1996). In addition, some PMN submitters are beginning to develop and use syntheses that require fewer toxic reagents or solvents, or do not produce toxic byproducts. More detailed discussions of approaches that can be used for the design of safer chemicals and the design of environmentally friendly syntheses are available (Devito and Garrett 1996; Anastas and Farris 1994; Anastas and Williamson 1996).

PMN submitters may find the following considerations helpful in implementing pollution practices prior to submission of PMN substances to EPA.

- ***Consider any toxicity or environmental hazard potential of the chemical product.*** Decide if the chemical product must be made, or if an analogous substance (or use substitute) that is known or likely to have less hazard potential can be used instead. Gather any available toxicity data on related substances and, if possible, use the data to design a new substance that is less toxic.

- ***Consider potential savings by thinking of environmentally safer products or reaction pathways during product development.*** Keep in mind that regulations generally have become stricter over time and may become even more strict in the future. For example, certain methods of disposal and treatment of hazardous wastes may one day be outlawed or become prohibitively costly. On-site disposal or treatment may not be practical or economically feasible. It is best to consider the long-term cost of making a PMN substance.

- ***Rethink your approach to organic chemistry and the synthetic reactions traditionally used to construct chemical substances.*** Do not consider reaction yield only; put more emphasis on alternative, environmentally-friendly reaction pathways. When selecting a reaction, consider the following:

  - what reactions can be used to make the PMN substance ?

  - why has a particular reaction been selected ?

  - is it environmentally friendly ?

  - is the reaction cost-effective in the long run ?

  - how feasible is commercial scale-up of the reaction ?

  - what will disposal of the PMN substance and associated substances cost ?

  - what are the liability costs of waste treatment on-site ?

  - what are the liability costs from potential release of the PMN substance and associated substances ?

  - what are the costs of storing hazardous wastes on site ?

These considerations help to establish a framework that can be used to incorporate pollution prevention strategies in the design and synthesis of new chemical substances, and ultimately prevent many of the environmental and human health problems that have occurred in the past as a result of the manufacture and use of chemicals.

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List of Selected Readings for Chapter 3

For Additional Information on Pollution Prevention and EPA Pollution Prevention Initiatives see:

Chemical and Engineering News, September 5, 1994 issue.

Breen JJ, Dellarco M. 1992. Pollution Prevention: The New Environmental Ethic. In: Pollution Prevention in Industrial Processes; the Role of Process Analytic Chemistry. Breen JJ, Dellarco MJ, eds. ACS Symposium Series 508, American Chemical Society, Washington, DC, 1992, pp 2-12.

Ford AM, Kimerle RA, Werner AF, Beaver ER, Keffer CW. 1992. Industrial Approaches to Pollution Prevention. In: Pollution Prevention in Industrial Processes; the Role of Process Analytic Chemistry. Breen JJ, Dellarco MJ, eds. ACS Symposium Series 508, American Chemical Society, Washington, DC, 1992, pp 13-20.

Appendix

THE TOXIC SUBSTANCES CONTROL ACT: HISTORY AND IMPLEMENTATION

A.1 Introduction

The Toxic Substances Control Act (TSCA 1976) was the result of six years of negotiating and compromising among the House and Senate, the President's Council on Environmental Quality (CEQ), the Environmental Protection Agency (EPA), the chemical industry, the Commerce Department, and other interested parties. TSCA expanded existing federal authority to regulate the chemical industry by giving EPA the authority to require testing, as well as to regulate the production, use, and disposal of new and existing chemicals. Because it was one of the most important pieces of legislation ever passed to regulate the chemical industry, its provisions were hotly debated by all parties. The following is a brief history of the events that led to the enactment of TSCA.

The CEQ was established by the 1969 National Environmental Policy Act as an agency within the Executive Office of the President. This occurred shortly before the establishment of the EPA in December, 1970. Soon after its inception, CEQ began a study of the potential for metals and synthetic organic chemicals to endanger human health and the environment. At that time, the government had no power to require that chemicals, with the exception of those used as pesticides, drugs, and food additives, be tested before they were put into commerce.

By late 1970, the CEQ had produced a draft report of its study. The publication of this report was delayed until April, 1971, however, so that the CEQ staff could draft the Toxic Substances Control Act of 1971, the first version of the present TSCA. The CEQ report reached the following major conclusions:

1. Toxic Substances are Entering the Environment

> "U.S. consumption of metals with known toxic effects has increased greatly in the last 20 years. ... Similarly, use of synthetic organic chemicals is growing rapidly. ... Although many of these substances are not toxic, the sheer number of them, their increasing diversity and use, and the environmental problems already encountered from some indicate the existence of a problem." (CEQ 1971)

2. These Substances can have Severe Effects

> "The environmental effects of most of the substances discussed in this report are not well understood. Testing has largely been confined to their acute effects, and knowledge of the chronic, long-term effects, such as genetic mutation, is inadequate. Although far from complete, available data indicate the potential

or actual danger of a number of these substances." (CEQ 1971)

3. Existing Legal Authorities are Inadequate

"Government controls over the introduction of toxic substances into the environment are of two types. The first is control over the initial production of a substance and its distribution. ... Although this control technique can be very effective, current authorities cover only a small portion of the total number of potentially toxic substances and do not deal with all uses of a substance which may produce toxic effects." (CEQ 1971)

"The second type of control is media oriented and thus is directed at air and water pollution from various sources. ... Most toxic substances are not exclusively air or water pollutants but can be found in varying quantities in air, water, soil, food, and industrial and consumer products. The multiplicity of ways by which man can be exposed to these substances makes it difficult for the media-oriented authorities to consider the *total* exposure of an individual to a given substance, a consideration necessary for the establishment of adequate environmental standards. Also, in the past no agency has considered itself completely responsible for all such substances in all media." (CEQ 1971)

4. New Legal Authority is Required

"The Council's study indicates the high-priority need for a program of testing and control of toxic substances. ... We should no longer be limited to repairing damage after it has been done; nor should we continue to allow the entire population or the entire environment to be used as a laboratory." (CEQ 1971)

The CEQ report concluded that there were essentially no laws regulating the manufacture, importation, or use of toxic chemical substances in the United States and, therefore, that regulation was critical. Hence, the findings in this report became the basis for TSCA. By early December of 1970, the CEQ was ready to circulate a draft bill to other government agencies for comment. Among its provisions, this bill required manufacturers to notify the EPA at least 90 days before manufacture and distribution of a new chemical substance, gave EPA authority to require testing of the new chemical before manufacture could begin, and gave EPA the power to ban or restrict chemicals that posed substantial risks to human health or the environment.

The issues of premanufacture notification and testing were of concern to the Department of Commerce and the Office of Management and Budget, and were raised to President Nixon for a decision in early February, 1971. The President decided that the premanufacture testing provision should be removed from the bill. Finally, the bill was sent to Congress on February 11, 1971, by EPA Administrator William Ruckelshaus.

The U.S. House of Representatives and Senate passed separate versions of the bill during 1972. Among other differences, the Senate version had considerably more stringent premanufacture controls over chemical substances than the House version, requiring EPA to expressly approve new chemicals. The chemical industry generally supported the much weaker House version.

Early versions of the bill died in the Senate-House Conference Committee during the 92nd and 93rd Congresses. During this time, President Ford's administration first supported and later opposed the premarket provisions of TSCA. In the end, it was the Congressional and chemical companies' Washington staffs who hammered out the compromise bill that was finally passed.

In 1976, Congress was still agonizing over the bill. As fate would have it, Kepone, an insecticide for home use that was manufactured in a dusty refurbished gas station in Hopewell, Virginia, caused an outbreak of severe neurological disorders in dozens of workers. Virginia's Governor closed the nearby James River to commercial and sport fishing. CBS's "60 Minutes" segment on Kepone gave the chemical national media exposure and increased public pressure for the passage of TSCA. There was also considerable public pressure over the risks from polychlorinated biphenyls (PCBs), fluorocarbons, and vinyl chloride.

Finally, the Senate-House Conference Committee reached agreement on the provisions of TSCA in the fall of 1976, just before the Presidential election. The lobbying efforts on all sides had been intense. Chemical industry representatives expressed afterwards that they had agreed to premanufacture notification (which remained in the final bill) in exchange for reduced reporting provisions.

During September, 1976, both the Senate and the House of Representatives finally approved the bill, and sent it to President Ford for his signature. The President's support for the bill was in doubt, because Ford had stated his opposition to major new federal spending programs, especially those that would impose new regulations on industry. The wide-ranging support for the bill, however, effectively precluded his veto. President Ford signed TSCA into law just hours before the bill would have died from a pocket veto. The next day, the President released a statement in support of the bill.

TSCA, as finally passed, covers all organic and inorganic chemical substances and mixtures, both synthetic and naturally-occurring, with the exception of food, food additives, drugs, cosmetics, nuclear materials, tobacco, and pesticides, which are all covered by other legislation. TSCA provides the Agency with authority to:

- require that manufacturers and importers submit information on all new chemical substances prior to manufacture for commercial purposes;

- require that manufacturers and processors collect, maintain, and possibly submit information on chemical substances; and

- regulate chemical substances (both new and existing) that are expected to present or are presenting unreasonable risks to health and the environment.

The provisions for premanufacture review of new chemical substances[20] are contained in section 5 of TSCA. Congress intended section 5 "to provide the administrator with an opportunity to review and evaluate information with respect to the substance to determine if manufacture, processing, distribution in commerce, use or disposal should be limited, delayed or prohibited because data is [sic] insufficient to evaluate the health and environmental effects or because the substance or the new use presents or will present an unreasonable risk of injury to health or the environment." Congress also realized that "the most desirable time to determine the health and environmental effects of the 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 action in terms of loss of jobs and capital investment is minimized." (U.S. Congress 1976)

Congress charged EPA with the responsibility of preventing chemicals from presenting unreasonable risks to health and the environment: the Act specifies that the risks of using a substance must be compared with the benefits derived from its use. Further, the Agency was directed to implement TSCA in such a manner as not to "unduly impede technological innovation." The objective of creating a balance between preventing unreasonable risk and not hampering innovation has been at the heart of the Agency's premanufacture review program since its beginning.

A.2 The Premanufacture Provisions of TSCA

The Toxic Substances Control Act provides EPA with the authority to identify and control the use of new and existing chemical substances in order to protect human health and the environment. Under section 5 of TSCA, titled Manufacturing and Processing Notices, the EPA is given the authority to regulate new chemical substances prior to their manufacture or import[21] for commercial purposes. The text below discusses the provisions of TSCA that are relevant to the premanufacture authority. First, the terms "chemical substance" and "new" are defined, then section 5 is summarized. Finally, other sections of TSCA that are tangentially relevant to premanufacture review are briefly mentioned.

To date, Congress has not modified the basic provisions of TSCA as presented

20. The term "new chemical substance" is defined in section 3 of TSCA as any chemical substance not included in the Chemical Substance Inventory that is compiled and published under section 8(b).

21. TSCA applies both to substances that are manufactured within the U.S. and to substances imported into the U.S. In the following discussion, the words manufacture or manufacturer are meant to include import or importer.

below. The Agency, in its implementation of TSCA, has promulgated a variety of regulations. Summaries of EPA's regulations are found in Section 1.5, below.

A.2.1 Definition of "Chemical Substance" Under TSCA

The term "chemical substance" is defined in section 3 of TSCA as:

> "any organic or inorganic substance of a particular molecular identity, including (*i*) any combination of such substances occurring in whole or in part as a result of a chemical reaction or occurring in nature, and (*ii*) any element or uncombined radical."

This definition does *not* include:

> "(*i*) any mixture, (*ii*) any pesticide (as defined by the Federal Insecticide, Fungicide, and Rodenticide Act) when manufactured, processed, or distributed in commerce for use as a pesticide, (*iii*) tobacco or any tobacco product, (*iv*) any source material, special nuclear material, or byproduct material (as...defined in the Atomic Energy Act...), (*v*) any article[22]..., and (*vi*) any food, food additive, drug, cosmetic, or device (as...defined in section 201 of the Federal Food, Drug, and Cosmetic Act) when manufactured, processed, or distributed in commerce for use as a food, food additive, drug, cosmetic, or device."

A.2.2 Definition of "New" Chemical Substance

Section 8(b) of TSCA requires the EPA to identify, compile, keep current, and publish the TSCA Inventory, a list of chemical substances manufactured, imported, or processed for commercial purposes in the United States. The Inventory defines what chemical substances are "existing" in U.S. commerce for TSCA purposes. The Inventory includes not only chemical substances that have been manufactured or imported since January 1, 1975 for "distribution in commerce" but also substances manufactured as intermediates for use by the manufacturer. Substances that are subject to TSCA but are not on the Inventory are considered "new" and are subject to premanufacture notification under section 5 of TSCA. Further discussion of the Inventory and EPA's Inventory reporting regulations is found in the final section of this chapter (A.3.9).

A.2.3 Section 5: Manufacturing and Processing Notices

One of the primary provisions of TSCA is the requirement in section 5 that

22. The Agency has clarified its interpretation of "article" in USEPA 1977c.

manufacturers or importers of new chemicals notify the Agency 90 days before manufacturing a new chemical substance. EPA uses this time to determine if an unreasonable risk may or will be presented by any aspect of the new chemical's lifecycle: its manufacture, processing, distribution in commerce, use, or disposal. If the chemical may or will present an unreasonable risk, EPA has the authority to limit or ban it, thereby reducing the potential for adverse effects to human health and the environment.

Unlike the Federal Food, Drug and Cosmetic Act (FFDCA 1982) administered by the Food and Drug Administration (FDA), which requires drug manufacturers to submit a plethora of test data for a new substance, section 5 of TSCA does not require PMN submitters to test their chemical substances before PMN submission. In short, the FFDCA is a registration statute, whereas TSCA is a weaker notification statute. Frequently, little or no data on health or environmental effects are available for PMN substances, yet EPA must decide within 90 days if such chemical substances are likely to present hazards to human health or the environment. Because EPA is usually operating in the absence of data, section 5(e) of TSCA gives EPA the authority to regulate a new chemical substance if EPA concludes that a chemical substance *may* present an unreasonable risk. If there is sufficient information to make the determination that the substance *will* present an unreasonable risk, EPA has the authority to regulate a new chemical substance under section 5(f).

The nine subsections of section 5 are as follows:

Subsection 5(a). In general. Manufacturers must submit a PMN to the Agency at least 90 days before manufacturing a chemical substance that is not either listed on the TSCA Chemical Substance Inventory or being used for a significant new use. This section also gives EPA authority to promulgate rules establishing significant new uses for certain chemicals if the new uses would increase exposure.

Subsection 5(b). Submission of Test Data. This section relates the section 4 requirements for test data to the requirements for PMN notices and Significant New Use Notices (SNUNs). Any test data required by a section 4 rule must be submitted along with a PMN or SNUN. If a section 4(c) exemption has been granted pending submission of test data, the submitter of a PMN or SNUN substance may not commence manufacture until at least 90 days following submission of the section 4 test data to EPA. In section 5(b)(4), the EPA is given authority to promulgate rules listing chemicals and their respective uses (or other activities) that present or may present an unreasonable risk. If a PMN or SNUN is required for a chemical on this 5(b)(4) list, the PMN or SNUN must contain data to show that the proposed uses will not present an unreasonable risk to health or the environment. Data submitted to EPA under section 5(b) must be made available to the public, subject to the limitations of section 14 (Disclosure of Data, under which EPA must protect certain confidential business information).

Subsection 5(c). Extension of Notice Period. The Administrator may extend the review period for a PMN, a SNUN, or test data by up to 90 additional days if the Administrator has good cause to do so. The extension and the reasoning behind it must be published in the Federal Register (subject to section 14 constraints).

Subsection 5(d). Content of Notice; Publications in the Federal Register. This subsection lists the information to be included in a PMN: (1) information listed in TSCA section 8(a)(2)[23] that is known to or reasonably ascertainable by the submitter; (2) any test data in the possession or control of the submitter that are related to effects on health or the environment; and (3) a description of any other reasonably ascertainable data concerning health or environmental effects. Under section 5(d)(2), EPA is required to publish periodic notices in the Federal Register (FR) subject to the limitations of section 14. Within five working days following receipt of a new PMN, SNUN, or test data, EPA must publish the following information: chemical identity (or generic name), use, and a description of test data received. Monthly, EPA must publish in the FR a list of chemical notices received since the last FR notice, and a list of notices for which the review period has expired since the last notice.

Subsection 5(e). Regulation Pending Development of Information. Under section 5(e), if the Agency determines (1) that the information submitted for a chemical substance is insufficient for assessment of health or environmental effects and that the chemical substance *may* present an unreasonable risk or (2) that the chemical substance *may* result in substantial human or environmental exposure, it may issue an order that limits or bans manufacture, processing, distribution in commerce, use, or disposal of the substance. The order cannot take effect if the Agency does not provide affected parties with 45 days notice prior to the PMN or SNUN expiration date, or if the affected parties object to the order. If objections are filed and the Agency has made the required determination, the Agency is required to file for an injunction in the U.S. District Court. The injunction is given if the court determines that the information provided with the notice is insufficient and that continuing to allow the manufacture or processing of the chemical would present unreasonable risks to human health and the environment. The court has the right to extend the notification period if it will expire before the injunction proceedings are

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23. The items required by TSCA are: the common or trade name, chemical identity, and molecular structure of each chemical substance; the categories or proposed categories of use for such substance; estimates of the total amount of the substance that is manufactured and used, and estimates of the amount that will be manufactured and used, broken out by category of use; a description of the byproducts associated with the substance; the number of individuals exposed, the number that is estimated to be exposed, and the exposure duration; and the manner by which the substance will be disposed. Note that subparagraph 8(a)(2)(e) requires health and safety data, but these data are not under the "reasonably ascertainable" standard.

concluded. The injunction is dissolved once the needed data have been submitted to and evaluated by the Agency.

Subsection 5(f). Protection Against Unreasonable Risks. Section 5(f) gives EPA the authority to limit or ban a PMN or SNUN chemical substance if the use of the substance will present an unreasonable risk before the time that the Agency could promulgate a standard rule under section 6 to protect against such risk. The Agency may issue a proposed rule under section 6(a) that is effective immediately upon its publication in the Federal Register to limit manufacture or use. Alternatively, the Agency may issue a proposed section 5(f) order to prohibit manufacture or use, or may seek a court injunction to prohibit manufacture or use.

Subsection 5(g). Statement of Reasons for Not Taking Action. If EPA does not take regulatory action under sections 5, 6, or 7 against a chemical for which SNUN or section 4 test data are submitted, it then must publish in the Federal Register the reasons explaining why it did not do so.

Subsection 5(h). Exemptions. The Agency may grant exemptions from some or all of the requirements for PMN, SNUN, and test data submissions. Exemptions may be granted from: (1) a PMN or SNUN for a chemical used only for test marketing purposes if there will be no unreasonable risk; (2) test data requirements for a substance that is identical to the one on which data have been submitted under section 5(b)(2); (3) all or part of section 5 requirements for a substance that will not present an unreasonable risk to human health or the environment; and (4) PMN, SNUN, or test data requirements for a substance that is produced temporarily as the result of a chemical reaction used to produce another chemical and to which there will be no human or environmental exposure.

Further, a substance used for scientific experimentation, research, and analysis is exempt from PMN, SNUN, and test data requirements, provided that all parties involved are informed of the risks associated with the particular chemical.

Subsection 5(i). Definition. The terms "manufacturing" and "processing" are defined as manufacturing and processing for commercial purposes.

A.2.4 Other Sections of TSCA Related to Section 5

A.2.4.1 Section 4. Testing of Chemical Substances and Mixtures. The EPA, under TSCA section 4, has the authority to promulgate rules to require manufacturers and processors to test certain new or existing substances for their effects on human health and the environment. This section also establishes the Interagency Testing Committee to assist EPA in prioritizing the chemicals to be tested.

A.2.4.2 Section 6. Regulation of Hazardous Chemical Substances and Mixtures. The EPA has the authority under TSCA section 6, to promulgate rules that regulate the manufacture, processing, distribution, use, or disposal of an existing chemical substance, if it determines that these activities pose an unreasonable risk to human health or the environment. Section 6(e) requires that PCBs be regulated

immediately, and that their manufacture and use be phased out over time.

A.2.4.3 Section 7. Imminent Hazards. EPA may commence a civil action in a U.S. District Court to seize an imminently hazardous chemical substance or mixture, or for relief against its manufacturer or user. An imminently hazardous chemical substance or mixture is one that will present an unreasonable risk of serious or widespread injury to health and the environment before a final section 6 rule could protect against the risk.

A.2.4.4 Section 8. Reporting and Retention of Information. Section 8(a) gives EPA the authority to promulgate rules to require manufacturers and processors to collect, maintain, and submit data about the manufacture and processing of chemical substances in response to Agency requests. These rules do not apply to small manufacturers or processors, or to substances produced only in small quantities for research and development purposes.

Under section 8(b), EPA is required to compile, keep current and publish the Chemical Substance Inventory. Either individual chemical substances or categories of chemical substances may be listed on the Inventory. New substances are added to the Inventory following PMN review and actual manufacture for commercial purposes.

Section 8(c) requires manufacturers, processors, and distributors to maintain records of significant adverse reactions to health or the environment alleged to have been caused by chemical substances.

Section 8(d) allows EPA to promulgate rules under which manufacturers, processors, and distributors are required to submit health and safety data known to or reasonably ascertainable by them.

Under section 8(e), manufacturers, processors, or distributors must immediately submit to EPA any information supporting the conclusion that a chemical substance presents a substantial risk of injury to health and the environment.

A.2.4.5 Section 12. Exports. In general, chemical substances manufactured or processed solely for export are exempt from regulation under TSCA. However, if a substance produced for export presents an unreasonable risk to health or the environment of the United States, EPA may regulate the substance. The Agency may also require section 4 testing of an exported substance to determine whether the substance presents such a risk. A person who intends to export a substance for which information is required under sections 4 or 5(b), or that is subject to a regulatory order or action under Section 5, 6, or 7, must notify EPA, which will, in turn, notify the government of the recipient country.

A.2.4.6 Section 13. Entry into Customs Territory of the United States. No chemical substance, mixture, or article containing a chemical substance or mixture will be allowed into the customs territory of the United States if it fails to comply with any rule or is otherwise in violation of the Act.

A.2.4.7 Section 14. Disclosure of Data. EPA is required to protect confidential business information submitted to the Agency under TSCA from disclosure to the public. Such confidential business information may be disclosed if EPA determines that disclosure is necessary to protect against an unreasonable risk; thus, all data from health and safety studies submitted under TSCA are subject to disclosure.

A.3 Implementation of TSCA

Since TSCA was signed into law in 1976, the EPA has promulgated rules, issued orders, and developed interpretations to implement the provisions of TSCA. This section highlights those rules, orders, and policies that are the most relevant to premanufacture review.

A.3.1 The TSCA Inventory

The TSCA Chemical Substance Inventory, compiled under section 8(b) of TSCA, defines which chemical substances are "existing" in U.S. commerce for purposes of implementing TSCA. The Inventory is not a list of toxic chemicals; toxicity was not a criterion used in determining the eligibility of chemical substances for inclusion on the Inventory.

In 1977, EPA issued its Inventory Reporting Regulations (USEPA 1977a). These regulations and their associated instruction manual (USEPA 1977b) provided guidance for manufacturers to report their existing substances for the Inventory, and, more importantly, established the rules under which all reported substances would be listed on the Inventory. During 1977 and 1978 (USEPA 1979a), manufacturers reported their substances for the Inventory, which was first published in 1979 (USEPA 1979b). Shortly thereafter, there was a reporting period during which processors reported substances they processed that were not already listed on the Inventory (USEPA 1979c). Since that time, new substances have been added following premanufacture review[24] and through corrections of initial Inventory reports and PMNs, incorrectly-reported substances have been removed (for example, see USEPA 1985a). Currently, the Inventory lists over 70,000 chemical substances whose manufacture or processing for commercial purposes in the U.S. has taken place since January 1, 1975. Section 710.4 of the Inventory Reporting Regulations contains the detailed rules for determining which chemical substances were subject to initial Inventory reporting and describes the circumstances under which the manufacture of a substance would be excluded from reporting. These rule provisions were largely carried over into

24. Following PMN review, if EPA has not banned a PMN substance under section 5(f) of TSCA, the manufacturer is free to begin production within any restrictions the Agency may have placed on the substance. The manufacturer must submit a Notice of Commencement (NOC) to the Agency within 30 days following the start of manufacture. Submitters must use EPA Form 7710-56 (USEPA 1995a) for NOCs. Upon receipt of the NOC form, EPA places the PMN substance on the TSCA Inventory. For more information, see 40 CFR Part 720. Premanufacture Notification. Subpart F. Commencement of Manufacture or Import.

section 720.30 of the PMN rule, and are used to determine which substances are subject to PMN notification requirements; because they are so central to the PMN program, they are included in section A.3.9 at the end of this chapter. In addition, the Agency has published two clarifications of the definition of articles, which are excluded from TSCA reporting (USEPA 1985c).

Manufacturers are responsible for determining whether a substance is a new chemical substance under TSCA. The TSCA Chemical Substance Inventory: 1985 Edition (USEPA 1986a) and the 1990 Supplement to the 1985 Edition of the TSCA Inventory (USEPA 1990a) are the most recent hard-copy publications of the non-confidential chemical substance identities. They are available at some public libraries and all federal depository libraries, or may be purchased from the Government Printing Office and National Technical Information Service (NTIS). The NTIS also has computer tape, diskette, and CD-ROM versions of the Inventory that are updated twice a year. In addition, several commercial or government databases including CAS On-line and Dialog Information Services contain up-to-date versions of the non-confidential Inventory. Table A-1 (located at the end of this chapter) lists some of the sources for inventory and other OPPT information.

No publicly available printed or electronic version of the Inventory can be completely up-to-date, because the Inventory is continually changing. Furthermore, detailed information regarding chemical identities claimed as confidential is not included in the published version of the Inventory. The Agency, however, maintains and continually updates a Master Inventory File, which includes all eligible substances that have been reported.

The Agency provides a service to assist those who wish to query the Inventory. A person who intends to manufacture a chemical substance that does not appear on the published Inventory may ask EPA to determine whether the substance in question is included in the Master Inventory File. The Agency will provide an answer only if the person who submits the inquiry is able to demonstrate a "bona fide intent" to manufacture the substance for a commercial purpose.

To demonstrate this intent, in a notice of bona fide intent to manufacture, a manufacturer must submit certain information to EPA. This information includes: the specific chemical identity of the substance (using the currently correct Chemical Abstracts Service name); a signed statement of intent to manufacture for a commercial purpose; a description of the research and development activities conducted to date and the year they were started or, for importers unable to provide this information, substitute information concerning foreign use of the substance; a description of the major intended application or use; an infrared (IR) spectrum or other spectrum if an IR spectrum is not suitable; the estimated date of PMN submission (if the substance is not found on the Inventory); the address of the facility for that is most likely to be used for manufacture or processing; and a description of the most probable manufacturing process. The exact procedures for establishing and submitting a notice of bona fide intent are discussed in detail in the Agency's recent Revision of

Premanufacture Notification Regulations (USEPA 1995a; this supersedes the Agency's former guidance, found in USEPA 1983a). When a bona fide intent has been established with a formal submission, the Agency will perform a comprehensive search of the Master Inventory File to determine conclusively whether the substance in question is already included. The Agency has made a commitment to respond to a bona fide inquiry within 30 days.

A.3.2 Inventory Update Rule

In 1986, the EPA promulgated a rule that requires manufacturers to submit data on production volumes and manufacturing sites for certain chemicals every four years (USEPA 1986b). This rule does not affect the status of any chemicals as being on or not on the TSCA Inventory.

A.3.3 Premanufacture Notification Rule and Form

Any person who plans to manufacture a new chemical substance must submit a PMN, SNUN, or an exemption application[25] to EPA at least 90 days prior to the intended date of the activity. The EPA promulgated regulations governing the PMN process and established the mandatory PMN form in 1983 (USEPA 1983b, USEPA 1983c); the rule and form were revised in 1986 (USEPA 1986c). The form was revised in 1991 (USEPA 1991a), and again in May 1995 (USEPA 1995e). The rule was revised again in 1995 (USEPA 1995a; see also USEPA 1993a). Copies of the current rule, form, and the Instructions Manual for Premanufacture Notification[26] (USEPA 1991b) for PMN submissions are available from the TSCA Assistance Information Service at (202) 554-1404.

As part of the New Chemical Program, the Office of Pollution Prevention and Toxics (OPPT) reviews PMN submissions and determines whether the proposed activities will or may present unreasonable risks. In recent years, an average of nearly 2,300 new chemical substances have been reviewed annually within the New Chemical Program.

The PMN form, as revised in 1995, is used for routine PMNs as well as PMN exemptions and SNUNs; it includes three main sections with additional pages for optional pollution prevention information and a physicochemical properties worksheet. Part I, general information, includes submitter and chemical identity as well as production, import, and use information. Part II contains human exposure and environmental release information for industrial sites controlled by the submitter and for sites controlled by others. Part III is a list of attachments for information requested in Parts I and II and for test data or other information related to the chemical. The submitter is required to provide all information requested in the form to the

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25. Certain classes of chemicals are eligible for exemptions under rules promulgated under section 5(h)(4) of TSCA. An exemption application may replace a PMN in these cases, and may allow manufacture sooner than 90 days.

26. A new instructions manual is under development.

extent that it is known or reasonably ascertainable. If a requested item is not applicable or truly unavailable, the submitter should explain that on the form. Any item that is left blank may cause EPA to declare the PMN incomplete. The 90-day review period for the PMN (or less for exemptions) cannot begin until the submitter provides the missing information.

In 1988, the EPA promulgated a rule requiring PMN submitters to pay user fees (USEPA 1988a). Submitters must remit a user fee of $2,500. This fee is reduced under the certain circumstances: if the submitter is a small business, the user fee is $100; if a PMN for an intermediate substance is submitted simultaneously with a final product PMN, the fee for the intermediate product is $1,000; and if a PMN is filed (with prior Agency consent) for multiple chemicals that are related, the total fee is $2,500.

A.3.4 Biotechnology

TSCA applies to all chemical applications not specifically exempted in the Act. Microorganisms intended for general commercial and environmental applications (e.g., metal leaching, pollutant degradation, enhanced nitrogen fixation) are subject to TSCA. In 1986, the federal agencies involved with the review of biotechnology products announced a policy requiring, among other things, PMN reporting for commercial uses of certain genetically modified microorganisms (OSTP 1986). The notice also requested voluntary reporting for research and development (R&D) uses of these microorganisms involving introductions into the environment. EPA has published a proposed rule under TSCA section 5 that would deal specifically with microorganisms (USEPA 1994). Until this rule is promulgated, submitters should use EPA's Points to Consider (USEPA 1990b) as guidance in the preparation of PMNs for microorganisms. Submitters are also strongly encouraged to have a prenotice consultation with EPA before submitting a PMN for a microorganism. Submitters interested in determining whether a microorganism is already on the TSCA Inventory may submit bona fide inquiries following the Agency's guidance, given in USEPA 1990b.

A.3.5 Exemptions

A.3.5.1 Test Market Exemptions

TSCA section 5(h)(1) authorizes an exemption from PMN requirements for new chemical substances manufactured for test marketing purposes, as long as this activity does not present an unreasonable risk to human health or the environment. These exemptions are granted or denied by EPA following review of a test market exemption application (TMEA). The Agency's regulations for TMEAs are found in the PMN rule and instruction manual, referenced above, and are also addressed in a New Chemical Information Bulletin (USEPA 1986d). The exemption permits a company to assess the commercial viability of a new chemical and to receive customer feedback on product performance before proceeding with a PMN. TMEAs also are advantageous to submitters because the Agency must grant or deny them within 45 days and they require no user fee. EPA reviews a TMEA in essentially the same

manner as a PMN[27] and thus needs similar information from submitters.

A.3.5.2 5(h)(3) Exemption for Research and Development

Section 5(h)(3) of TSCA exempts chemical substances from PMN provisions if they are manufactured only in small quantities solely for purposes of scientific experimentation, analysis, or research and development. The Agency's interpretation of this exemption is given in two Federal Register notices (USEPA 1984b; USEPA 1986c) and a New Chemical Information Bulletin (USEPA 1986d).

A.3.5.3 5(h)(4) Exemptions

To date, EPA has promulgated three 5(h)(4) exemption rules to limit reporting requirements for new chemical substances (see USEPA 1991c and other references given with the specific exemptions):

- substances used in or for instant or "peel-apart" film articles;
- substances manufactured or imported in small quantities and substances with low release and exposure; and,
- polymers that meet certain specified criteria.

More detail about these exemptions is provided below.

A.3.5.4 Instant Film Exemption

Under the terms of this rarely-used exemption, manufacturers may commence manufacture of new chemical substances for incorporation into instant photographic articles immediately after submitting an exemption notice to EPA. The manufacturer must file a PMN and wait until the review period has expired, however, before distributing the new chemical in commerce. Special procedures to contain exposure must also be used until PMN review is completed (USEPA 1982).

A.3.5.5 Low Volume Exemption

In 1985, EPA published a TSCA section 5(h)(4) rule granting a partial exemption from TSCA section 5 reporting requirements for persons who manufacture chemical substances produced in quantities less than 1,000 kilograms per 12 month period (USEPA 1985b). This rule was developed in response to petitions by the Chemical Manufacturers Association (CMA) and other industry groups[28]. The Agency published proposed revisions to this

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27. Because the review period for TMEAs is only 45 days, the Agency uses its usual PMN review process only until the Focus Meeting. During this meeting, Agency staff decide whether to grant or deny any TMEA still in the review process at this point. Refer to Chapter 1 for a discussion of the PMN review process.

28. Section 21 of TSCA allows citizens to petition the Agency for changes in the Agency's implementation of TSCA.

rule in 1993 (USEPA 1993d) and a final revised rule in 1995 (USEPA 1995c).

Under the revised rule, chemical substances may qualify for exemption if their annual production volume is less than 10,000 kg. Manufacturers must submit exemption notices 30 days prior to commencement of manufacture. Exemptions granted previously under the superseded rule will remain effective (and binding).

A.3.5.6 Low Release and Exposure Exemption

Along with the revised low volume exemption, the Agency proposed (USEPA 1993d) and later made final a new exemption, the low release and exposure exemption (LoREX; USEPA 1995c). Substances may qualify for the LoREX exemption, regardless of their production volume, if they meet the release and exposure criteria stated in the rule. To apply for an exemption, manufacturers must submit an exemption notification at least 30 days before beginning production. The Agency is preparing an instruction manual for this new rule; a draft manual is available for comment through the TSCA Assistance Information Service (USEPA 1995f).

A.3.5.7 Polymer Exemption

In 1984, EPA published a TSCA section 5(h)(4) rule granting an exemption for persons who manufacture or import certain polymers (USEPA 1984a). This rule was developed in response to petitions by industry groups. In February 1993, the Agency proposed revisions to this exemption rule (USEPA 1993b) and in March 1995, the Agency published the final rule (USEPA 1995b). A technical guidance manual to assist submitters in complying with the revised exemption is in preparation; a draft manual is available through the TSCA Assistance Information Service (USEPA 1995g).

In general, to be manufactured under this exemption a polymer must meet the polymer definition given in the rule and one or more of three criteria:

- polymers with number-average molecular weight (MW) greater than or equal to 1,000 and less than 10,000 daltons (and oligomer content less than 10 percent below MW 500 and less than 25 percent below MW 1,000);
- polymers with number-average MW greater than or equal to 10,000 daltons (and oligomer content less than 2 percent below MW 500 and less than 5 percent below MW 1,000); and
- polyester polymers manufactured solely from one or more reactants listed in the exemption rule.

In addition, certain classes of polymers cannot be manufactured under this exemption. These polymers include:

- certain cationic polymers;
- polymers that do not meet certain elemental limitations;
- polymers that degrade, decompose, or depolymerize;

- polymers manufactured or imported from monomers and reactants not on the TSCA Chemical Substance Inventory; and

- water-absorbing polymers with number-average MW 10,000 and greater.

Submitters using this exemption are required to keep certain records to verify their eligibility for and compliance with the exemption. They are not required to submit an exemption notification or a Notice of Commencement, but are to report annually the number of polymers being manufactured for the first time during the preceding calendar year under the exemption. In part because submitters do not report the chemical identities of their polymers to EPA, the Agency does not list these polymers on the Inventory.

Manufacturers who submitted polymers to EPA under the previous polymer exemption rule (prior to the effective date of the new rule, May 30, 1995) may either continue to comply with the requirements of the previous exemption rule (USEPA 1984a) or may follow all of the requirements of the new, revised exemption rule (USEPA 1995b).

A.3.6 TSCA Section 5(e) Consent Orders and Significant New Use Rules

Under certain circumstances, EPA uses a section 5(e) order to place restrictions on the manufacture of a new chemical pending development of test data. The order allows manufacture of the new chemical to commence subject to restrictions on processing methods, production volume, and/or use that reduce or limit risks to human health or the environment. Under TSCA, EPA has authority to impose a section 5(e) order by unilateral action, but in practice, EPA usually negotiates section 5(e) consent orders with the affected PMN submitter.

An order restricts the PMN submitter to the aforementioned conditions, but it is not binding on other companies wishing to produce or use the same chemical once the chemical is listed on the TSCA Inventory. Hence, the Agency often promulgates a Significant New Use Rule (SNUR) to restrict the exposure and use of the substance to those identified as acceptable under the section 5(e) order. SNURs apply to all manufacturers. Anyone who desires to use a substance that is subject to a SNUR for a use defined as a significant new use in the SNUR must submit a SNUN at least 90 days before starting to manufacture the substance for the new use. The Agency uses the standard PMN review process to review SNUNs and make an appropriate regulatory determination.

The SNUR procedures (USEPA 1988b; USEPA 1993c; USEPA 1995d) and subsequent SNUN submissions allow EPA to control exposures (and thus, risks) associated with new uses of PMN (or existing) chemicals, changes in processing, and increased production volumes before they become potential problems. Designation of PMN substances for a TSCA section 5(e) order, and subsequently for a SNUR, is based on information received during the initial PMN review. Often, the Agency is forced to base its review of the risks posed by new chemicals on inadequate information received from submitters. In

these instances, the Agency may need to make worst-case (i.e., highest exposure and risk) estimates regarding certain use or exposure factors because submitter data have not been provided. This may lead to more stringent control than necessary. Therefore, if submitters provide comprehensive information, the Agency will be able to make more realistic determinations of the potential for unreasonable risk, such that restrictions may not be necessary.

A.3.7 Polymers: The Two Percent Rule

Originally, identification of new polymers for TSCA Inventory and PMN purposes was based on the amounts of monomers and other reactants used in the reaction, "as charged" to the reaction vessel, and on the dry weight of the polymer (USEPA 1977a). This approach was adopted because it was believed that it would be difficult to identify the exact amounts of monomers or other reactants incorporated in the final polymers. More recently, the Agency revised its two percent rule (USEPA 1995a) so that the two percent could either be interpreted as "as charged" or "as incorporated." For a discussion of the practical application of the revised two percent rule, refer to the Agency's polymer technical guidance manual.

All constituents of a polymer must be listed in a PMN, but a submitter may choose which constituents present at two percent or less will be used in the Inventory description of the polymer. Since July 28, 1989 (USEPA 1989), free radical initiators charged to the reaction vessel at over two percent have also been required to be part of the chemical identity[29]. At present, if free radical initiators are incorporated at less than or equal to two percent, they do not have to be part of the chemical name (USEPA 1995a).

Any constituent listed in the Inventory description must always be present in the PMN substance. The use of additional monomers or reactants will not result in a "new" chemical substance if each of the additional monomers or reactants, as charged or incorporated, amounts to two percent or less of the weight of the polymer.

A.3.8 Importing Chemical Substances

The U.S. Department of the Treasury has amended its customs regulations to fully support the implementation of TSCA (TREAS 1983a; TREAS 1983b; TREAS 1983c). The EPA published companion requirements at about the same time (USEPA 1983d). Importers are required to certify that their shipments are on the TSCA Inventory and are not in violation of TSCA. The EPA has published a two-volume Guide for Chemical Importers/Exporters (USEPA 1991d) that is available from the TSCA Assistance Information Service. Also available are copies of the Agency's database, Chemicals on Reporting Rules Database (CORR) (USEPA 1991e).

A.3.9 Addendum to Appendix: Inventory Reporting Regulations

The following text is copied from the

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29. Initiators used at > 2% have only had to be included in the chemical identity of polymers added to the Inventory since July 28, 1989, the effective date of the Agency's clarification in the Federal Register (USEPA 1989).

Agency's Inventory Reporting Regulations, 40 CFR 710.4. Its purpose here is to clarify the definition of chemical substances for TSCA purposes.

Section 710.4 Scope of the Inventory

(a) *Chemical substances subject to these regulations*. Only chemical substances which are manufactured, imported, or processed "for a commercial purpose," as defined in section 710.2, are subject to these regulations.

(b) *Naturally occurring chemical substances automatically included*. Any chemical substance which is naturally occurring and

(1) which is (I) unprocessed or (ii) processed only by manual, mechanical, or gravitational means; by dissolution in water; by flotation; or by heating solely to remove water; or

(2) which is extracted from air by any means, shall automatically be included in the inventory under the category "Naturally Occurring Chemical Substances." Examples of such substances are: raw agricultural commodities; water, air, natural gas, and crude oil; and rocks, ores, and minerals.

(c) *Substances excluded by definition or section 8(b) of TSCA*. The following substances are excluded from the Inventory:

(1) Any substance which is not considered a "chemical substance" as provided in subsection 3(2)(B) of the Act and in the definition of "chemical substance" in section 710.2(h);

(2) Any mixture as defined in section 710.2(q);

NOTE. -- A chemical substance that is manufactured as part of a mixture is subject to these reporting regulations. This exclusion applies only to the mixture and not to the chemical substances of which the mixture is comprised. The term "mixture" includes alloys, inorganic glasses, ceramics, frits, and cements, including Portland cement.

(3) Any chemical substance which is manufactured, imported, or processed solely in small quantities for research and development, as defined in section 710.2(y); and

(4) Any chemical substance not manufactured, processed or imported for a commercial purpose since January 1, 1975.

(d) *Chemical substances excluded from the inventory*. The following chemical substances are excluded from the inventory. Although they are considered to be manufactured or processed for a commercial purpose for the purpose of section 8 of the Act, they are not manufactured or processed for distribution in commerce as chemical substances *per se* and have no commercial purpose separate from the substance, mixture, or article of which they may be a part. NOTE: In addition, chemical substances excluded here will not be subject to premanufacture notification under section 5 of the Act.

(1) Any impurity.

(2) Any byproduct which has no commercial purpose.

NOTE: A byproduct which has commercial value only to municipal or private organizations who (I) burn it as a fuel, (ii) dispose of it as a waste, including in a landfill or for enriching soil, or (iii) extract component chemical substances which have

commercial value, may be reported for the inventory, but will not be subject to premanufacturing notification under section 5 of the Act if not included.

(3) Any chemical substance which results from a chemical reaction that occurs incidental to exposure of another chemical substance, mixture, or article to environmental factors such as air, moisture, microbial organisms, or sunlight.

(4) Any chemical substance which results from a chemical reaction that occurs incidental to storage of another chemical substance, mixture or article.

(5) Any chemical substance which results from a chemical reaction that occurs upon end use of other chemical substances, mixtures, or articles such as adhesives, paints, miscellaneous cleansers or other household products, fuels and fuel additives, water softening and treatment agents, photographic, (sic) films, batteries, matches, and safety flares, and which is not itself manufactured for distribution in commerce or for use as an intermediate.

(6) Any chemical substance which results from a chemical reaction that occurs upon use of curable plastic or rubber molding compounds, inks, drying oils, metal finishing compounds adhesives, or paints; or other chemical substances formed during manufacture of an article destined for the marketplace without further chemical change of the chemical substance except for those chemical changes that may occur as described elsewhere in this section 710.4(d).

(7) Any chemical substance which results from a chemical reaction that occurs when (I) a stabilizer, colorant, odorant, antioxidant, filler, solvent, carrier, surfactant, plasticizer, corrosion inhibitor, antifoamer or de-foamer, dispersant, precipitation inhibitor, binder, emulsifier, de-emulsifier, dewatering agent, or quality control reagent functions as intended or (ii) a chemical substance, solely intended to impart a specific physicochemical characteristic, functions as intended.

(8) Chemical substances which are not intentionally removed from the equipment in which they were manufactured.

NOTE. -- See note to definition of "intermediate" at section 710.2(n) for explanation of "equipment in which it was manufactured."

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Government Printing Office
c/o Superintendent of Documents
Washington, D.C. 20402
(202) 783-3238

National Library of Medicine
TRI Representative
Specialized Information Services
8600 Rockville Pike
Bethesda, MD 20894
(301) 496-6531

National Technical Information Service
5285 Port Royal Road
Springfield, VA 22161
(703) 487-4650

OPPT Document Control Office
U.S. EPA
401 M Street, S.W. (TS-790)
Washington, DC 20460
(202) 260-1532

OPPT Public Docket Office
U.S. EPA
401 M Street, S.W. (TS-793)
Room G-004, Northeast Mall
Washington, DC 20460
(202) 260-7099

Toxic Release Inventory User Support (TRI/US)
U.S. EPA
401 M Street, S.W. (TS-793)
Room B-0011, Northeast Mall
Washington, DC 20460
(202) 260-1531

TSCA Assistance Information Service (TSCA hotline)
U.S. EPA
401 M Street, S.W. (TS-799)
Washington, DC 20460
(202) 554-1404
Fax: (202) 554-5603
TDD: (202) 554-0551

OPPT Chemical Library
U.S. EPA
401 M Street, S.W. (TS-793)
Room B-002, Northeast Mall
Washington, DC 20460
(202) 260-3944

CAS Inventory Expert Service
2540 Olentangy River Road
P.O. Box 3012
Columbus OH 43210-0012
(800) 848-6538, ext. 2308
or (614) 447-3600
Fax: (614) 447-3747

Dialog Information Services
TSCA Inventory search requests:
(800) ALERT91 (253-7891)
Online access to inventory:
(800) 334-2564

Chemical Information Systems, Inc.
7215 York Road
Baltimore, MD 21212
(301) 321-8440
(800) CIS-USER (247-8737)

Biotechnology Program Information
David Giamporcaro, Chief
Section II
(202) 260-6362

Pollution Prevention Information Clearinghouse (PPIC)
(202) 260-1023 (24-hour answering machine)

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