

# CHEMICAL INFORMATION NEEDED FOR RISK ASSESSMENT

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### 2.1 Introduction

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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.

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## **2.2 Important Chemical Information**

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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

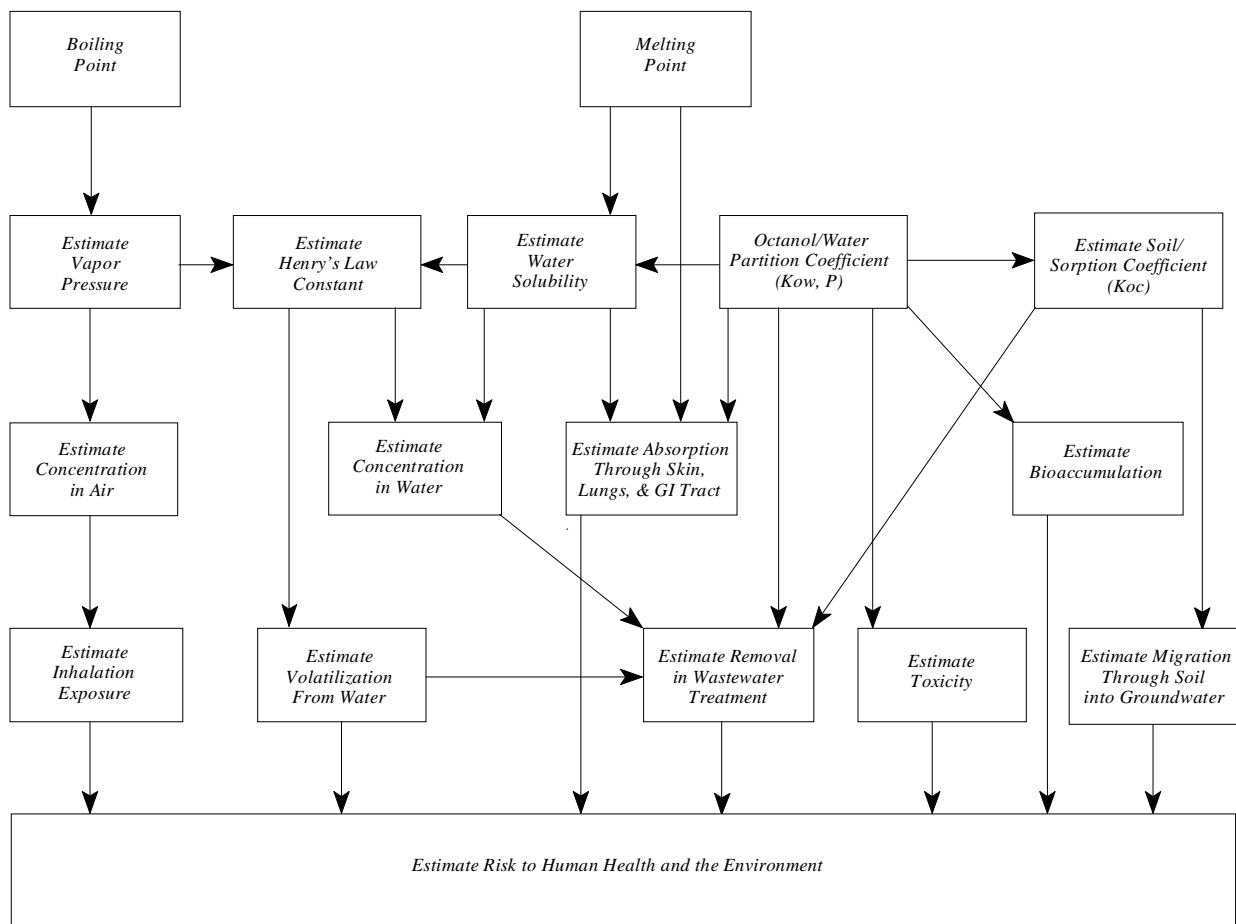
predicting environmental fate, exposure, toxicity, and pharmacologic response are listed under the Suggested Readings heading at the end of this chapter.

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:

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

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<sub>2</sub>, 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.

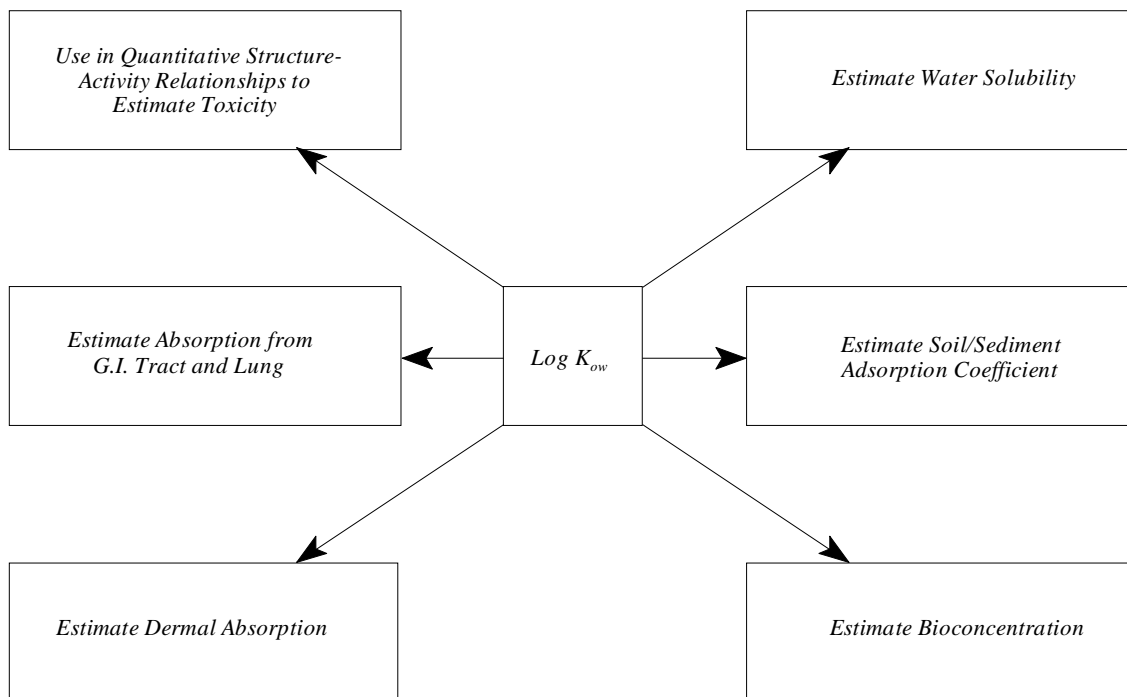
Substances with high ( $> 5$ )  $\log K_{ow}$  values are so hydrophobic that they partition very poorly into the aqueous components of biological systems, remain within the lipid components and are generally poorly absorbed following acute exposure. Chemical substances with high  $\log K_{ow}$  values, 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; Sasaki 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.<sup>17</sup> 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.<sup>18</sup>

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 °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:

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

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  $1 \times 10^7$  (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:

$$\frac{x}{m} = KC^n$$

where

$$x/m = (\mu\text{g of chemical absorbed})/(\text{g soil or sediment})$$

$$C = (\mu\text{g of chemical})/(\text{mL of solution})$$

$n = \text{a parameter ranging from 0.7 to 1.1 (Lyman et al. 1982)}$

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

$$K_{oc} = \frac{K}{\%oc} \times 100$$

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:

$$H = \frac{[\text{chemical substance}] \text{ in air}}{[\text{chemical substance}] \text{ in water}}$$

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:

$$H = \frac{\text{equilibrium vapor pressure}}{\text{solubility}}$$

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 ( $\text{atm}\cdot\text{m}^3/\text{mol}$ ), 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 Siwoloboff 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 Siwoloboff 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 °C, since these substances are most likely to volatilize readily. High melting solids (> 150 °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  $7.5 \times 10^{-8}$  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 °C, since these substances are most likely to volatilize readily, which can result in significant exposure during manufacture or use. High melting solids (> 150 °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  $\alpha,\beta$ -unsaturated carbonyls (acrylates, acrylamides, quinones), may undergo nucleophilic attack by free amino ( $\text{NH}_2$ ) 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 ( $^1\text{H}$ ) and carbon ( $^{13}\text{C}$ ) 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 ( $\bullet\text{OH}$ ). 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).

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### **2.3 Use of Chemical Information in Assessment of PMN Chemicals**

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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.

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### **2.4 How EPA Obtains Physicochemical Information**

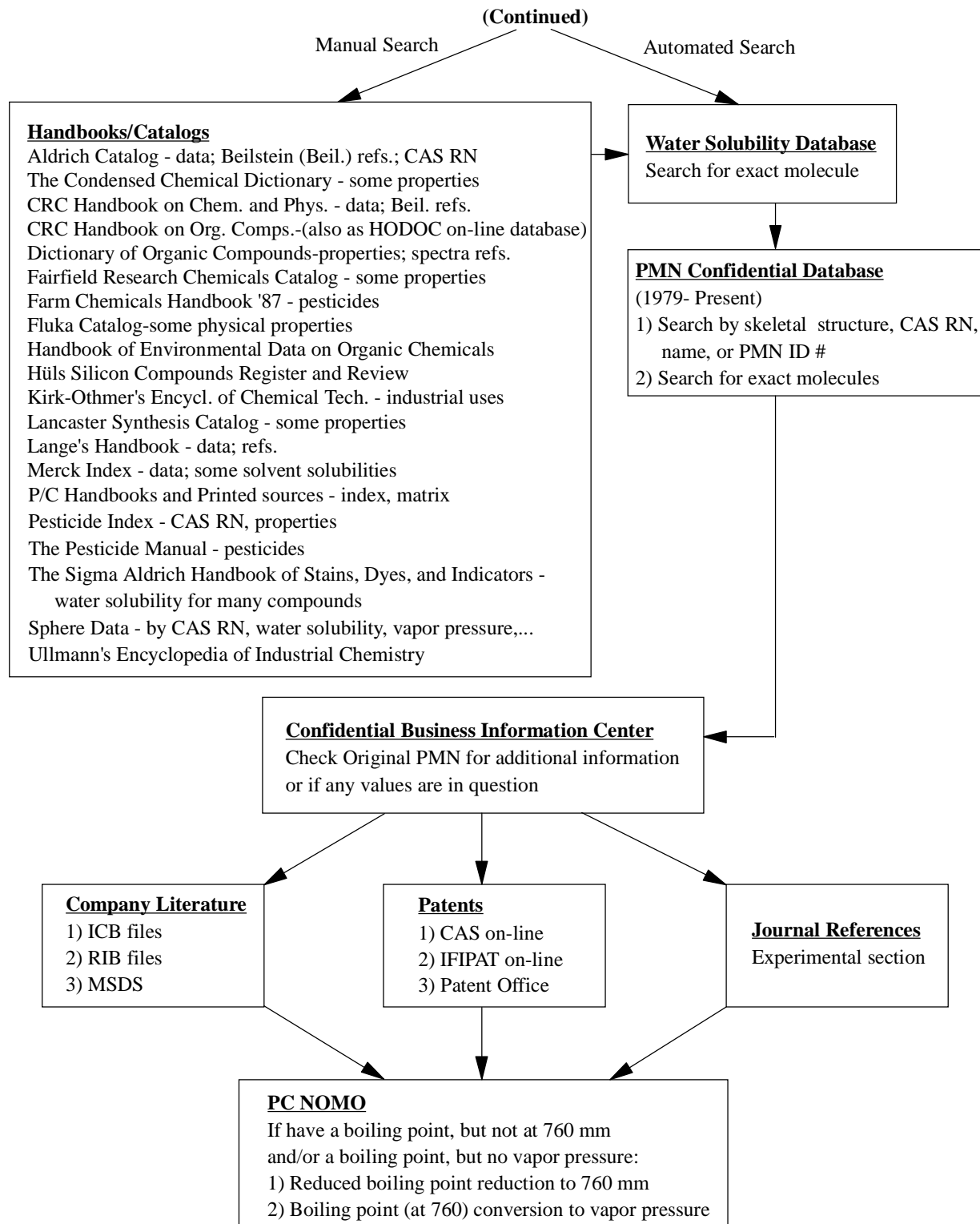
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#### **2.4.1 General Approach**

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**

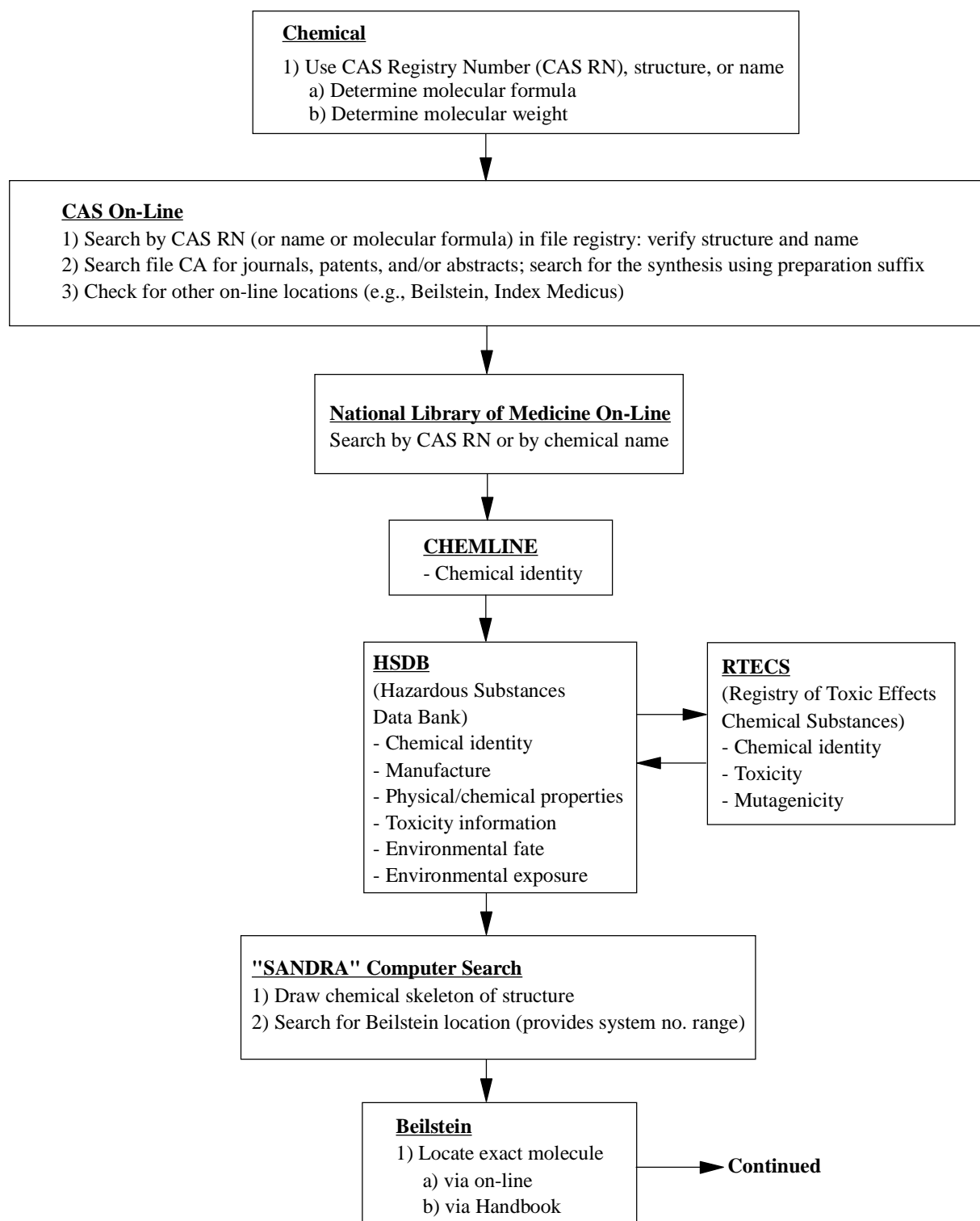
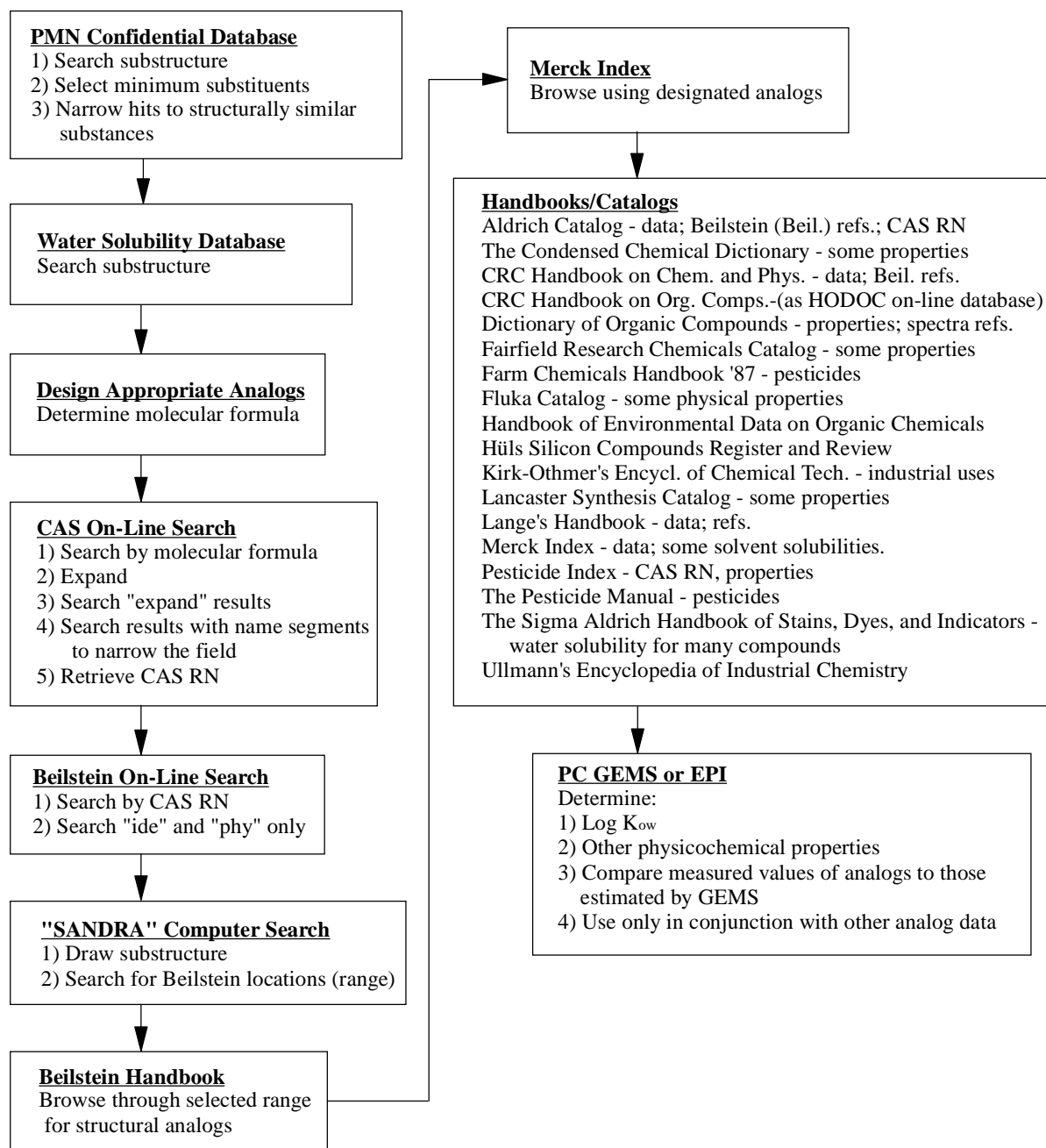


Figure 2-4. Methods for Identifying Analogs of PMN Substances and Their Physicochemical Properties



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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