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Predictive Methods for Chemical Fate

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ABSTRACT: *A strategy is proposed to predict physical properties, partitioning, bioconcentration and degradability of nonionized, nonpolymeric organic chemicals. The strategy uses structural features of organic chemicals, structure activity relationships, sequenced estimation techniques (including recently developed computerized methods), and laboratory screening tests. The cost to use this strategy is compared with the cost of conducting a standard menu of tests to measure physical properties, partitioning, bioconcentration and degradability.*

This chapter proposes a strategy for using structural features of organic chemicals, structure activity relationships, sequenced estimation techniques (including some recently developed computerized methods) and laboratory screening tests to predict the chemical fate of nonionized, nonpolymeric organic chemicals (figure 13-1). It emphasizes the need to consider computerized methods to make these predictions, especially as these methods relate to the "cost and time considerations" emphasized by the April 24-25, 1995, Congressional Office of Technology Assessment (OTA) "Workshop on Testing and Screening Technologies for Review of Chemicals in Commerce. "

Many of the computerized estimation methods discussed in this chapter have been validated with large data sets of chemicals that were not used to derive the methods, e.g., the computerized methods developed by Meylan and Howard for estimating aerobic biodegradation, boiling point, Henry's law constant, octanol-water partition coefficient, soil or sediment sorption coefficient, vapor pressure and water volubility are quite 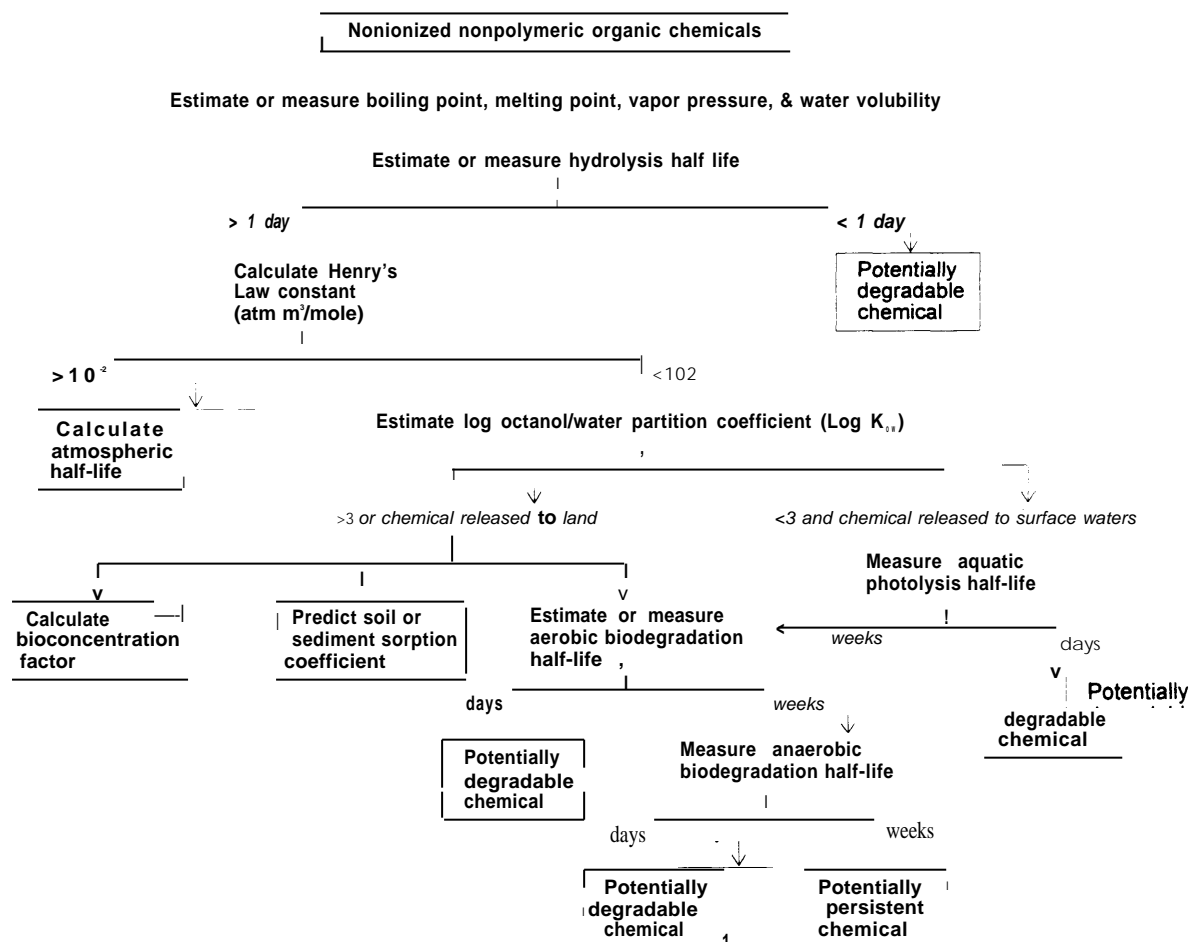accurate and certainly accurate enough for the proposed strategy. While laboratory measurements may be preferred, it should be noted that these measurements cost time and money and for many chemicals, the resources to make these measurements may not be warranted, especially with the availability of computer software and mathematical models that can be used to accurately predict the data that would be obtained from measurements.

The strategy for making chemical fate predictions for physical properties, partitioning, bioconcentration and degradability uses a number of decision criteria to progress through these predictions. While all these decision criteria are supported by data, there is still need for professional judgment when progressing through the predictions. The initial predictions use estimation techniques, structure activity relationships and computerized methods to predict physical properties, partitioning, bioconcentration and degradability. The final predictions also use these methods, but may also require some laboratory screening tests to predict potential degradability.

The proposed strategy as well as the schemes used to implement ecological effects testing under the Toxic Substances Control Act (TSCA) are different than the chemical testing approaches taken by the Organisation for Economic Cooperation and Development (OECD) and others. The OECD's Screening Information Data Set (SIDS) program for example, requires that a standard menu of chemical fate, ecological effects and health effects tests be conducted for all chemicals. Clearly there are advantages and

Figure 13-1: Proposed Strategy to Identify Persistent Organic Chemicals

Nonionized nonpolymeric organic chemicals

Estimate or measure boiling point, melting point, vapor pressure, & water volubility

Estimate or measure hydrolysis half life

> 1 day   < 1 day → Potentially degradable chemical

Calculate Henry's Law constant (atm m³/mole)

>10² ←   →<10²

Calculate atmospheric half-life

Estimate log octanol/water partition coefficient (Log K_{ow})

>3 or chemical released to land   <3 and chemical released to surface waters

Measure aquatic photolysis half-life

Calculate bioconcentration factor   Predict soil or sediment sorption coefficient   Estimate or measure aerobic biodegradation half-life   weeks / days

days   weeks → Potentially degradable chemical

Potentially degradable chemical   Measure anaerobic biodegradation half-life

days   weeks

Potentially degradable chemical   Potentially persistent chemical

disadvantages to both approaches, e.g. an advantage of the SIDS approach is that all the data are available for all chemicals should it be necessary to make comparative assessments related to pollution prevention, use of substitutes, risk reduction, etc. To illustrate the economic aspects of these different approaches, the cost of developing data for individual predictions in the proposed strategy is compared to the cost of conducting a base set or standard menu of tests to measure physical properties, partitioning, bioconcentration and degradability (table 13-1).

In response to the request from OTA, the chapter focuses on TSCA, the cost and time considerations for screening chemicals, and the organizations that are required to recommend,

implement and conduct testing under TSCA. These organizations include the TSCA Interagency Testing Committee (ITC), EPA's new and existing TSCA chemical testing programs and the manufacturers and processors of TSCA chemicals. The proposed strategy was previously presented at an American Society for Testing and Materials Symposium on Environmental Toxicology and Risk Assessment (27).

CHEMICAL TESTING UNDER TSCA

Three sections of TSCA relate to chemical testing, *viz.,* sections 2, 4 and 5.

Section 2 of TSCA states that the U.S. Congress finds that humans and the environment are exposed to large numbers of chemicals, and that

Table 13-1: Cost of Laboratory Tests for Basic Physical Properties	
Test	**Cost ($)a**
Boiling point	420-560
Melting point	430-565
Vapor pressure	1,360-2,520
Water volubility	2,870-14,080
Physical property data	5,080-17,725
Octanol-water partition coefficient	1,310-2,370
Soil sorption Coefficient	6,680-9,430
Volatilization	6,180-8,800
Partitioning data	14,170-20,600
Hydrolysis	5,470-7,790
Photolysis	11,880-16,910
Aerobic biodegradation	8,250-11,800
Anaerobic biodegradation	5,980-8,480
Degradability data	31,580-44,980
Bioconcentration data	15,580-41,690
TOTAL	**66,410-124,995**

a Cost estimatesfrom Mathtech (1995)

some of those chemicals may present an unreasonable risk of injury to health or the environment. Section 2 states that it is the policy of the United States that "adequate data should be developed with respect to the effect of chemical substances and mixtures on health and the environment and that the development of such data should be the responsibility of those who manufacture and those who process such chemical substances and mixtures. "

Section 4 requires the testing of existing chemical substances and mixtures ("chemicals"). Existing chemicals are those chemicals that were produced in or imported into the United States before TSCA became effective in 1977 or those chemicals for which notice to commence production were issued after 1977 by EPA under TSCA section 5. Section 4 of TSCA was enacted by Congress in response to concerns that the effects of existing chemical substances and mixtures on human health and the environment were inadequately documented and understood. To alleviate these concerns, Congress created the ITC to screen, prioritize and recommend existing chemicals for testing to the EPA Administrator and em-

powered the EPA Administrator with author ity to require that manufacturers or processors test their chemicals to develop adequate data. These data are used by EPA, other U.S. Government, Foreign Government and International Organizations as well as state and local governments to develop hazard and exposure assessments that are necessary to promote pollution prevention or chemical regulation (27).

Section 4(a) ensures that existing chemicals which may present an "unreasonable risk" to human health or the environment, or may involve substantial production or exposure, receive priority testing consideration and that manufacturers or processors of these chemicals test them to assure that adequate data are developed to assess their potential risk to humans or the environment. Section 4(a) requires that the EPA Administrator make three findings before requiring the manufacturers or processors of a chemical to conduct testing. Historical details of these findings are discussed in EPA's first two TSCA section 4(a) test rules (20, 21). Section 4(b) requires that EPA publish standards for development of test data and review the standards at least every 12 months. Section 4(c) allows manufactures and processors of chemicals to apply for exemptions for testing under section 4(a). Section 4(d) requires EPA to publish in the *Federal Register* the receipt of any data developed under section 4(a) within 15 days of its receipt.

Section 4(e) describes the statutory responsibilities of the ITC. The ITC is described in a previous publication (27) as is an ITC case study that provides all of the milestones from the time of ITC's initial work until EPA completes its risk assessment (30). Section 4(f) requires EPA to prevent or reduce risks to substances that present a significant risk of serious or widespread harm from cancer, gene mutations or birth defects. Section 4(g) allows manufactures to petition the EPA to prescribe standards for the development of data. Section 5 requires manufactures that want to produce new chemicals to submit premanufacturing notices to the EPA before initiating commercial production. New chemicals are those that were not produced in or imported

into the United States before 1977. EPA has 90 days to approve a premanufacturing notice. EPA can approve these notices with no contingencies, with contingencies for chemical testing or pollution prevention or not approve them, thereby banning the chemical from production. EPA approves a premanufacturing notice by issuing a commencement notice. Those chemicals for which commencement notices are issued and for which commercial production is initiated become existing chemicals and are subject to the requirements of TSCA section 4. Additional details about the TSCA section 5 process have been recently published (16).

▮ TSCA ENVIRONMENTAL TESTING SCHEMES

Two testing schemes have been used to implement environmental testing under TSCA sections 4 and 5. Both are used to implement ecological effects testing. Details of the ecological effects testing scheme used for existing chemicals under TSCA Section 4 have been described in detail previously (23, 24). The TSCA section 4 ecological effects testing scheme uses physical property, partitioning and degradability data to develop predicted environmental concentrations (PECs) of chemicals and then uses these PECs as one factor to determine whether ecological effects testing should be considered.

Details of the ecological effects testing scheme used for new chemicals under TSCA section 5 have been described in a series of papers published in the proceedings of a 1991 American Society for Testing and Materials Symposium (2, 16, 18, 33). The TSCA section 5 scheme uses ecological effects decision criteria or "concern levels" to determine whether higher tier tests should be conducted. The TSCA section 5 scheme relies on structure activity relationships, because of the scarcity of data associated with new chemicals.

The proposed strategy described in this chapter is designed to complement both the TSCA section 4 and section 5 ecological effects testing schemes. This strategy focuses on chemical fate structure activity relationships, predictions and testing to provide information that can be integrated with that generated from the ecological effects testing schemes to estimate environmental risk, promote pollution prevention, etc.

▮ THE PROPOSED STRATEGY

The proposed strategy uses structural features of organic chemicals, structure activity relationships, sequenced estimation techniques (including some recently developed computerized methods) and laboratory screening tests to predict physical properties, partitioning, bioconcentration and degradability of nonionized, nonpolymeric organic chemicals.

Structural Features and Structure Activity Relationships

Structural features and structure activity relationships have been used for many years to develop mathematical models that can be used predict the fate of chemicals (5). It is well known, for example, that chemicals with certain structural features (described below) will be more susceptible to hydrolysis than chemicals not containing those features. Similarly, it is well known that structural features related to molecular topology can be used to estimate physical properties, partition coefficients, bioconcentration potential and degradability. Structural features and structure activity relationships have been used to develop the estimation techniques and computerized methods described below.

Cost Comparisons for Estimation Techniques and Screening Tests

Laboratory tests that provide a standard menu of basic physical chemical property, partitioning, bioconcentration and degradability data are listed in table 13-1. If all of these tests were conducted, the cost could range from $66,410 to $124,995 U.S. dollars (table 13-1). If empirical data are not required, then estimation techniques (including some recently developed computerized methods) can be used to estimate some of these data at substantial time and cost savings compared to laboratory measurements.

As explained below, some of the cost ranges for tests to develop the physical properties and partitioning data listed in table 13-1 are large because they were estimated for more than one method. Costs for conducting hydrolysis, photolysis, aerobic biodegradation, anaerobic biodegradation and fish bioconcentration tests are all estimates for one method and the size of the cost range is usually a reflection of the cost of the analytical method used to develop the data.

The proposed strategy described in figure 1 does not require all the tests listed in table 13-1, but suggests that it may be possible to sequentially use estimation techniques (including some recently developed computerized methods) or screening tests to estimate physical properties, partitioning, bioconcentration and degradability of nonionized, nonpolymeric organic chemicals. Based on the type of organic chemical that is being evaluated, the sequencing allows the minimum predictions to be made or the minimum number of screening tests to be conducted. For example, if there were no data for a chemical, the structure suggested that it would be susceptible to hydrolysis and a decision was made to develop empirical data *in lieu* of making predictions, then it should cost from $2,210 to $3,645 to conduct boiling point, melting point and vapor pressure tests and $5,470 to $7,790 to conduct a hydrolysis test (table 13-1). The water volubility test would not be conducted, until after the results from hydrolysis were available. If the hydrolysis half life was > 1 day, then water volubility should be measured at a cost of $2,870 to $14,080 (table 13-1). If the hydrolysis half life was < 1 day, the total cost of conducting chemical fate testing for this chemical would range from $10,550 to $25,515 as opposed to $66,410 to $124,995 for conducting all the chemical fate tests listed in table 13-1. The methods in table 13-1 for which costs have been estimated are all TSCA test methods that have been harmonized with OECD and others. These methods (listed below) are described in Volume 40 of the Code of Federal Regulations (CFR), parts 795, 796 and 797. The methods that have been used to develop data for existing chemicals recommended by the ITC to

measure physical-chemical properties and environmental persistence have been described (25) as have those to measure bioconcentration (28, 29). The TSCA section 4 chemical fate and ecological effects test data developed from using those methods have been published (26, 31, 32).

Physical Properties

Estimated costs for conducting boiling point, melting point, vapor pressure and water volubility tests range from $5,080 to $17,725 (table 13-1). The cost range estimated for vapor pressure testing ($1,360 to $2,520) is actually from two estimates for measuring vapor pressure by isoteniscope ($1,360 to $1,900) or by gas saturation ($1,790 to $2,520). The large cost range estimated for water volubility testing ($2,870 to $14,080) is a composite of three estimates for measuring water volubility by an analytical method after centrifugation ($2,870 to $4,070), by high pressure liquid chromatography after column generation ($7,740 to $1 1,080) or by gas chromatography after column generation ($9,840 to $14,080). Lyman et al. (5) describe methods for estimating boiling point, vapor pressure and water volubility. Recently, methods for personal computers have been developed to estimate melting point, boiling point and vapor pressure (11) and water volubility (12). If reliable measured data for these physical properties are not available for a chemical (especially vapor pressure and water volubility data at 20°C or 25°C), they should all be predicted using the computerized methods listed above, unless as noted above the structure suggests that the chemical would be susceptible to hydrolysis.

Partitioning, Bioconcentration and Degradability

Estimated costs for measuring octanol-water partition coefficient, soil or sediment sorption coefficient and volatilization range from $14,170 to $20,600 (table 13-1). The cost range estimated for measuring octanol-water partition coefficient is a composite of two estimates by liquid chromatography ($1,310 to $1,730) or by generator column ($1,820 to $2,370). Lyman et al. (5) de-

scribe methods for estimating octanol-water partition coefficient, soil or sediment sorption coefficient and volatilization. Recently, methods for personal computers have been developed to estimate octanol-water partition coefficients (13) and soil or sediment sorption coefficients (10).

- **Hydrolysis.** Hydrolysis is a chemical fate process in which an organic chemical, reacts with water resulting in the cleavage of a carbon-X bond and the formation a new carbon-oxygen bond. X could be represented by structural features (groups) such as alkyl halides, epoxides, esters, hydrazines, isocyanates, nitriles, silanes, etc. Hydrolysis is probably the first indicator of degradability that should be estimated, because almost all chemicals entering the environment contact water (fig. 13-1). If a chemical contains a structural feature that is susceptible to hydrolysis, then hydrolysis should be estimated or measured. Hydrolysis half life can be estimated using the method of Mill et al. (15) or the personal computer methods developed by Meylan and Howard (8). If empirical data are required, then hydrolysis can be measured using the methods in 40 CFR 796.3500 at a cost of $5,470 to $7,790 (table 13-1). If the half life is < 1 day, then the chemical is likely to degrade in aqueous systems (figure 13-1). If the hydrolysis half life is > 1 day, then the Henry's Law Constant should be estimated (figure 13-1). A one day half life was selected as the decision criteria based on an analysis of the data of Maybe and Mill (6). Factors that may influence hydrolysis rates include the pH of the receiving aqueous system (especially if hydrolysis is acid or based catalyzed), temperature of the receiving aquatic system (hydrolysis increases with temperature), concentration of a chemical entering an aqueous system (at high concentrations some chemicals will polymerize before they can hydrolyze) and potential of a chemical to sorb to sediment, suspended sediment or soil (especially if the chemical is released to landfills). Sorption can be estimated as described below.

- **Henry's Law Constant.** Henry's Law Constant is the vapor pressure (in atm) divided by water volubility (in moles/m^3) of a chemical at one temperature and physical state; it provides information on air-water partitioning. The Henry's Law Constant can be calculated using the personal computer method of Meylan and Howard (9). If measured or estimated vapor pressure and water volubility data are not available to calculate Henry's Law Constants, then they can be estimated or measured using the methods described above. A chemical with a Henry's Law Constant $> 10^{-2}$ atm m^3/mole should partition to air and its half life in the atmosphere should be calculated (Fig. 1). If the Henry's Law Constant is $< 10^{-2}$ atm m^3/mole, it should partition to water and its log octanol-water partition coefficient (log K_{ow}) should be estimated (figure 13-1).

. A Henry's Law Constant of 10-3 atm m^3/mole is usually used to describe highly volatile chemicals (29) and is a requirement if volatilization is measured using the method described below. A Henry's Law Constant of 10^{-2} atm m^3/mole was selected as a more conservative decision criteria than 10^{-3} atm m^3/mole, because there are likely to be fewer chemicals with a Henry's Law Constant of 10^{-2} atm m^3/mole that could also partition to sediment, suspended sediment or soil if they could not rapidly escape from aqueous systems. Chemicals such as chloroethane, chloropropane and dichloroethylene with Henry's Law Constants $>10^{-2}$ atm m^3/mole and water solubilities $>= 1$ mole/m^3 and log K_{ow} values $<$ 2 are likely to rapidly escape from aqueous systems before they are sorbed. In contrast a chemical such as octane with a Henry's Law Constant $> 10^{-2}$ atm m^3/mole, water solubility value $< 10^{-2}$ mole/m^3 and log K_{ow} values > 2 may sorb to sediments or soil before significant quantities can escape from aqueous systems. If there uncertainties regarding the influence of sediment, suspended sediment or soil on air-water partitioning, then the log K_{ow} should be estimated as described below and be used to estimate the influence of sorption on air-water partitioning. In general, chemicals with Henry's Law Constants $> 10^{-2}$ atm m^3/mole and log K_{ow} values <2 should almost totally partition to air.

- **Atmospheric half life.** Atmospheric half life is an estimate of the degradation time of chemicals that partition to air and react with hydroxyl radicals or ozone. Atmospheric half life can be calculated using the personal computer method of Meylan and Howard (lo).

- **Octanol-water partition coefficient (K_{ow}).** K_{ow} is used to estimate a chemical's potential to partition between water and octanol (as a surrogate for lipids) and to bioconcentrate in fatty tissues of aquatic organisms. Log K_{ow} can be estimated using the personal computer method of Meylan and Howard (13) or measured using the methods in 40 CFR 796.1570 or 1720 at a cost of $1,310 to **$2,370** (table 13-1). If the log K_{ow} >3 or if the chemical is released to land, a bioconcentration factor should be calculated, a soil or sediment sorption coefficient should be predicted and aerobic biodegradation half life should be estimated or measured (figure 13-1). If the log K_{ow} < 3 and the chemical is released to surface waters, then aquatic photolysis should be measured (figure 13-1).

- **Bioconcentration factor.** The bioconcentration factor is used to estimate the potential for chemicals to concentrate in aquatic organisms after uptake from water. The bioconcentration factor can be calculated using the method of Veith et al. (22) or measured using the methods in 40 CFR 797.1520 at a cost of $15,580-$41,690 (table 13-1). If the estimated bioconcentration factor is > 10,000, some consideration should be given to measuring the bioconcentration factor to determine if metabolism significantly decreases actual bioconcentration.

- **Soil or sediment sorption coefficient.** The soil or sediment sorption coefficient is used to estimate the potential of a chemical to partition between water and the organic fraction of soil or sediment. The soil or sediment sorption coefficient can be predicted using the personal computer method of Meylan et al. (10) or measured using the method in 40 CFR 796.2750 at a cost of $6,680 to $9,430 (table 13-1).

- **Aquatic photolysis half life** Estimates of aquatic photolysis half lives predict the po-

tential of chemicals released to surface waters to degrade directly in sunlight or indirectly in sunlight or sunlight in the presence of humic acids. Chemicals that degrade directly must contain a structural feature that absorbs sunlight. Aquatic photolysis can be measured using the methods in 40 CFR 795.70 at a cost of $11,880-$16,910 (table 13-1). If the aquatic photolysis half life is a few days, then the chemical is likely to degrade (figure 13-1). However, if the aquatic photolysis half life is a few weeks, then aerobic biodegradation half life should be estimated or measured (figure 13-1).

- **Aerobic biodegradation half life.** Aerobic biodegradation is used to estimate the degradation of chemicals by microorganisms in oxygenated water, sediment, sludge, soil, etc. Aerobic biodegradation half life can be predicted using the method of Boethling et al. (l), Gombar and Enslein (3), Klopman et al. (4), Niemi et al. (17) or Tabak and Govind (19) or estimated from the measured values obtained from using the method in 40 CFR 796.3100 at a cost of $8,250-$11,800 (table 13-1). If the predicted or estimated aerobic biodegradation half life is a few days, then the chemical is likely to degrade (figure 13-1). However, if the aerobic biodegradation half life is a few weeks, then anaerobic biodegradation half life should be measured (figure 13-1).

- **Anaerobic biodegradation half life.** Anaerobic biodegradation is used to estimate the degradation of chemicals by microorganisms in anoxic water, sediment, sludge, soil, etc. Anaerobic biodegradation half life can be estimated from the measured values obtained from using the method in 40 CFR 796.3140 at a cost of $5,980-$8,480 (table 13-1). If anaerobic biodegradation half life is a few days, then the chemical is likely to degrade (figure 13-1). However, if the anaerobic biodegradation half life is a few weeks, then the chemical is likely to persist (figure 13-1).

- **Estimation techniques that need to be developed.** Aquatic photolysis, anaerobic biodegradation, oxidation and reduction are important environmental processes that deserve

some consideration for development of validated computerized estimation techniques. For example, it is known that certain chemicals (multi-halogenated aliphatic hydrocarbons) undergo reductive dehalogenation by anaerobic bacteria while other chemicals (nitroaromatics) undergo abiotic reduction in anaerobic environments. Generating rules that could be used as in computer programs to reliably predict aquatic photolysis, anaerobic biodegradation, oxidation and reduction would considerably reduce the time and money needed to generate measured data.

Hypothetical Case Studies

Chemical A. Chemical A is a short-chain phthalate ester that is likely to be released to surface waters. Reliable physical property data are available and do not have to be measured or predicted. The measured hydrolysis half life was > year, the calculated Henry's Law Constant $= 1 \times 10^{-7}$ atm m^3/mole, the estimated log $K_{ow} = 2$, the measured aquatic photolysis half life was > year and the estimated aerobic biodegradation half life was 2 days. It cost $17,350 to $24,700 to develop these data, a savings of about $49,060 to $100,295, when compared to the cost of a standard menu of chemical fate tests (table 13-1). These data suggest that if the chemical were released to surface waters, that it would partition to water and be rapidly biodegraded.

Chemical B. Chemical B is a branched chain alcohol that is likely to be released to surface waters. No reliable physical property data were available and a decision was made to develop measured data at a cost of $5,080 to $17,725 (table 13-1). The estimated hydrolysis half life was > year, the calculated Henry's Law Constant 1×10^{-9} atm m^3/mole, the estimated log $K_{ow} = -1$, the measured aquatic photolysis half life was > year and the measured aerobic biodegradation half life was 0.5 days. It cost $20,130 to $28,710 to develop these data, a savings of about $46,280 to $96,285, when compared to the cost of a standard menu of chemical fate tests (table 13-1). These data suggest that if the chemical were released to surface waters, it would partition to water and be very rapidly biodegraded.

Chemical C. Chemical C is a halogenated silane. Measured boiling point, melting point and vapor pressure were available and did not have to be measured or predicted. The measured hydrolysis half life was 3 minutes. It cost $5,470 to $7,790 to develop these data, a savings of about $60,440 to $117,205, when compared to the cost of a standard menu of chemical fate tests (table 13-1). These data suggest that if the chemical were to contact water it would be rapidly degraded.

Chemical D. Chemical D is a phenol with branched hydrocarbon chain that is likely to be released to land. No reliable physical property data were available and a decision was made to predict the physical properties listed in table 13-1 using the personal computer methods of Meylan and Howard (1 1, 12). The measured hydrolysis half life was > year, the calculated Henry's Law Constant 1×10^{-5} atm m^3/mole, the estimated log $K_{ow} = 5$, the measured fish bioconcentration factor $= 347$, the predicted sediment sorption coefficient was > 5,000, the estimated aerobic biodegradation half life was 3 weeks and the measured anaerobic biodegradation half life was 7 months. It cost $39,380 to $57,960 to develop these data, a savings of about $27,030 to $67,035, when compared to the cost of a standard menu of chemical fate tests (table 13-1). These data suggest that if the chemical were released to land or water, it would partition to water, soil and sediment, be available for bioconcentration by aquatic organisms, be tightly bound to soil and sediment and persist in aerobic and anaerobic environments.

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