PART B - CHAPTER 10

BIOLOGICAL MONITORING

PART B - CHAPTER 10
BIOLOGICAL MONITORING
GUIDELINE 875.2600

10.1 INTRODUCTION

Biological monitoring provides the basis for estimating an internal chemical dose by measuring pesticide and/or metabolite compound concentrations in selected tissues, fluids, or bodily wastes (feces and/or urine) (Woollen, 1993). The data generated using this guideline will serve as the basis for regulating chemicals in various settings, including agriculture, industry, and the residential market. This regulation will be based on the exposure and risk assessment process using the data. Additionally, this data can be used in conjunction with concurrently gathered ambient chemical dissipation data to establish total exposure transfer coefficients. These transfer coefficients can be used in the exposure and risk assessment process to predict exposures for specific activities using ambient concentration data in the absence of scenario-specific exposure data. Monitoring pesticide or metabolite levels associated with short biological half-lives (e.g., blood levels) may be an appropriate measure of current or very recent exposures; monitoring associated with long biological half-lives may be an appropriate measure of integrated exposure over an extended period of time (ACGIH, 1990). The most appropriate methods for biological monitoring should be chosen based on a thorough knowledge and understanding of the pharmacokinetics of the specific pesticide in humans, whether recent or long-term exposures are to be captured by the monitoring technique (Woollen, 1993; Chester, 1993).

In contrast to biological monitoring which measures the pesticide or its metabolites in human tissue, biological effects monitoring (i.e., use of biomarkers) has been used to detect evidence of chemical exposure by measuring a biochemical response, such as changes in enzyme activity (Chester, 1993). In other words, pesticide exposure is estimated based on an indicator property rather than through direct quantification of the chemical itself. This type of monitoring does not provide a direct measure of internal dose, but it can provide an indication of the potential for adverse effects. Dose cannot be estimated unless the correlation between exposure and biochemical response is well understood.

Biological effects monitoring has a long history of use in occupational settings. Correlations between levels of exposure to various industrial chemicals and covalent adducts between the chemical, or its metabolite, and hemoglobin have been reported (Tannenbaum and Skipper, 1984; Pereira and Chang, 1982; Popendorf, 1992). Specific examples of industrial chemicals for which this approach has proved useful include ethylene oxide (Calleman et al., 1978), chloroform (Pereira and Chang, 1982), and aniline (Neumann, 1984). One example of biological effects monitoring with regard to pesticides is the use of cholinesterase levels in the blood as an indicator of worker exposure to organophosphate pesticides (Peoples and Knaak,

1982; ACGIH, 1990). Attempts to correlate levels of cholinesterase inhibition with concentrations of pesticides and/or their metabolite/analog compounds in blood have been generally unsuccessful (Bradway et al., 1977, Roan et al., 1969, Drevenkar et al., 1983) because of the wide variability in cholinesterase levels among individuals (Popendorf and Leffingwell, 1982). Because biological effects monitoring does not yet provide quantitative estimates of pesticide exposure, the focus of this chapter is on biological monitoring of pesticides and their metabolites in human body tissues or body fluids.

Analyses of blood and urine are the most frequently used types of pesticide biological monitoring. Blood analysis is used to measure current or recent exposures. However, it is not as frequently used because of the invasive nature of the collection method. Urine analysis is used to measure the elimination of a pesticide and/or its metabolite/analog compounds as an indicator of exposure. The presence of the parent compound or known urinary metabolites has been used for almost four decades as an indicator of exposure to a number of pesticides including paraquat (Swan, 1969), arsenic (Gollop and Glass, 1979; Wagner and Weswig, 1974), parathion (Lieben et al., 1953), chlorobenzilate (Levy et al., 1981), the phenoxy acid herbicides (Kolmodin-Hedman et al., 1983), and organophosphate pesticides (Kutz and Strassman, 1977; ACGIH, 1990). In recent studies, Dong et al. (1996) used urine monitoring with a pharmacokinetic model to simulate doses of malathion in individuals exposed to aerial sprays, and Krieger at al. (1996) evaluated urinary clearance of disodium octaborate tetrahydrate used for flea control on carpets and furniture. Besides being used as an indicator of exposure, urinary metabolites have been used to confirm poisoning cases involving pesticides, including those involving organophosphates and carbamates (Davies et al., 1979). Such studies have noted the relationship of the pesticide(s) and/or metabolite/analog compounds in urine to exposure. However, more typically, no accurate quantification of exposure was able to be made from these data, partly because of a lack of adequate understanding of the pharmacokinetics of the pesticides. Therefore, it is emphasized that a thorough knowledge of the human metabolism and pharmacokinetics associated with the pesticide of interest is required for biological monitoring to be a useful technique for estimating dose. Pesticides and/or the metabolite/analog compounds may also be monitored through fecal analysis even though there is, by comparison, relatively little literature on this approach. Analysis of sweat as a biological monitoring medium for pesticides has some potential, but is severely limited by potential contamination from the skin of exposed workers. Breath analysis has some limited use for monitoring very recent exposures to volatile nonpolar pesticides, particularly some fumigants (Wilson, 1986). Based on methodological considerations and ease of use, the main focus in biological monitoring of pesticide exposure will be the elimination of pesticides in urine. Urine is an ideal sampling matrix because its collection is relatively simple and non-invasive.

NOTE: Additional information is available on biological monitoring in NIOSH 1984. NIOSH Manual of Analytical Methods. National Institute of Occupational Safety and Health, Cincinnati, Ohio.

The Agency does not routinely require submission of biological monitoring data. However, if a study investigator believes that the criteria for biological monitoring described below can be met for a particular pesticide and chooses to monitor worker exposure using biological monitoring, the Agency will evaluate the resulting data and, if judged to be adequate, will incorporate the results into the risk assessment process. If a study investigator decides to undertake a biological monitoring study, adequate pharmacokinetic data must exist to effectively interpret the data. Prior to initiating a biological monitoring study, the study investigator must receive Agency approval of the specific study protocol.

Biological monitoring studies may be considered and proposed by study investigators as an alternative to passive dosimetry at both outdoor and indoor sites if the first criterion below is satisfied. Biological monitoring studies may be required by the Agency for a specific pesticide when both criteria below are satisfied:

Criterion 1 -- The pharmacokinetics of a pesticide and/or metabolite/analog compounds (i.e., whichever method is selected as an indicator of body burden or internal dose) in humans is understood well enough that a back-calculation to actual dose is possible.

Criterion 2 -- Passive dosimetry techniques are determined not to be applicable for a particular exposure scenario (e.g., for extremely volatile pesticides such as some fumigants or prolonged immersion or saturation of the skin with a nonvolatile pesticide).

Pesticides that are rapidly absorbed and are neither sequestered or metabolized to a great extent are usually good candidates for biological monitoring (Ritter and Franklin, 1989). Also, pesticides for which a quantitative relationship between exposure and urinary metabolites can be established, are good candidates for biological monitoring (Ritter and Franklin, 1989). In contrast, pesticides may not be suitable for biological monitoring if they are extensively metabolized into a large number of metabolites (Chester, 1993) or if they are substantially retained in the skin. Also, biological monitoring should not be considered if the pharmacokinetics in humans are not well characterized.

10.2 SAMPLE COLLECTION

This section provides guidance on collecting samples from the sites of interest. Consult Part B, Chapter 2 - Study Design for information on points to be considered in choosing sample sites and Part C, Quality Control and Quality Assurance for details on ensuring the integrity of the submitted data.

10.2.1 Test Substance

As stated at 40 CFR 158.390, the test substance to be used for inhalation exposure measurements must be a typical end-use product. Where metabolites, breakdown components, or contaminants of pesticide end-use products pose a potential toxicological concern, investigators may need to consider sampling for them on a case-by-case basis.

10.2.2 Timing of Application

Sample collection should be conducted during the intended use season or under climatic conditions that are essentially identical to those encountered during the intended use season. Weather forecasts should be studied to avoid initiating the testing immediately (e.g., within 24 hours) before a precipitation event. For further information on climatological considerations, see Part B, Chapter 2 - Study Design.

10.2.3 Pesticide Application Rate and Frequency

Generally, the typical end-use product chosen for the study should be applied at the maximum rate specified on the label. In addition to applying the product at the maximum label rate, it is suggested that the product be applied using a lower application rate. For example, the typical rate is often used in cancer assessments (U.S. EPA, 1997). Monitoring at more than one rate will provide additional information about the relationship between the application and exposure levels. Also, testing at a lower rate may prove to be beneficial in the event that the data from use of the product at the maximum application rate results in an unacceptable risk.

Where multiple applications are recommended, the minimum time interval between applications should be used. Also, the potential accumulation of residues from multiple applications should be considered. The application method and equipment typical for the selected test substance should be used.

10.2.4 Sampling Parameters

- A sufficient number of replicates should be generated to address the exposure issues associated with each population of interest. In general, each study should include a minimum of 15 replicates per activity. Where possible, these replicates should be distributed as follows: 5 replicates (e.g., individuals) on each of three monitoring periods (e.g., "n" days after application). Investigators must be flexible concerning the number and distribution (e.g., locations and intervals after application) of the monitoring replicates. Because the aforementioned guideline cannot be expected to apply to all potential scenarios, the Agency requires investigators to submit protocols for review purposes prior to the inception of a study.

- The exposure monitoring period must be of sufficient duration, and the analytical method must have adequate sensitivity to ensure that each monitored activity has been sufficiently evaluated . Minimum sample volume and analytical quantification limits should be reflective of appropriate toxicology endpoints. (See Part C - QA/QC for a discussion of determining appropriate limits of quantification). The activity must be well defined and be representative of typical practice. Most postapplication activities range from 4 hours (e.g., harvesting roses/chrysanthemums in a greenhouse) to 8 hours (e.g., harvesting strawberries). Thus, a representative monitoring duration based on typical activities is recommended for each replicate. Justifications for determining monitoring durations should be provided in the study protocol.

- Biological monitoring must be carried out concurrently with transferable residue studies. Refer to the appropriate chapters for guidance concerning the types and numbers of transferable residue samples that are appropriate

- The selected sites and seasonal timing of monitoring must be appropriate to the activity. The need for studies under different geographical/climatological conditions should be considered.

- If biological monitoring is conducted concurrently with passive dosimetry, consideration should be given during the study design phase to ensure that the methods used for one monitoring technique do not invalidate the other (e.g., multiple handwashes during a monitoring period may reduce the amount of pesticide residues available for absorption or multiple layers of clothing).

- Monitoring should be conducted before residues have dissipated beyond the limit of quantification.

10.2.5 Sampling Techniques

The biological monitoring techniques described in this Guideline include measurement of pesticides and their metabolites in blood and urine. Although the Agency accepts both techniques, urine is the preferred

method because it is relatively easy to collect, is non-invasive, and is biokinetically more stable. The proposed method for biological monitoring should be presented to the Agency for review in the study protocol for approval prior to commencing work on the study.

10.2.5.1 Blood

Because prior exposures to some pesticides may have a significant impact on blood levels, baseline blood samples should be taken from each individual prior to exposure. A brief history should be taken from each participant relating to known prior exposures to pesticides for at least the last 2 weeks, including reentry into potentially treated fields (ACGIH, 1990).

Sampling of pesticides or their metabolites in blood should be conducted in a manner that accounts for the considerations summarized in Table 10-1. Blood may be sampled using venous blood or capillary blood from fingers or ear lobes, except under the restriction that capillary blood is not an acceptable media when more than 0.5 mL of blood is needed for an adequate method sensitivity (i.e., to obtain a quantification limit that is low enough to be meaningful), when the chemical to be analyzed is present at the location where the samples are collected (because of the risk of external contamination), or when a specimen is being analyzed for volatile chemicals (because of loss by evaporation) (ACGIH, 1990). Venous blood should be collected in sealed containers. For volatile pesticides or metabolites, special procedures may be required to minimize the headspace in sample containers into which pesticides can be lost. If headspace exists in the sample containers in which volatile pesticide residues are collected, it must be analyzed separately from the blood.

For each 10 mL of unclotted blood, the sample container should contain one of the following anticoagulants designated as appropriate by consultation with the laboratory: 20 mg of potassium oxalate or sodium oxalate, 50 mg of sodium citrate, 15 mg of disodium-EDTA, or 2 mg of heparin. The potential for the anticoagulant interacting with the analytes of interest must be considered in selecting an appropriate anticoagulant. The anticoagulant of choice should have been dispersed along the bottom wall of the tube and then dried. Immediately after sample collection, the sample tube should be rotated gently to thoroughly mix the blood with the anticoagulant. A variety of blood collection devices are commercially available. Investigators should be careful to adhere to the manufacturers' guidelines and protocols when using the equipment (e.g., vacutainer tubes). The potential for the analyte of interest to adsorb to syringes and collection tubes must also be considered.

Table 10-1. Methodological Issues in Sampling, Storage, and Analysis of Blood, and Urine

Issue	Blood	Urine
SAMPLING		
Suitable determinants	Any	Any (although most convenient for polar determinants)
Specimen characteristics	Whole blood, plasma, serum, cells, clotted blood	Timed specimen
Invasiveness	Invasive	Noninvasive
Collection period	Instantaneous	Short-term (24 hours to several days)
Special qualification of health personnel	Medical staff required to obtain sample	Minimal training required
Infection protection	Sterile needle	Clean container
Container requirements	Anticoagulant	Wide Mouth
	Made of material that does not react or absorb determinant	
Volume	Depends on method	50 mL or more aliquot taken from a 24-hour sample
Precautions	Proper timing of sample collection required	
	Venus blood preferred (versus capillary blood, which is only appropriate in limited cases); proper anticoagulant; dry syringe	Sample only persons with normal renal function
Potential sources of contamination	Skin exposure, cleaning solutions, syringe, needle, anticoagulant	Cross contamination from exposed hands, hair, clothing (sampling after shower and clean clothes preferred)
Health hazards	Hepatitis, HIV[a]	Minimal[b]
TRANSPORTATION AND STORAGE		
Potential sources of contamination	Container	
Source of deterioration	Hemolysis, bacterial decomposition, light	Bacterial decomposition, light
Other transport issues	Low temperature required	Large volume and weight of samples
Storage temperature	Refrigerated or frozen (after separation of serum and plasma)	Refrigerated or frozen

Table 10-1. Methodological Issues in Sampling, Storage, and Analysis of Blood, and Urine (continued)

Issue	Blood	Urine
ANALYTICAL		
Cleanup procedure	Complex	Some
Possible interferences	Protein binding, conjugation, and chelation (impact dependent on analytical method)	
Method	Sensitive and specific	
DETERMINANTS REQUIRING SPECIAL CONSIDERATIONS		
Parent chemical	Avoid contamination during sampling procedure	
Volatile chemicals	Use airtight containers with controlled head space	

[a] Personnel involved in the collection and handling of human blood are subject to the provisions of OSHA regulation of Bloodborne Pathogens 29 CFR 1910.1030.

[b] While urine does not normally contain blood and is therefore not explicitly covered by OSHA regulation of Bloodborne Pathogens 29 CFR 1910.1030, protective measures are suggested by the potential for blood cells to be in urine due to various disease entities in participants.

Source: ACGIH 1990.

In addition, a number of precautions should be taken relating to blood monitoring: (1) medical staff should take appropriate precautions to protect both the study participants and staff from exposure to infectious agents (such as HIV); (2) samples should not be drawn from body parts that are known to be contaminated (e.g., from a spill onto skin); (3) prior to drawing blood, the collection site (e.g., arm, finger) should be washed with either detergent and water or isopropyl alcohol and dried; (4) appropriate precautions should be taken so that other chemicals do not contaminate the sample; (5) during analysis, samples should be well mixed prior to removing an aliquot for analysis to avoid errors because of sedimentation; and (6) analyses should account for the fact that some determinants can be present in free, conjugated, and protein-bound forms (samples analyzed for total determinant may require appropriate acid or enzymatic hydrolysis prior to analysis) (ACGIH, 1990).

10.2.5.2 Urine

Prior exposures to the test pesticide or structurally related compounds may interfere with the results of urine sampling for a biological monitoring study. Thus, a sufficient time period between such exposures and participation in the study is required to ensure adequate urinary clearance of the compound and its metabolites, based on pharmacokinetic data.

Sampling of pesticides and/or their metabolite/analog compounds in urine should be conducted in a manner that accounts for the considerations summarized in Table 10-1. Urine collection should cover 24-hour periods. Collections should begin on the day before participating in the postapplication exposure monitoring activities and continue on the day of postapplication monitoring and for an appropriate time period after these activities have been completed, depending on the excretion kinetics of the compound. The 24-hour collection cycle should begin with the first void after beginning work activities and end with the first void on the following morning, continuing this 24-hour cycle on subsequent days. All urine specimens collected should be logged in at the time of collection. The subjects sampled should be provided with readily sealable containers (i.e., that prevent spillage) of approximately 500 mL volume for every 6 hours or a larger container for collecting urine over the entire 24-hour period. These should be prerinsed with an appropriate solvent, or heated to 250°C (if glass) for 1 to 2 hours to prevent contamination.

The material used in the construction of the collection bottle should not interfere with (e.g., absorb) the analytes of interest. Materials may include polypropylene or polyethylene collection vessels and caps or glass bottles. Inert materials such as polytetrafluoroethylene (PTFE) should be used for caps. Special precautions are needed for specimens collected for measurement of volatile chemicals. If a large container of known volume is used, the laboratory must sample and analyze both the liquid and its head space. In either case, samples must be collected in containers that can be immediately sealed and kept airtight, and the

containers should be able to withstand the pressure changes caused by changes in temperature during transportation and storage. Another consideration in selecting appropriate collection vessels is the light sensitivity of the analyte (i.e., amber bottles can be used if the analytes are degraded by light). Based on the stability of the analyte of interest at field temperatures, urine samples may be refrigerated or other methods of cooling may be used to preserve the integrity of the samples. Preservatives should be added as needed if they do not interfere with measuring the analyte.

After collection of a 24-hour urine sample has been completed, the urine volume should be measured and two aliquots of 50 mL or more should be taken and stored depending on the requirements of the analytical method. One sample may be transported to the analytical facility for analysis while the other set remains in local frozen storage at least until the first set has arrived at its destination at the laboratory. The considerations for selecting appropriate storage containers are the same as those described for sample collection containers.

10.3 SAMPLE STORAGE

Once the field samples have been collected, the next step is to transport the samples to the analytical laboratory and store them until analysis. Samples should be transported on either wet or dry ice, as appropriate, to minimize analyte dissipation. After arrival at the analytical laboratory, samples should be stored as noted below. Because of the diverse nature and properties of potential biological monitoring indicators, some analytes may exhibit unusual behavior under these storage and transport guidelines. If investigators deviate from the aforementioned guidelines because of the unusual physical/chemical characteristics of the analyte(s) of interest, the rationale must be documented in any submission to the Agency.

If biological monitoring media are to be stored after exposure, a stability test for the analyte(s) of interest should be documented in conformance with the medium-specific storage precautions noted below. See Part C, QA/QC for more information regarding procedures for initiating a stability study. In short, fortified media must be stored under the same conditions that will be used for field samples. In addition, the storage stability samples are to be handled and analyzed by the same methods that will be employed for field samples.

10.3.1 Blood

All blood samples should be treated with a minimum of agitation and temperature changes during transportation and storage to minimize the extent of hemolysis (ACGIH, 1990). If the analysis is to be done

on separated serum, the collected venous blood should be allowed to clot in collection containers that are not treated with anticoagulant. The clot is then removed about 10 minutes after collection, and the serum is withdrawn by syringe (ACGIH, 1990). Whole blood samples should never be frozen; for overnight storage, refrigeration at 4°C is usually satisfactory. For longer storage, samples should be centrifuged, and the plasma should be removed for storage. Field blanks and other appropriate control samples (e.g., field fortifications) should be included in the analysis (ACGIH, 1990).

10.3.2 Urine

All urine specimens should be stored frozen after the specific gravity is measured.

10.4 SAMPLE ANALYSIS

The selection of analytical procedures will depend on the particular chemical or metabolite being studied. Consequently, this decision is left to the discretion of the investigator.

Urine samples collected over a 24-hour period should be well mixed before aliquots are taken for chemical analyses. The investigator should determine creatinine levels as a way of qualitatively monitoring completeness of urine collection samples. Corrections to adjust urinary residue levels in incomplete samples on the basis of urinary creatinine levels have limited utility because of the wide intra- and inter-individual variability of creatinine output (Alessio et al., 1985; Boeniger et al., 1993). Therefore, the quantitative use of creatine as a basis for adjusting urinary chemical residue output is discouraged by the Agency. Creatinine may be measured using a colorimetric method known as the Jaffe Reaction (Boeniger et al., 1993). Specific gravity, as another measure of 24-hour sample completeness (Alessio et al., 1983), can be read using a densitometer; this analysis should be performed as soon after collection as possible (and before sample storage) before irreversible sedimentation of solids occurs in the samples. Most clinical laboratories can perform these two analyses at relatively low cost. Specimens showing physiologically impossible low levels of creatinine or specific gravity should be viewed as having been tampered with and should be either discarded or reported with an appropriate footnote.

10.5 CALCULATIONS

Refer to Part D of this document for a description of the calculations needed for estimating exposure and risk.

10.6 DATA PRESENTATION

The amount of chemical should be reported for each sample and as a cumulative total for each exposure period. Residue data should be reported electronically in tabular form (i.e., spreadsheets). Distributional data should be provided, to the extent possible.

REFERENCES FOR PART B, CHAPTER 10

ACGIH. (1990) Documentation of the Threshold Limit Values and Biological Exposure Indices. Cincinnati, Ohio: American Conference of Governmental Industrial Hygienists.

Alessio, L.; Berlin, A.; Dell'Orto, A.; Toffoletto, F.; Ghezzi, I. (1985) Reliability of Urinary Creatinine as a Parameter Used to Adjust Values of Urinary Biological Indicators. Int. Arch. Occup. Environ. Health. 55:99-106.

Boeniger, M.F.; Lowry, L.K.; Rosenberg, J. (1993) Interpretation of Urine Results Used to Assess Chemical Exposure with Emphasis on Creatinine Adjustments: A Review. Am. Ind. Hyg. Assoc. J. 54(10):615-627.

Bradway, D.E.; Shafik, T.M.; Lores, E.N. (1977) Comparison of Cholinesterase Activity, Residue Levels, and Urinary Metabolite Excretion of Rats Exposed to Organophosphorus Pesticides. J. Agr. Food Chem. 25(6):1353-1358.

Calleman, C.J.; Ehrenberg, L.; Jansson, B.; Osterman-Golkar, S.; Segerback, D.; Svenson, K.; Wachtmeister, C.A. (1978) Monitoring and Risk Assessment by Means of Alkyl Groups in Hemoglobin in Persons Occupationally Exposed to Ethylene Oxide. J. Environ. Path. Toxicol. 2:427-442.

Chester, G. (1993) Evaluation of Agricultural Worker Exposure to, and Absorption of, Pesticides. Ann. Occup. Hyg. 37:509-523.

Davies, J.E.; Enos, H.F.; Barquet, A.; Morgade, C.; Danauskas, J.X. (1979) Developments in Toxicology and Environmental Science. Pesticide Monitoring Studies. The Epidemiologic and Toxicologic Potential of Urinary Metabolites. In: Toxicology and Occupational Medicine. W.B. Deichman, ed. NY. pp. 369-380

Dong, M.H.; Ross, J.H.; Thongsinthusak, T.; Krieger, R.I. (1996) Use of Spot Urine Sample Results in Physiologically Based Pharmacokinetic Modeling of Absorbed Malathion Doses in Humans. In: Biomarkers for Agrochemicals and Toxic Substances. Washington, D.C.: American Chemical Society.

Drevenkar, V.B.; Stengl, B.; Tkalcevic, B.; Vasilic, Z. (1983) Occupational Exposure Control by Simultaneous Determination of N-methylcarbamates and Organophosphorus Pesticide Residues in Human Urine. Int. J. Environ. Anal. Chem. 14:215-230.

Gallop, B.R.; Glass, W.I. (1979) Urinary Arsenic Levels in Lumber Treatment Operators. N.Z. Med. J. 89:10-11.

Kolmoden-Hedman, B.; Hoglund, S.; Swenson, A.; Okerblom, M. (1983) Studies on Phenoxy Acid Herbicides. II. Oral and dermal uptake and elimination in urine of MCPA in humans. Arch. Toxicol. Contam. 54:267-273.

Krieger, R.I.; Dinoff, T.M.; Peterson, J. (1996) Human Disodium Octaborate Tetrahydrate Exposure Following Carpet Flea Treatment is Not Associated with Significant Dermal Absorption. J. Exp. Anal. Environ. Epid. 6(3):279-288.

Kutz, F.W.; Strassman, S.C. (1977) Human Urinary Metabolites of Organophosphate Insecticides Following Mosquito Adulticiding. Mos. News. 37(12):211-218.

Levy, K.A.; Brady, S.S.; Pfaffenberger, C.D. (1981) Chlorobenzilate Residues in Citrus Worker Urine. Bull. Environ. Contam. Toxicol. 27(2):235-238.

Lieben, J.R.; Waldman, K.; Krause, L. (1953) Urinary Excretion of Paranitrophenol Following Exposure to Parathion. Ind. Hyg. Occ. Med. 7:93-98.

Neumann, H. (1984) Analysis of Hemoglobin as a Dose Monitor for Alkylating and Arylating Agents. Arch. Toxicol. 56:1-6.

NIOSH. (1984) NIOSH Manual of Analytical Methods. National Institute of Occupational Safety and Health, Cincinnati, Ohio.

Peoples, S.A.; Knaak, J.B. (1982) Monitoring Pesticide Blood Cholinesterase and Analyzing Blood and Urine for Pesticides and Their Metabolites. In: Pesticide Residue and Exposure, J.R. Plimmer, ed. ACS Symposium Series, No. 182, American Chemical Society, Washington, DC, pp. 41-57.

Pereira, M.A.; Chang, L.W. (1982) Hemoglobin Binding as a Dose Monitor for Chemical Carcinogens. In: Bradway Report 13, Indicators of Genotoxic Exposure, B.A. Bridges, B.E. Butterworth, and I.B. Weinstein, eds., Cold Spring Harbor Laboratory, pp. 177-187.

Popendorf, W.; Leffingwell, J.T. (1982) Regulating Organophosphate Pesticide Residues for Farmworker Protection. Residue Rev. 85:125-201.

Popendorf, W. (1992) Reentry Field Data and Conclusions. Reviews Environ. Contam. Toxicol. 128:71-117.

Ritter, L.; Franklin, C.A. (1989) Use of Biological Monitoring in the Regulatory Process. In: Biological Monitoring for Pesticide Exposure. ACS Symp, Series 382, American Chemical Society, Washington, DC.

Roan, C.C.; Morgan, D.P.; Cook, N.; Paschal, E.H. (1969) Blood Cholinesterases, Serum Parathion Concentrations and Urine p-Nitrophenol Concentrations in Exposed Individuals. Bull. Environ. Contam. Toxicol. 4:362-369.

Swan, A.A.B. (1969) Exposure of spray operators to paraquat. Brit. J. Ind. Med. 26:322-329.

Tannenbaum, S.R.; Skipper, P.L. (1984) Biological Aspects to the Evaluation of Risk: Dosimetry of Carcinogens in Man. Fund. Appl. Toxicol. 4:S367-S373.

U.S. EPA. (1997) Standard Operating Procedures (SOPs) for Residential Exposure Assessments, draft report. Washington, D.C.: U.S. Environmental Protection Agency, Office of Pesticide Programs.

Wagner, S.L.; Weswig, P. (1974) Arsenic in Blood and Urine of Forest Workers. Arch. Environ. Hlth. 28:77-79.

Wilson, H.K. (1986) Breath Analysis: Physiological Basis and Sampling Techniques. Scand. J. Work Environ. Health 12: 174-192.

Woollen, B.H. (1993) Biological Monitoring for Pesticide Absorption. Am. Occup. Hyg. 37:525-540.