

APPENDIX F TO §1910.1027
NONMANDATORY PROTOCOL FOR BIOLOGICAL MONITORING

1.00 Introduction

Under the final OSHA cadmium rule (29 CFR part 1910), monitoring of biological specimens and several periodic medical examinations are required for eligible employees. These medical examinations are to be conducted regularly, and medical monitoring is to include the periodic analysis of cadmium in blood (CDB), cadmium in urine (CDU) and beta-2-microglobulin in urine (B2MU). As CDU and B2MU are to be normalized to the concentration of creatinine in urine (CRTU), then CRTU must be analyzed in conjunction with CDU and B2MU analyses.

The purpose of this protocol is to provide procedures for establishing and maintaining the quality of the results obtained from the analyses of CDB, CDU and B2MU by commercial laboratories. Laboratories conforming to the provisions of this nonmandatory protocol shall be known as "participating laboratories." The biological monitoring data from these laboratories will be evaluated by physicians responsible for biological monitoring to determine the conditions under that employees may continue to work in locations exhibiting airborne-cadmium concentrations at or above defined actions levels (see paragraphs (I)(3) and (I)(4) of the final rule). These results also may be used to support a decision to remove workers from such locations.

Under the medical monitoring program for cadmium, blood and urine samples must be collected at defined intervals from workers by physicians responsible for medical monitoring; these samples are sent to commercial laboratories that perform the required analyses and report results of these analyses to the responsible physicians. To ensure the accuracy and reliability of these laboratory analyses, the laboratories to that samples are submitted should participate in an ongoing and efficacious proficiency testing program. Availability of proficiency testing programs may vary with the analyses performed.

To test proficiency in the analysis of CDB, CDU and B2MU, a laboratory should participate either in the interlaboratory comparison program operated by the Centre de Toxicologie du Quebec (CTQ) or an equivalent program. (Currently, no laboratory in the U.S. performs proficiency testing on CDB, CDU or B2MU.) Under this program, CTQ sends participating laboratories 18 samples of each analyte (CDB, CDU and/or B2MU) annually for analysis. Participating laboratories must return the results of these analyses to CTQ within four to five weeks after receiving the samples.

The CTQ program pools analytical results from many participating laboratories to derive consensus mean values for each of the samples distributed. Results reported by each laboratory then are compared against these consensus means for the analyzed samples to determine the relative performance of each laboratory. The proficiency of a participating laboratory is a function of the extent of agreement between results submitted by the participating laboratory and the consensus values for the set of samples analyzed.

Proficiency testing for CRTU analysis (that should be performed with CDU and B2MU analyses to evaluate the results properly) also is recommended. In the U.S., only the College of American Pathologists (CAP) currently conducts CRTU proficiency testing; participating laboratories should be accredited for CRTU analysis by the CAP.

Results of the proficiency evaluations will be forwarded to the participating laboratory by the proficiency-testing laboratory, as well as to physicians designated by the participating laboratory to receive this information. In addition, the participating laboratory should, on request, submit the results of their internal Quality Assurance/Quality Control (QA/QC) program for each analytic procedure (i.e., CDB, CDU and/or B2MU) to physicians designated to receive the proficiency results. For participating laboratories offering CDU and/or B2MU analyses, QA/QC documentation also should be provided for CRTU analysis. (Laboratories should

provide QA/QC information regarding CRTU analysis directly to the requesting physician if they perform the analysis in-house; if CRTU analysis is performed by another laboratory under contract, this information should be provided to the physician by the contract laboratory.)

QA/QC information, along with the actual biological specimen measurements, should be provided to the responsible physician using standard formats. These physicians then may collate the QA/QC information with proficiency test results to compare the relative performance of laboratories, as well as to facilitate evaluation of the worker monitoring data. This information supports decisions made by the physician with regard to the biological monitoring program, and for mandating medical removal.

This protocol describes procedures that may be used by the responsible physicians to identify laboratories most likely to be proficient in the analysis of samples used in the biological monitoring of cadmium; also provided are procedures for record keeping and reporting by laboratories participating in proficiency testing programs, and recommendations to assist these physicians in interpreting analytical results determined by participating laboratories. As the collection and handling of samples affects the quality of the data, recommendations are made for these tasks. Specifications for analytical methods to be used in the medical monitoring program are included in this protocol as well.

In conclusion, this document is intended as a supplement to characterize and maintain the quality of medical monitoring data collected under the final cadmium rule promulgated by OSHA (29 CFR part 1910). OSHA has been granted authority under the Occupational Safety and Health Act of 1970 to protect workers from the effects of exposure to hazardous substances in the work place and to mandate adequate monitoring of workers to determine when adverse health effects may be occurring. This non-mandatory protocol is intended to provide guidelines and recommendations to improve the accuracy and reliability of the procedures used to analyze the biological samples collected as part of the medical monitoring program for cadmium.

2.0 Definitions

When the terms below appear in this protocol, use the following definitions.

Accuracy: A measure of the bias of a data set. Bias is a systematic error that is either inherent in a method or caused by some artifact or idiosyncrasy of the measurement system. Bias is characterized by a consistent deviation (positive or negative) in the results from an accepted reference value.

Arithmetic Mean: The sum of measurements in a set divided by the number of measurements in a set.

Blind Samples: A quality control procedure in that the concentration of analyte in the samples should be unknown to the analyst at the time that the analysis is performed.

Coefficient of Variation: The ratio of the standard deviation of a set of measurements to the mean (arithmetic or geometric) of the measurements.

Compliance Samples: Samples from exposed workers sent to a participating laboratory for analysis.

Control Charts: Graphic representations of the results for quality control samples being analyzed by a participating laboratory.

Control Limits: Statistical limits that define when an analytic procedure exceeds acceptable parameters; control limits provide a method of assessing the accuracy of analysts, laboratories, and discrete analytic runs.

Control Samples: Quality control samples.

F/T: The measured amount of an analyte divided by the theoretical value (defined below) for that analyte in the sample analyzed; this ratio is a measure of the recovery for a quality control sample.

Geometric Mean: The natural antilog of the mean of a set of natural log-transformed data.

Geometric Standard Deviation: The antilog of the standard deviation of a set of natural

log-transformed data.

Limit of Detection: Using a predefined level of confidence, this is the lowest measured value at that some of the measured material is likely to have come from the sample.

Mean: A central tendency of a set of data; in this protocol, this mean is defined as the **arithmetic mean** (see definition of **arithmetic mean** above) unless stated otherwise.

Performance: A measure of the overall quality of data reported by a laboratory.

Pools: Groups of quality-control samples to be established for each target value (defined below) of an analyte. For the protocol provided in attachment 3, for example, the theoretical value of the quality control samples of the pool must be within a range defined as plus or minus (\pm) 50% of the target value. Within each analyte pool, there must be quality control samples of at least 4 theoretical values.

Precision: The extent of agreement between repeated, independent measurements of the same quantity of an analyte.

Proficiency: The ability to satisfy a specified level of analyte performance.

Proficiency Samples: Specimens, the values of that are unknown to anyone at a participating laboratory, and that are submitted by a participating laboratory for proficiency testing.

Quality or Data Quality: A measure of the confidence in the measurement value.

Quality Control (QC) Samples: Specimens, the value of that is unknown to the analyst, but is known to the appropriate QA/QC personnel of a participating laboratory; when used as part of a laboratory QA/QC program, the theoretical values of these samples should not be known to the analyst until the analyses are complete. QC samples are to be run in sets consisting of one QC sample from each pool (see definition of "pools" above).

Sensitivity: For the purposes of this protocol, the limit of detection.

Standard Deviation: A measure of the distribution or spread of a data set about the mean; the standard deviation is equal to the positive square root of the variance, and is expressed in the same units as the original measurements in the data set.

Standards: Samples with values known by the analyst and used to calibrate equipment and to check calibration throughout an analytic run. In a laboratory QA/QC program, the values of the standards must exceed the values obtained for compliance samples such that the lowest standard value is near the limit of detection and the highest standard is higher than the highest compliance sample or QC sample. Standards of at least three different values are to be used for calibration, and should be constructed from at least 2 different sources.

Target Value: Those values of CDB, CDU or B₂MU that trigger some action as prescribed in the medical surveillance section of the regulatory text of the final cadmium rule. For CDB, the target values are 5, 10 and 15 $\mu\text{g/l}$. For CDU, the target values are 3, 7, and 15 $\mu\text{g/g CRTU}$. For B₂MU, the target values are 300, 750 and 1500 $\mu\text{g/g CRTU}$. (Note that target values may vary as a function of time.)

Theoretical Value (or Theoretical Amount): The reported concentration of a quality-control sample (or calibration standard) derived from prior characterizations of the sample.

Value or Measurement Value: The numerical result of a measurement.

Variance: A measure of the distribution or spread of a data set about the mean; the variance is the sum of the squares of the differences between the mean and each discrete measurement divided by one less than the number of measurements in the data set.

3.0 Protocol

This protocol provides procedures for characterizing and maintaining the quality of analytic results derived for the medical monitoring program mandated for workers under the final cadmium rule.

3.1 Overview

The goal of this protocol is to assure that medical monitoring data are of sufficient quality to facilitate proper interpretation. The data quality objectives (DQOs) defined for the medical monitoring program are summarized in Table 1. Based on available information, the DQOs

presented in Table 1 should be achievable by the majority of laboratories offering the required analyses commercially; OSHA recommends that only laboratories meeting these DQOs be used for the analysis of biological samples collected for monitoring cadmium exposure.

**TABLE 1.
RECOMMENDED DATA QUALITY OBJECTIVES (DQOs) FOR THE
CADMIUM MEDICAL MONITORING PROGRAM**

Analyte/concentration pool	Limit of detection	Precision (CV) (%)	Accuracy
Cadmium in blood ≤ 2 µg/l > 2 µg/l	0.5 µg/l	----	± µg/l or 15% of the mean.
	----	40	
	----	20	
Cadmium in urine ≤ 2 µg/l creatinine > 2 µg/l creatinine	0.5 µg/g creatinine	----	± µg/l or 15% of the mean.
	----	40	
	----	20	
β ₂ -microglobulin in urine: 100 µg/g creatine.	100 µg/g creatinine	5	±15% of the mean.

To satisfy the DQOs presented in Table 1, OSHA provides the following guidelines:

1. Procedures for the collection and handling of blood and urine are specified (Section 3.4.1 of this protocol);
2. Preferred analytic methods for the analysis of CDB, CDU and B2MU are defined (and a method for the determination of CRTU also is specified since CDU and B2MU results are to be normalized to the level of CRTU).
3. Procedures are described for identifying laboratories likely to provide the required analyses in an accurate and reliable manner;
4. These guidelines (Sections 3.2.1 to 3.2.3, and Section 3.3) include recommendations regarding internal QA/QC programs for participating laboratories, as well as levels of proficiency through participation in an interlaboratory proficiency program;
5. Procedures for QA/QC record keeping (Section 3.3.2), and for reporting QC/QA results are described (Section 3.3.3); and,
6. Procedures for interpreting medical monitoring results are specified (Section 3.4.3).

Methods recommended for the biological monitoring of eligible workers are:

1. The method of Stoepler and Brandt (1980) for CDB determinations (limit of detection: 0.5 µg/l);
2. The method of Pruszkowska et al. (1983) for CDU determinations (limit of detection: 0.5 µg/l of urine); and,
3. The Pharmacia Delphia test kit (Pharmacia 1990) for the determination of B2MU (limit of detection: 100 µg/l urine).

Because both CDU and B2MU should be reported in µg/g CRTU, an independent determination of CRTU is recommended. Thus, both the OSHA Salt Lake City Technical Center (OSLTC) method (OSHA, no date) and the Jaffe method (Du Pont, no date) for the determination of CRTU are specified under this protocol (i.e., either of these 2 methods may be used). Note that although detection limits are not reported for either of these CRTU methods, the range of measurements expected for CRTU (0.9-1.7 µg/l) are well above the likely limit of detection for either of these methods (Harrison, 1987).

Laboratories using alternate methods should submit sufficient data to the responsible physicians demonstrating that the alternate method is capable of satisfying the defined data quality objectives of the program. Such laboratories also should submit a QA/QC plan that documents the performance of the alternate method in a manner entirely equivalent to the QA/QC plans proposed in Section 3.3.1.

3.2 Duties of the Responsible Physician

The responsible physician will evaluate biological monitoring results provided by participating laboratories to determine whether such laboratories are proficient and have satisfied the QA/QC recommendations. In determining that laboratories to employ for this purpose, these physicians should review proficiency and QA/QC data submitted to them by the participating laboratories.

Participating laboratories should demonstrate proficiency for each analyte (CDU, CDB and B2MU) sampled under the biological monitoring program. Participating laboratories involved in analyzing CDU and B2MU also should demonstrate proficiency for CRTU analysis, or provide evidence of a contract with a laboratory proficient in CRTU analysis.

3.2.1 Recommendations for Selecting Among Existing Laboratories

OSHA recommends that existing laboratories providing commercial analyses for CDB, CDU and/or B2MU for the medical monitoring program satisfy the following criteria:

1. Should have performed commercial analyses for the appropriate analyte (CDB, CDU and/or B2MU) on a regular basis over the last 2 years;
2. Should provide the responsible physician with an internal QA/QC plan;
3. If performing CDU or B2MU analyses, the participating laboratory should be accredited by the CAP for CRTU analysis, and should be enrolled in the corresponding CAP survey (note that alternate credentials may be acceptable, but acceptability is to be determined by the responsible physician); and,
4. Should have enrolled in the CTQ interlaboratory comparison program for the appropriate analyte (CDB, CDU and/or B2MU).

Participating laboratories should submit appropriate documentation demonstrating compliance with the above criteria to the responsible physician. To demonstrate compliance with the first of the above criteria, participating laboratories should submit the following documentation for each analyte they plan to analyze (note that each document should cover a period of at least 8 consecutive quarters, and that the period designated by the term "regular analyses" is at least once a quarter):

1. Copies of laboratory reports providing results from regular analyses of the appropriate analyte (CDB, CDU and/or B2MU);
2. Copies of 1 or more signed and executed contracts for the provision of regular analyses of the appropriate analyte (CDB, CDU and/or B2MU); or,
3. Copies of invoices sent to 1 or more clients requesting payment for the provision of regular analyses of the appropriate analyte (CDB, CDU and/or B2MU). Whatever the form of documentation submitted, the specific analytic procedures conducted should be identified directly. The forms that are copied for submission to the responsible physician also should identify the laboratory that provided these analyses.

To demonstrate compliance with the second of the above criteria, a laboratory should submit to the responsible physician an internal QA/QC plan detailing the standard operating procedures to be adopted for satisfying the recommended QA/QC procedures for the analysis of each specific analyte (CDB, CDU and/or B2MU). Procedures for internal QA/QC programs are detailed in Section 3.3.1 below.

To satisfy the third of the above criteria, laboratories analyzing for CDU or B2MU also should submit a QA/QC plan for creatinine analysis (CRTU); the QA/QC plan and characterization analyses for CRTU must come from the laboratory performing the CRTU analysis, even if the CRTU analysis is being performed by a contract laboratory.

Laboratories enrolling in the CTQ program (to satisfy the last of the above criteria) must remit, with the enrollment application, an initial fee of approximately \$100 per analyte. (Note that this fee is only an estimate, and is subject to revision without notice.) Laboratories should indicate on the application that they agree to have proficiency test results sent by the CTQ directly to the physicians designated by participating laboratories.

Once a laboratory's application is processed by the CTQ, the laboratory will be assigned a code number that will be provided to the laboratory on the initial confirmation form, along with identification of the specific analytes for that the laboratory is participating. Confirmation of participation will be sent by the CTQ to physicians designated by the applicant laboratory.

3.2.2 Recommended Review of Laboratories Selected to Perform Analyses

Six months after being selected initially to perform analyte determinations, the status of participating laboratories should be reviewed by the responsible physicians. Such reviews should then be repeated every 6 months or whenever additional proficiency or QA/QC documentation is received (whichever occurs first).

As soon as the responsible physician has received the CTQ results from the first 3 rounds of proficiency testing (i.e., 3 sets of 3 samples each for CDB, CDU and/or B2MU) for a participating laboratory, the status of the laboratory's continued participation should be reviewed. Over the same initial 6-month period, participating laboratories also should provide responsible physicians the results of their internal QA/QC monitoring program used to assess performance for each analyte (CDB, CDU and/or B2MU) for that the laboratory performs determinations. This information should be submitted using appropriate forms and documentation.

The status of each participating laboratory should be determined for each analyte (i.e., whether the laboratory satisfies minimum proficiency guidelines based on the proficiency samples sent by the CTQ and the results of the laboratory's internal QA/QC program). To maintain competency for analysis of CDB, CDU and/or B2MU during the first review, the laboratory should satisfy performance requirements for at least 2 of the 3 proficiency samples provided in each of the 3 rounds completed over the 6-month period. Proficiency should be maintained for the analyte(s) for that the laboratory conducts determinations.

To continue participation for CDU and/or B2MU analyze, laboratories also should either maintain accreditation for CRTU analysis in the CAP program and participate in the CAP surveys, or they should contract the CDU and B2MU analyses to a laboratory that satisfies these requirements (or that can provide documentation of accreditation/participation in an equivalent program).

The performance requirement for CDB analysis is defined as an analytical result within $\pm 1 \mu\text{g/l}$ blood or 15% of the consensus mean (whichever is greater). For samples exhibiting a consensus mean less than $1 \mu\text{g/l}$, the performance requirement is defined as a concentration between the detection limit of the analysis and a maximum of $2 \mu\text{g/l}$. The purpose for redefining the acceptable interval for low CDB values is to encourage proper reporting of the actual values obtained during measurement; laboratories, therefore, will not be penalized (in terms of a narrow range of acceptability) for reporting measured concentrations smaller than $1 \mu\text{g/l}$.

The performance requirement for CDU analysis is defined as an analytical result within $\pm 1 \mu\text{g/l}$ urine or 15% of the consensus mean (whichever is greater). For samples exhibiting a consensus mean less than $1 \mu\text{g/l}$ urine, the performance requirement is defined as a concentration between the detection limit of the analysis and a maximum of $2 \mu\text{g/l}$ urine. Laboratories also should demonstrate proficiency in creatinine analysis as defined by the CAP. Note that reporting CDU results, other than for the CTQ proficiency samples (i.e., compliance samples), should be accompanied with results of analyses for CRTU, and these 2 sets of results should be combined to provide a measure of CDU in units of $\mu\text{g/g}$ CRTU.

The performance requirement for B2MU is defined as analytical results within $\pm 15\%$ of the consensus mean. Note that reporting B2MU results, other than for CTQ proficiency samples (i.e., compliance samples), should be accompanied with results of analyses for CRTU, and these 2 sets of results should be combined to provide a measure of B2MU in units of $\mu\text{g/g}$ CRTU.

There are no recommended performance checks for CRTU analyses. As stated previously, laboratories performing CRTU analysis in support of CDU or B2MU analyses should be accredited by the CAP, and participating in the CAP's survey for CRTU.

Following the first review, the status of each participating laboratory should be reevaluated at regular intervals (i.e., corresponding to receipt of results from each succeeding round of proficiency testing and submission of reports from a participating laboratory's internal QA/QC program).

After a year of collecting proficiency test results, the following proficiency criterion should be added to the set of criteria used to determine the participating laboratory's status (for analyzing CDB, CDU and/or B2MU): A participating laboratory should not fail performance requirements for more than 4 samples from the 6 most recent consecutive rounds used to assess proficiency for CDB, CDU and/or B2MU separately (i.e., a total of 18 discrete proficiency samples for each analyte). Note that this requirement does not replace, but supplements, the recommendation that a laboratory should satisfy the performance criteria for at least 2 of the 3 samples tested for each round of the program.

3.2.3 Recommendations for Selecting Among Newly-Formed Laboratories (or Laboratories that Previously Failed to Meet the Protocol Guidelines)

OSHA recommends that laboratories that have not previously provided commercial analyses of CDB, CDU and/or B2MU (or have done so for a period less than 2 years), or that have provided these analyses for 2 or more years but have not conformed previously with these protocol guidelines, should satisfy the following provisions for each analyte for that determinations are to be made prior to being selected to analyze biological samples under the medical monitoring program:

1. Submit to the responsible physician an internal QA/QC plan detailing the standard operating procedures to be adopted for satisfying the QA/QC guidelines (guidelines for internal QA/QC programs are detailed in Section 3.3.1);
2. Submit to the responsible physician the results of the initial characterization analyses for each analyte for which determinations are to be made;
3. Submit to the responsible physician the results, for the initial 6-month period, of the internal QA/QC program for each analyte for which determinations are to be made (if no commercial analyses have been conducted previously, a minimum of 2 mock standardization trials for each analyte should be completed per month for a 6-month period);
4. Enroll in the CTQ program for the appropriate analyte for that determinations are to be made, and arrange to have the CTQ program submit the initial confirmation of participation and proficiency test results directly to the designated physicians. Note that the designated physician should receive results from 3 completed rounds from the CTQ program before approving a laboratory for participation in the biological monitoring program;
5. Laboratories seeking participation for CDU and/or B2MU analyses should submit to the responsible physician documentation of accreditation by the CAP for CRTU analyses performed in conjunction with CDU and/or B2MU determinations (if CRTU analyses are conducted by a contract laboratory, this laboratory should submit proof of CAP accreditation to the responsible physician); and,
6. Documentation should be submitted on an appropriate form.

To participate in CDB, CDU and/or B2MU analyses, the laboratory should satisfy the above criteria for a minimum of 2 of the 3 proficiency samples provided in each of the 3 rounds of the CTQ program over a 6-month period; this procedure should be completed for each appropriate analyte. Proficiency should be maintained for each analyte to continue participation. Note that laboratories seeking participation for CDU or B2MU also should address the performance requirements for CRTU, that involves providing evidence of accreditation by the CAP and participation in the CAP surveys (or an equivalent program).

The performance requirement for CDB analysis is defined as an analytical result within $\pm 1 \mu\text{g/l}$ or 15% of the consensus mean (whichever is greater). For samples exhibiting a consensus mean less than $1 \mu\text{g/l}$, the performance requirement is defined as a concentration between the detection limit of the analysis and a maximum of $2 \mu\text{g/l}$. The purpose of redefining the acceptable interval for low CDB values is to encourage proper reporting of the actual values obtained during measurement; laboratories, therefore, will not be penalized (in terms of a narrow range of acceptability) for reporting measured concentrations less than $1 \mu\text{g/l}$.

The performance requirement for CDU analysis is defined as an analytical result within $\pm 1 \mu\text{g/l}$ urine or 15% of the consensus mean (whichever is greater). For samples exhibiting a consensus mean less than $1 \mu\text{g/l}$ urine, the performance requirement is defined as a concentration that falls between the detection limit of the analysis and a maximum of $2 \mu\text{g/l}$ urine. Performance requirements for the companion CRTU analysis (defined by the CAP) also should be met. Note that reporting CDU results, other than for CTQ proficiency testing should be accompanied with results of CRTU analyses, and these 2 sets of results should be combined to provide a measure of CDU in units of $\mu\text{g/g}$ CRTU.

The performance requirement for B2MU is defined as an analytical result within $\pm 15\%$ of the consensus mean. Note that reporting B2MU results, other than for CTQ proficiency testing should be accompanied with results of CRTU analysis, these 2 sets of results should be combined to provide a measure of B2MU in units of $\mu\text{g/g}$ CRTU.

Once a new laboratory has been approved by the responsible physician for conducting analyte determinations, the status of this approval should be reviewed periodically by the responsible physician as per the criteria presented under Section 3.2.2.

Laboratories that have failed previously to gain approval of the responsible physician for conducting determinations of 1 or more analytes due to lack of compliance with the criteria

defined above for existing laboratories (Section 3.2.1), may obtain approval by satisfying the criteria for newly-formed laboratories defined under this section; for these laboratories, the second of the above criteria may be satisfied by submitting a new set of characterization analyses for each analyte for that determinations are to be made.

Reevaluation of these laboratories is discretionary on the part of the responsible physician. Reevaluation, that normally takes about 6 months, may be expedited if the laboratory can achieve 100% compliance with the proficiency test criteria using the 6 samples of each analyte submitted to the CTQ program during the first 2 rounds of proficiency testing.

For laboratories seeking reevaluation for CDU or B2MU analysis, the guidelines for CRTU analyses also should be satisfied, including accreditation for CRTU analysis by the CAP, and participation in the CAP survey program (or accreditation/participation in an equivalent program).

3.2.4 Future Modifications to the Protocol Guidelines

As participating laboratories gain experience with analyses for CDB, CDU and B2MU, it is anticipated that the performance achievable by the majority of laboratories should improve until it approaches that reported by the research groups that developed each method. OSHA, therefore, may choose to recommend stricter performance guidelines in the future as the overall performance of participating laboratories improves.

3.3 Guidelines for Record Keeping and Reporting

To comply with these guidelines, participating laboratories should satisfy the above-stated performance and proficiency recommendations, as well as the following internal QA/QC, record keeping, and reporting provisions.

If a participating laboratory fails to meet the provisions of these guidelines, it is recommended that the responsible physician disapprove further analyses of biological samples by that laboratory until it demonstrates compliance with these guidelines. On disapproval, biological samples should be sent to a laboratory that can demonstrate compliance with these guidelines, at least until the former laboratory is reevaluated by the responsible physician and found to be in compliance.

The following record keeping and reporting procedures should be practiced by participating laboratories.

3.3.1 Internal Quality Assurance/Quality Control Procedures

Laboratories participating in the cadmium monitoring program should develop and maintain an internal quality assurance/quality control (QA/QC) program that incorporates procedures for establishing and maintaining control for each of the analytic procedures (determinations of CDB, CDU and/or B2MU) for that the laboratory is seeking participation. For laboratories analyzing CDU and/or B2MU, a QA/QC program for CRTU also should be established.

Written documentation of QA/QC procedures should be described in a formal QA/QC plan; this plan should contain the following information: Sample acceptance and handling procedures (i.e., chain-of-custody); sample preparation procedures; instrument parameters; calibration procedures; and, calculations. Documentation of QA/QC procedures should be sufficient to identify analytical problems, define criteria under that analysis of compliance samples will be suspended, and describe procedures for corrective actions.

3.3.1.1 QA/QC procedures for establishing control of CDB and CDU analyses

The QA/QC program for CDB and CDU should address, at a minimum, procedures involved in calibration, establishment of control limits, internal QC analyses and maintaining control, and corrective-action protocols. Participating laboratory should develop and maintain procedures to assure that analyses of compliance samples are within control limits, and that these procedures are documented thoroughly in a QA/QC plan.

A non-mandatory QA/QC protocol is presented in Attachment 1. This attachment is illustrative of the procedures that should be addressed in a proper QA/QC program.

Calibration. Before any analytic runs are conducted, the analytic instrument should be calibrated. Calibration should be performed at the beginning of each day on that QC and/or compliance samples are run. Once calibration is established, QC or compliance samples may be run. Regardless of the type of samples run, about every fifth sample should serve as a standard to assure that calibration is being maintained.

Calibration is being maintained if the standard is within $\pm 15\%$ of its theoretical value. If a standard is more than $\pm 15\%$ of its theoretical value, the run has exceeded control limits due to

calibration error; the entire set of samples then should be reanalyzed after recalibrating or the results should be recalculated based on a statistical curve derived from that set of standards.

It is essential that the value of the highest standard analyzed be higher than the highest sample analyzed; it may be necessary, therefore, to run a high standard at the end of the run, that has been selected based on results obtained over the course of the run (i.e., higher than any standard analyzed to that point).

Standards should be kept fresh; as samples age, they should be compared with new standards and replaced if necessary.

Internal Quality Control Analyses. Internal QC samples should be determined interspersed with analyses of compliance samples. At a minimum, these samples should be run at a rate of 5% of the compliance samples or at least one set of QC samples per analysis of compliance samples, whichever is greater. If only 2 samples are run, they should contain different levels of cadmium.

Internal QC samples may be obtained as commercially-available reference materials and/or they may be internally prepared. Internally-prepared samples should be well characterized and traced, or compared to a reference material for that a consensus value is available.

Levels of cadmium contained in QC samples should not be known to the analyst prior to reporting the results of the analysis.

Internal QC results should be plotted or charted in a manner that describes sample recovery and laboratory control limits.

Internal Control Limits. The laboratory protocol for evaluating internal QC analyses per control limits should be clearly defined. Limits may be based on statistical methods (e.g., as 2 σ from the laboratory mean recovery), or on proficiency testing limits (e.g., $\pm 1 \mu\text{g}$ or 15% of the mean, whichever is greater). Statistical limits that exceed $\pm 40\%$ should be reevaluated to determine the source error in the analysis.

When laboratory limits are exceeded, analytic work should terminate until the source of error is determined and corrected; compliance samples affected by the error should be reanalyzed. In addition, the laboratory protocol should address any unusual trends that develop that may be biasing the results. Numerous, consecutive results above or below laboratory mean recoveries, or outside laboratory statistical limits, indicate that problems may have developed.

Corrective Actions. The QA/QC plan should document in detail specific actions taken if control limits are exceeded or unusual trends develop. Corrective actions should be noted on an appropriate form, accompanied by supporting documentation.

In addition to these actions, laboratories should include whatever additional actions are necessary to assure that accurate data are reported to the responsible physicians.

Reference Materials. The following reference materials may be available:

Cadmium in Blood (CDB)

1. Centre de Toxicologie du Quebec, Le Centre Hospitalier de l'Universite Laval, 2705 boul. Laurier, Quebec, Que., Canada G1V 4G2. (Prepared 6 times per year at 1-15 $\mu\text{g Cd/l}$.)
2. H. Marchandise, Community Bureau of Reference-BCR, Directorate General XII, Commission of the European Communities, 200, rue de la Loi, B-1049, Brussels, Belgium. (Prepared as BI CBM-1 at 5.37 $\mu\text{g Cd/l}$, and BI CBM-2 at 12.38 $\mu\text{g Cd/l}$.)
3. Kaulson Laboratories Inc., 691 Bloomfield Ave., Caldwell, NJ 07006; tel: (201) 226-9494, FAX (201) 226-3244. (Prepared as #0141 [As, Cd, Hg, Pb] at 2 levels.)

Cadmium in Urine (CDU)

1. Centre de Toxicologie du Quebec, Le Centre Hospitalier de l'Universite Laval, 2705 boul. Laurier, Quebec, Que., Canada G1V 4G2. (Prepared 6 times per year.)
2. National Institute of Standards and Technology (NIST), Dept. of Commerce, Gaithersburg, MD; tel: (301) 975-6776. (Prepared as SRM 2670 freeze-dried urine [metals]; set includes normal and elevated levels of metals; cadmium is certified for elevated level of 88.0 $\mu\text{g/l}$ in reconstituted urine.)
3. Kaulson Laboratories Inc., 691 Bloomfield Ave., Caldwell, NJ 07006; tel: (201) 226-9494, FAX (201) 226-3244. (Prepared as #0140 [As, Cd, Hg, Pb] at 2 levels.)

3.3.1.2 QA/QC procedures for establishing control of B2MU

A written, detailed QA/QC plan for B2MU analysis should be developed. The QA/QC plan should contain a protocol similar to those protocols developed for the CDB/CDU analyses.

Differences in analyses may warrant some differences in the QA/QC protocol, but procedures to ensure analytical integrity should be developed and followed.

Examples of performance summaries that can be provided include measurements of accuracy (i.e., the means of measured values versus target values for the control samples) and precision (i.e., based on duplicate analyses). It is recommended that the accuracy and precision measurements be compared to those reported as achievable by the Pharmacia Delphia kit (Pharmacia 1990) to determine if and when unsatisfactory analyses have arisen. If the measurement error of 1 or more of the control samples is more than 15%, the run exceeds control limits. Similarly, this decision is warranted when the average CV for duplicate samples is greater than 5%.

3.3.2 Procedures for Record Keeping

To satisfy reporting requirements for commercial analyses of CDB, CDU and/or B2MU performed for the medical monitoring program mandated under the cadmium rule, participating laboratories should maintain the following documentation for each analyte:

1. For each analytic instrument on that analyte determinations are made, records relating to the most recent calibration and QC sample analyses;
2. For these instruments, a tabulated record for each analyte of those determinations found to be within and outside of control limits over the past 2 years;
3. Results for the previous 2 years of the QC sample analyses conducted under the internal QA/QC program (this information should be: Provided for each analyte for that determinations are made and for each analytic instrument used for this purpose, sufficient to demonstrate that internal QA/QC programs are being executed properly, and consistent with data sent to responsible physicians.
4. Duplicate copies of monitoring results for each analyte sent to clients during the previous 5 years, as well as associated information; supporting material such as chain-of-custody forms also should be retained; and,
5. Proficiency test results and related materials received while participating in the CTQ interlaboratory program over the past 2 years; results also should be tabulated to provide a serial record of relative error (derived per Section 3.3.3 below).

3.3.3 Reporting Procedures

Participating laboratories should maintain these documents: QA/QC program plans; QA/QC status reports; CTQ proficiency program reports; and, analytical data reports. The information that should be included in these reports is summarized in Table 2; a copy of each report should be sent to the responsible physician.

Table 2.
REPORTING PROCEDURES FOR LABORATORIES PARTICIPATING IN THE CADMIUM MEDICAL MONITORING PROGRAM

Report	Frequency (time frame)	Contents
1. QA/QC Program Plan	Once (initially)	A detailed description of the QA/QC protocol to be established by the laboratory to maintain control of analyte determinations.
2. QA/QC Status Report	Every 2 months	Results of the QC samples incorporated into regular runs for each instrument (over the period since the last report).
3. Proficiency Report	Attached to every data report.	Results from the last full year of proficiency samples submitted to the CTQ program and Results of the 100 most recent QC samples incorporated into regular runs for each instrument.
4. Analytical Data Report	For all reports of data results.	Date the sample was received; Date the sample was analyzed; Appropriate chain-of-custody information; Types of analyses performed; Results of the requested analyses and Copy of the most current proficiency report.

As noted in Section 3.3.1, a QA/QC program plan should be developed that documents internal QA/QC procedures (defined under Section 3.3.1) to be implemented by the participating laboratory for each analyte; this plan should provide a list identifying each instrument used in making analyte determinations.

A QA/QC status report should be written bimonthly for each analyte. In this report, the results of the QC program during the reporting period should be reported for each analyte in the following manner: The number (N) of QC samples analyzed during the period; a table of the target levels defined for each sample and the corresponding measured values; the mean of F/T value (as defined below) for the set of QC samples run during the period; and, use of $X \pm 2\hat{\sigma}$ (as defined below) for the set of QC samples run during the period as a measure of precision.

As noted in Section 2, an F/T value for a QC sample is the ratio of the measured concentration of analyte to the established (i.e., reference) concentration of analyte for that QC sample. The equation below describes the derivation of the mean for F/T values, \bar{X} , (with N being the total number of samples analyzed):

$$\bar{X} = \frac{\sum (F/T)}{N}$$

The standard deviation, $\hat{\sigma}$, for these measurements is derived using the following equation (note that $2\hat{\sigma}$ is twice this value):

$$\hat{\sigma} = \left[\frac{\sum (F/T - \bar{X})^2}{N-1} \right]^{\frac{1}{2}}$$

The non-mandatory QA/QC protocol (see Attachment 1) indicates that QC samples should be divided into several discrete pools, and a separate estimate of precision for each pool then should be derived. Several precision estimates should be provided for concentrations that differ in average value. These precision measures may be used to document improvements in performance with regard to the combined pool.

Participating laboratories should use the CTQ proficiency program for each analyte. Results of the program will be sent by CTQ directly to physicians designated by the participating laboratories. Proficiency results from the CTQ program are used to establish the accuracy of results from each participating laboratory, and should be provided to responsible physicians for use in trend analysis. A proficiency report consisting of these proficiency results should accompany data reports as an attachment.

For each analyte, the proficiency report should include the results from the 6 previous proficiency rounds in the following format:

1. Number (N) of samples analyzed;
2. Mean of the target levels, $(1/N) \cdot T_i$, with T_i being a consensus mean for the sample;
3. Mean of the measurements, $(1/N) \cdot M_i$, with M_i being a sample measurement;
4. A measure of error defined by:

$$(1/N) \cdot (T_i - M_i)^2$$

Analytical data reports should be submitted to responsible physicians directly. For each sample, report the following information: The date the sample was received; the date the sample was analyzed; appropriate chain-of-custody information; the type(s) of analyses performed; and, the results of the analyses. This information should be reported on a form similar to the form provided an appropriate form. The most recent proficiency program report should accompany the analytical data reports (as an attachment).

Confidence intervals for the analytical results should be reported as $X \pm 2\sigma$, with X being the measured value and 2σ - the standard deviation calculated as described above.

For CDU or B2MU results, that are combined with CRTU measurements for proper reporting, the 95% confidence limits are derived from the limits for CDU or B2MU, (p), and the limits for CRTU, (q), as follows:

$$\frac{X}{Y} \pm \frac{(1)}{(Y^2)^{1/2}} (Y(2) \times p(2) + X(2) \times q(2))$$

For these calculations, $X \pm p$ is the measurement and confidence limits for CDU or B2MU, and $Y \pm q$ is the measurement and confidence limit for CRTU.

Participating laboratories should notify responsible physicians as soon as they receive information indicating a change in their accreditation status with the CTQ or the CAP. These physicians should not be expected to wait until formal notice of a status change has been received from the CTQ or the CAP.

3.4 Instructions to Physicians

Physicians responsible for the medical monitoring of cadmium-exposed workers must collect the biological samples from workers; they then should select laboratories to perform the required analyses, and should interpret the analytic results.

3.4.1 Sample Collection and Holding Procedures

Blood Samples. The following procedures are recommended for the collection, shipment and storage of blood samples for CDB analysis to reduce analytical variability; these recommendations were obtained primarily through personal communications with J.P. Weber of the CTQ (1991), and from reports by the Centers for Disease Control (CDC, 1986) and Stoeppler and Brandt (1980).

To the extent possible, blood samples should be collected from workers at the same time of day. Workers should shower or thoroughly wash their hands and arms before blood samples are drawn. The following materials are needed for blood sample collection: Alcohol wipes; sterile gauze sponges; band-aids; 20-gauge, 1.5-in. stainless steel needles (sterile); preprinted labels; tourniquets; vacutainer holders; 3-ml "metal free" vacutainer tubes (i.e., dark-blue caps), with EDTA as an anti-coagulant; and, styrofoam vacutainer shipping containers.

Whole blood samples are taken by venipuncture. Each blue-capped tube should be labeled or coded for the worker and company before the sample is drawn. (Blue-capped tubes are recommended instead of red-capped tubes because the latter may consist of red coloring pigment containing cadmium, which could contaminate the samples.) Immediately after sampling, the vacutainer tubes must be thoroughly mixed by inverting the tubes at least 10 times manually or mechanically using a Vortex device (for 15 sec). Samples should be refrigerated immediately or stored on ice until they can be packed for shipment to the participating laboratory for analysis.

The CDC recommends that blood samples be shipped with a "cool pak" to keep the samples cold during shipment. However, the CTQ routinely ships and receives blood samples for cadmium analysis that have not been kept cool during shipment. The CTQ has found no deterioration of cadmium in biological fluids that were shipped via parcel post without a cooling agent, even though these deliveries often take 2 weeks to reach their destination.

Urine Samples. The following are recommended procedures for the collection, shipment and storage of urine for CDU and B2MU analyses, and were obtained primarily through personal communications with J.P. Weber of the CTQ (1991), and from reports by the CDC (1986) and Stoeppler and Brandt (1980).

Single "spot" samples are recommended. As B2M can degrade in the bladder, workers should first empty their bladder and then drink a large glass of water at the start of the visit. Urine samples then should be collected within 1 hour. Separate samples should be collected for CDU and B2MU using the following materials: Sterile urine collection cups (250 ml); small sealable plastic bags; preprinted labels; 15-ml polypropylene or polyethylene screw-cap tubes; lab gloves ("metal free"); and, preservatives (as indicated).

The sealed collection cup should be kept in the plastic bag until collection time. The workers should wash their hands with soap and water before receiving the collection cup. The collection cup should not be opened until just before voiding and the cup should be sealed immediately after filling. It is important that the inside of the container and cap are not touched by, or come into contact with, the body, clothing or other surfaces.

For CDU analyzes, the cup is swirled gently to resuspend any solids, and the 15-ml tube is filled with 10-12 ml urine. The CDC recommends the addition of 100 μ l concentrated HNO_3 as a preservative before sealing the tube and then freezing the sample. The CTQ recommends minimal handling and does not acidify their interlaboratory urine reference materials prior to shipment, nor do they freeze the sample for shipment. At the CTQ, if the urine sample has much sediment, the sample is acidified in the lab to free any cadmium in the precipitate.

For B2M, the urine sample should be collected directly into a polyethylene bottle previously washed with dilute nitric acid. The pH of the urine should be measured and adjusted to 8.0 with 0.1 N NaOH immediately following collection. Samples should be frozen and stored at -20°C until testing is performed. The B2M in the samples should be stable for 2 days when stored at $2-8^\circ\text{C}$, and for at least 2 months at -20°C . Repeated freezing and thawing should be avoided to prevent denaturing the B2M (Pharmacia 1990).

3.4.2 Recommendations for Evaluating Laboratories

Using standard error data and the results of proficiency testing obtained from CTQ, responsible physicians can make an informed choice of that laboratory to select to analyze biological samples. In general, laboratories with small standard errors and little disparity between target and measured values tend to make precise and accurate sample determinations. Estimates of precision provided to the physicians with each set of monitoring results can be compared to previously-reported proficiency and precision estimates. The latest precision estimates should be at least as small as the standard error reported previously by the laboratory. Moreover, there should be no indication that precision is deteriorating (i.e., increasing values for the precision estimates). If precision is deteriorating, physicians may decide to use another laboratory for these analyses. QA/QC information provided by the participating laboratories to physicians can, therefore, assist physicians in evaluating laboratory performance.

3.4.3 Use and Interpretation of Results

When the responsible physician has received the CDB, CDU and/or B2MU results, these results must be compared to the action levels discussed in the final rule for cadmium. The comparison of the sample results to action levels is straightforward. The measured value reported from the laboratory can be compared directly to the action levels; if the reported value exceeds an action level, the required actions must be initiated.

4.0 Background

Cadmium is a naturally-occurring environmental contaminant to that humans are continually exposed in food, water, and air. The average daily intake of cadmium by the U.S. population is estimated to be 10-20 µg/day. Most of this intake is via ingestion, for that absorption is estimated at 4-7% (Kowal et al. 1979). An additional non-occupational source of cadmium is smoking tobacco; smoking a pack of cigarettes a day adds an additional 2-4 µg cadmium to the daily intake, assuming absorption via inhalation of 25-35% (Nordberg and Nordberg 1988; Friberg and Elinder 1988; Travis and Haddock 1980).

Exposure to cadmium fumes and dusts in an occupational setting where air concentrations are 20-50 µg/m³ results in an additional daily intake of several hundred micrograms (Friberg and Elinder 1988, p. 563). In such a setting, occupational exposure to cadmium occurs primarily via inhalation, although additional exposure may occur through the ingestion of material via contaminated hands if workers eat or smoke without first washing. Some of the particles that are inhaled initially may be ingested when the material is deposited in the upper respiratory tract, where it may be cleared by mucociliary transport and subsequently swallowed.

Cadmium introduced into the body through inhalation or ingestion is transported by the albumin fraction of the blood plasma to the liver, where it accumulates and is stored principally as a bound form complexed with the protein metallothionein. Metallothionein-bound cadmium is the main form of cadmium subsequently transported to the kidney; it is these 2 organs, the liver and kidney, in that the majority of the cadmium body burden accumulates. As much as one half of the total body burden of cadmium may be found in the kidneys (Nordberg and Nordberg 1988).

Once cadmium has entered the body, elimination is slow; about 0.02% of the body burden is excreted per day via urinary/fecal elimination. The whole-body half-life of cadmium is 10-35 years, decreasing slightly with increasing age (Travis and Haddock 1980).

The continual accumulation of cadmium is the basis for its chronic noncarcinogenic toxicity. This accumulation makes the kidney the target organ in that cadmium toxicity usually is first observed (Piscator 1964). Renal damage may occur when cadmium levels in the kidney cortex approach 200 µg/g wet tissue-weight (Travis and Haddock 1980).

The kinetics and internal distribution of cadmium in the body are complex, and depend on whether occupational exposure to cadmium is ongoing or has terminated. In general, cadmium in blood is related principally to recent cadmium exposure, while cadmium in urine reflects cumulative exposure (i.e., total body burden) (Lauwerys et al. 1976; Friberg and Elinder 1988).

4.1 Health Effects

Studies of workers in a variety of industries indicate that chronic exposure to cadmium may be linked to several adverse health effects including kidney dysfunction, reduced pulmonary function, chronic lung disease and cancer (Federal Register 1990). The primary sites for cadmium-associated cancer appear to be the lung and the prostate.

Cancer. Evidence for an association between cancer and cadmium exposure comes from both epidemiological studies and animal experiments. Pott (1965) found a statistically significant elevation in the incidence of prostate cancer among a cohort of cadmium workers. Other epidemiology studies also report an elevated incidence of prostate cancer; however, the increases observed in these other studies were not statistically significant (Meridian Research, Inc. 1989).

One study (Thun et al. 1985) contains sufficiently quantitative estimates of cadmium exposure to allow evaluation of dose-response relationships between cadmium exposure and lung cancer. A statistically significant excess of lung cancer attributed to cadmium exposure was found in this study, even after accounting for confounding variables such as co-exposure to arsenic and smoking habits (Meridian Research, Inc. 1989).

Evidence for quantifying a link between lung cancer and cadmium exposure comes from a single study (Takenaka et al. 1983). In this study, dose-response relationships developed from animal data were extrapolated to humans using a variety of models. OSHA chose the multistage risk model for estimating the risk of cancer for humans using these animal data. Animal injection studies also suggest an association between cadmium exposure and cancer, particularly observations of an increased incidence of tumors at sites remote from the point of injection. The International Agency for Research on Cancer (IARC) (Supplement 7, 1987) indicates that this, and related, evidence is sufficient to classify cadmium as an animal carcinogen. However, the results of these injection studies cannot be used to quantify risks

attendant to human occupational exposures due to differences in routes of exposure (Meridian Research, Inc. 1989).

Based on the above-cited studies, the U.S. Environmental Protection Agency (EPA) classifies cadmium as "B1," a probable human carcinogen (USEPA 1985). IARC in 1987 recommended that cadmium be listed as a probable human carcinogen.

Kidney Dysfunction. The most prevalent nonmalignant effect observed among workers chronically exposed to cadmium is kidney dysfunction. Initially, such dysfunction is manifested by proteinuria (Meridian Research, Inc. 1989; Roth Associates, Inc. 1989). Proteinuria associated with cadmium exposure is most commonly characterized by excretion of low-molecular weight proteins (15,000-40,000 MW), accompanied by loss of electrolytes, uric acid, calcium, amino acids, and phosphate. Proteins commonly excreted include β -2-microglobulin (B2M), retinol-binding protein (RBP), immunoglobulin light chains, and lysozyme. Excretion of low molecular weight proteins is characteristic of damage to the proximal tubules of the kidney (Iwao et al. 1980).

Exposure to cadmium also may lead to urinary excretion of high-molecular weight proteins such as albumin, immunoglobulin G, and glycoproteins (Meridian Research, Inc. 1989; Roth Associates, Inc. 1989). Excretion of high-molecular weight proteins is indicative of damage to the glomeruli of the kidney. Bernard et al. (1979) suggest that cadmium-associated damage to the glomeruli and damage to the proximal tubules of the kidney develop independently of each other, but may occur in the same individual.

Several studies indicate that the onset of low-molecular weight proteinuria is a sign of irreversible kidney damage (Friberg et al. 1974; Roels et al. 1982; Piscator 1984; Elinder et al. 1985; Smith et al. 1986). For many workers, once sufficiently elevated levels of B2M are observed in association with cadmium exposure, such levels do not appear to return to normal even when cadmium exposure is eliminated by removal of the worker from the cadmium-contaminated work environment (Friberg, exhibit 29, 1990).

Some studies indicate that cadmium-induced proteinuria may be progressive; levels of B2MU increase even after cadmium exposure has ceased (Elinder et al. 1985). Other researchers have reached similar conclusions (Frieburg testimony, OSHA docket exhibit 29, Elinder testimony, OSHA docket exhibit 55, and OSHA docket exhibits 8-86B). Such observations are not universal, however (Smith et al. 1986; Tsuchiya 1976). Studies in that proteinuria has not been observed, however, may have initiated the reassessment too early (Meridian Research, Inc. 1989; Roth Associates, Inc. 1989; Roels 1989).

A quantitative assessment of the risks of developing kidney dysfunction as a result of cadmium exposure was performed using the data from Ellis et al. (1984) and Falck et al. (1983). Meridian Research, Inc. (1989) and Roth Associates, Inc. (1989) employed several mathematical models to evaluate the data from the 2 studies, and the results indicate that cumulative cadmium exposure levels between 5 and 100 $\mu\text{g}\text{-years}/\text{m}^3$ correspond with a one-in-a-thousand probability of developing kidney dysfunction.

When cadmium exposure continues past the onset of early kidney damage (manifested as proteinuria), chronic nephrotoxicity may occur (Meridian Research, Inc. 1989; Roth Associates, Inc. 1989). Uremia, that is the loss of the glomerulus' ability to adequately filter blood, may result. This condition leads to severe disturbance of electrolyte concentrations, which may result in various clinical complications including atherosclerosis, hypertension, pericarditis, anemia, hemorrhagic tendencies, deficient cellular immunity, bone changes, and other problems. Progression of the disease may require dialysis or a kidney transplant.

Studies in that animals are chronically exposed to cadmium confirm the renal effects observed in humans (Friberg et al. 1986). Animal studies also confirm cadmium-related problems with calcium metabolism and associated skeletal effects, which also have been observed among humans. Other effects commonly reported in chronic animal studies include anemia, changes in liver morphology, immunosuppression and hypertension. Some of these effects may be associated with cofactors; hypertension, for example, appears to be associated with diet, as well as with cadmium exposure. Animals injected with cadmium also have shown testicular necrosis.

4.2 Objectives for Medical Monitoring

In keeping with the observation that renal disease tends to be the earliest clinical manifestation of cadmium toxicity, the final cadmium standard mandates that eligible workers must be medically monitored to prevent this condition (as well as cadmium-induced cancer). The objectives of medical-monitoring, therefore, are to: Identify workers at significant risk of

adverse health effects from excess, chronic exposure to cadmium; prevent future cases of cadmium-induced disease; detect and minimize existing cadmium-induced disease; and, identify workers most in need of medical intervention.

The overall goal of the medical monitoring program is to protect workers who may be exposed continuously to cadmium over a 45-year occupational lifespan. Consistent with this goal, the medical monitoring program should assure that:

1. Current exposure levels remain sufficiently low to prevent the accumulation of cadmium body burdens sufficient to cause disease in the future by monitoring CDB as an indicator of recent cadmium exposure;
2. Cumulative body burdens, especially among workers with undefined historical exposures, remain below levels potentially capable of leading to damage and disease by assessing CDU as an indicator of cumulative exposure to cadmium; and,
3. Health effects are not occurring among exposed workers by determining B2MU as an early indicator of the onset of cadmium-induced kidney disease.

4.3 Indicators of Cadmium Exposure and Disease

Cadmium is present in whole blood bound to albumin, in erythrocytes, and as a metallothionein-cadmium complex. The metallothionein-cadmium complex that represents the primary transport mechanism for cadmium delivery to the kidney. CDB concentrations in the general, non-exposed population average 1 µg Cd/l whole blood, with smokers exhibiting higher levels (see Section 5.1.6). Data presented in Section 5.1.6 shows that 95% of the general population not occupationally exposed to cadmium have CDB levels less than 5 µg Cd/l.

If total body burdens of cadmium remain low, CDB concentrations indicate recent exposure (i.e., daily intake). This conclusion is based on data showing that cigarette smokers exhibit CDB concentrations of 2-7 µg/l depending on the number of cigarettes smoked per day (Nordberg and Nordberg 1988), while CDB levels for those who quit smoking return to general population values (approximately 1 µg/l) within several weeks (Lauwerys et al. 1976). Based on these observations, Lauwerys et al. (1976) concluded that CDB has a biological half-life of a few weeks to less than 3 months. As indicated in Section 3.1.6, the upper 95th percentile for CDB levels observed among those who are not occupationally exposed to cadmium is 5 µg/l, that suggests that the absolute upper limit to the range reported for smokers by Nordberg and Nordberg may have been affected by an extreme value (i.e., beyond 2 above the mean).

Among occupationally-exposed workers, the occupational history of exposure to cadmium must be evaluated to interpret CDB levels. New workers, or workers with low exposures to cadmium, exhibit CDB levels that are representative of recent exposures, similar to the general population. However, for workers with a history of chronic exposure to cadmium, who have accumulated significant stores of cadmium in the kidneys/liver, part of the CDB concentrations appear to indicate body burden. If such workers are removed from cadmium exposure, their CDB levels remain elevated, possibly for years, reflecting prior long-term accumulation of cadmium in body tissues. This condition tends to occur, however, only beyond some threshold exposure value, and possibly indicates the capacity of body tissues to accumulate cadmium that cannot be excreted readily (Friberg and Elinder 1988; Nordberg and Nordberg 1988).

CDU is widely used as an indicator of cadmium body burdens (Nordberg and Nordberg 1988). CDU is the major route of elimination and, when CDU is measured, it is commonly expressed either as µg Cd/l urine (unadjusted), µg Cd/l urine (adjusted for specific gravity), or µg Cd/g CRTU (see Section 5.2.1). The metabolic model for CDU is less complicated than CDB, since CDU is dependent in large part on the body (i.e., kidney) burden of cadmium. However, a small proportion of CDU still be attributed to recent cadmium exposure, particularly if exposure to high airborne concentrations of cadmium occurred. Note that CDU is subject to larger interindividual and day-to-day variations than CDB, so repeated measurements are recommended for CDU evaluations.

CDU is bound principally to metallothionein, regardless of whether the cadmium originates from metallothionein in plasma or from the cadmium pool accumulated in the renal tubules. Therefore, measurement of metallothionein in urine may provide information similar to CDU, while avoiding the contamination problems that may occur during collection and handling urine for cadmium analysis (Nordberg and Nordberg 1988). However, a commercial method for the determination of metallothionein at the sensitivity levels required under the final cadmium rule is not currently available; therefore, analysis of CDU is recommended.

Among the general population not occupationally exposed to cadmium, CDU levels average less than 1 µg/l (see Section 5.2.7). Normalized for creatinine (CRTU), the average CDU concentration of the general population is less than 1 µg/g CRTU. As cadmium accumulates over the lifespan, CDU increases with age. Also, cigarette smokers may eventually accumulate twice the cadmium body burden of nonsmokers, CDU is slightly higher in smokers than in nonsmokers, even several years after smoking cessation (Nordberg and Nordberg 1988). Despite variations due to age and smoking habits, 95% of those not occupationally exposed to cadmium exhibit levels of CDU less than 3 µg/g CRTU (based on the data presented in Section 5.2.7).

About 0.02% of the cadmium body burden is excreted daily in urine. When the critical cadmium concentration (about 200 ppm) in the kidney is reached, or if there is sufficient cadmium-induced kidney dysfunction, dramatic increases in CDU are observed (Nordberg and Nordberg 1988). Above 200 ppm, therefore, CDU concentrations cease to be an indicator of cadmium body burden, and are instead an index of kidney failure.

Proteinuria is an index of kidney dysfunction, and is defined by OSHA to be a material impairment. Several small proteins may be monitored as markers for proteinuria. Below levels indicative of proteinuria, these small proteins may be early indicators of increased risk of cadmium-induced renal tubular disease. Analytes useful for monitoring cadmium-induced renal tubular damage include:

1. β-2-Microglobulin (B2M), currently the most widely used assay for detecting kidney dysfunction, is the best characterized analyte available (Iwao et al. 1980; Chia et al. 1989);
2. Retinol Binding Protein (RBP) is more stable than B2M in acidic urine (i.e., B2M breakdown occurs if urinary pH is less than 5.5; such breakdown may result in false [i.e., low] B2M values [Bernard and Lauwerys, 1990]);
3. N-Acetyl-B-Glucosaminidase (NAG) is the analyte of an assay that is simple, inexpensive, reliable, and correlates with cadmium levels under 10 µg/g CRTU, but the assay is less sensitive than RBP or B2M (Kawada et al. 1989);
4. Metallothionein (MT) correlates with cadmium and B2M levels, and may be a better predictor of cadmium exposure than CDU and B2M (Kawada et al. 1989);
5. Tamm-Horsfall Glycoprotein (THG) increases slightly with elevated cadmium levels, but this elevation is small compared to increases in urinary albumin, RBP, or B2M (Bernard and Lauwerys 1990);
6. Albumin (ALB), determined by the biuret method, is not sufficiently sensitive to serve as an early indicator of the onset of renal disease (Piscator 1962);
7. Albumin (ALB), determined by the Amido Black method, is sensitive and reproducible, but involves a time-consuming procedure (Piscator 1962);
8. Glycosaminoglycan (GAG) increases among cadmium workers, but the significance of this effect is unknown because no relationship has been found between elevated GAG and other indices of tubular damage (Bernard and Lauwerys 1990);
9. Trehalase seems to increase earlier than B2M during cadmium exposure, but the procedure for analysis is complicated and unreliable (Iwata et al. 1988); and,
10. Kallikrein is observed at lower concentrations among cadmium-exposed workers than among normal controls (Roels et al. 1990).

Of the above analytes, B2M appears to be the most widely used and best characterized analyte to evaluate the presence/absence, as well as the extent of, cadmium-induced renal tubular damage (Kawada, Koyama, and Suzuki 1989; Shaikh and Smith 1984; Nogawa 1984). However, it is important that samples be collected and handled so as to minimize B2M degradation under acidic urine conditions.

The threshold value of B2MU commonly used to indicate the presence of kidney damage 300 µg/g CRTU (Kjellstrom et al. 1977a; Buchet et al. 1980; and Kowal and Zirkes 1983). This value represents the upper 95th or 97.5th percentile level of urinary excretion observed among those without tubular dysfunction (Elinder, exbt L-140-45, OSHA docket H057A). In agreement with these conclusions, the data presented in Section 5.3.7 of this protocol generally indicate that the level of 300 µg/g CRTU appears to define the boundary for kidney dysfunction. It is not clear, however, that this level represents the upper 95th percentile of values observed among those who fail to demonstrate proteinuria effects.

Although elevated B2MU levels appear to be a fairly specific indicator of disease associated with cadmium exposure, other conditions that may lead to elevated B2MU levels

include high fevers from influenza, extensive physical exercise, renal disease unrelated to cadmium exposure, lymphomas, and AIDS (Iwao et al. 1980; Schardun and van Epps 1987). Elevated B2M levels observed in association with high fevers from influenza or from extensive physical exercise are transient, and will return to normal levels once the fever has abated or metabolic rates return to baseline values following exercise. The other conditions linked to elevated B2M levels can be diagnosed as part of a properly-designed medical examination. Consequently, monitoring B2M, when accompanied by regular medical examinations and CDB and CDU determinations (as indicators of present and past cadmium exposure), may serve as a specific, early indicator of cadmium-induced kidney damage.

4.4 Criteria for Medical Monitoring of Cadmium Workers

Medical monitoring mandated by the final cadmium rule includes a combination of regular medical examinations and periodic monitoring of 3 analytes: CDB, CDU and B2MU. As indicated above, CDB is monitored as an indicator of current cadmium exposure, while CDU serves as an indicator of the cadmium body burden; B2MU is assessed as an early marker of irreversible kidney damage and disease.

The final cadmium rule defines a series of action levels that have been developed for each of the 3 analytes to be monitored. These action levels serve to guide the responsible physician through a decision-making process. For each action level that is exceeded, a specific response is mandated. The sequence of action levels and the attendant actions, are described in detail in the final cadmium rule.

Other criteria used in the medical decision-making process relate to tests performed during the medical examination (including a determination of the ability of a worker to wear a respirator). These criteria, however, are not affected by the results of the analyte determinations addressed in the above paragraphs and, consequently, will not be considered further in these guidelines.

4.5 Defining to Quality and Proficiency of the Analyte Determinations

As noted above in Sections 2 and 3, the quality of a measurement should be defined along with its value to properly interpret the results. Generally, it is necessary to know the accuracy and the precision of a measurement before it can be properly evaluated. The precision of the data from a specific laboratory indicates the extent to that the repeated measurements of the same sample vary within that laboratory. The accuracy of the data provides an indication of the extent to that these results deviate from average results determined from many laboratories performing the same measurement (i.e., in the absence of an independent determination of the true value of a measurement). Note that terms are defined operationally relative to the manner in that they will be used in this protocol. Formal definitions for the terms in italics used in this section can be found in the list of definitions (Section 2).

Another data quality criterion required to properly evaluate measurement results is the limit of detection of that measurement. For measurements to be useful, the range of the measurement that is of interest for biological monitoring purposes must lie entirely above the limit of detection defined for that measurement.

The overall quality of a laboratory's results is termed the performance of that laboratory. The degree to that a laboratory satisfies a minimum performance level is referred to as the proficiency of the laboratory. A successful medical monitoring program, therefore, should include procedures developed for monitoring and recording laboratory performance; these procedures can be used to identify the most proficient laboratories.

5.0 Overview of Medical Monitoring Tests for CDB, CDU, B2MU and CRTU

To evaluate whether available methods for assessing CDB, CDU, B2MU and CRTU are adequate for determining the parameters defined by the proposed action levels, it is necessary to review procedures available for sample collection, preparation and analysis. A variety of techniques for these purposes have been used historically for the determination of cadmium in biological matrices (including CDB and CDU), and for the determination of specific proteins in biological matrices (including B2MU). However, only the most recent techniques are capable of satisfying the required accuracy, precision and sensitivity (i.e., limit of detection) for monitoring at the levels mandated in the final cadmium rule, while still facilitating automated analysis and rapid processing.

5.1 Measuring Cadmium in Blood (CDB)

Analysis of biological samples for cadmium requires strict analytical discipline regarding collection and handling of samples. In addition to occupational settings, where cadmium

contamination would be apparent, cadmium is a ubiquitous environmental contaminant, and much care should be exercised to ensure that samples are not contaminated during collection, preparation or analysis. Many common chemical reagents are contaminated with cadmium at concentrations that will interfere with cadmium analysis; because of the widespread use of cadmium compounds as colored pigments in plastics and coatings, the analyst should continually monitor each manufacturer's chemical reagents and collection containers to prevent contamination of samples.

Guarding against cadmium contamination of biological samples is particularly important when analyzing blood samples because cadmium concentrations in blood samples from non-exposed populations are generally less than 2 µg/l (2 ng/ml), while occupationally-exposed workers can be at medical risk to cadmium toxicity if blood concentrations exceed 5 µg/l (ACGIH 1991 and 1992). This narrow margin between exposed and unexposed samples requires that exceptional care be used in performing analytic determinations for biological monitoring for occupational cadmium exposure.

Methods for quantifying cadmium in blood have improved over the last 40 years primarily because of improvements in analytical instrumentation. Also, due to improvements in analytical techniques, there is less need to perform extensive multi-step sample preparations prior to analysis. Complex sample preparation was previously required to enhance method sensitivity (for cadmium), and to reduce interference by other metals or components of the sample.

5.1.1 Analytical Techniques Used to Monitor Cadmium in Biological Matrices

A number of analytical techniques have been used for determining cadmium concentrations in biological materials. A summary of the characteristics of the most widely employed techniques is presented in Table 3. The technique most suitable for medical monitoring for cadmium is atomic absorption spectroscopy (AAS).

To obtain a measurement using AAS, a light source (i.e., hollow cathode or electrode-free discharge lamp) containing the element of interest as the cathode, is energized and the lamp emits a spectrum that is unique for that element. This light source is focused through a sample cell, and a selected wavelength is monitored by a monochromator and photodetector cell. Any ground state atoms in the sample that match those of the lamp element and are in the path of the emitted light may absorb some of the light and decrease the amount of light that reaches the photodetector cell. The amount of light absorbed at each characteristic wavelength is proportional to the number of ground state atoms of the corresponding element that are in the pathway of the light between the source and detector.

Table 3.-COMPARISON OF ANALYTICAL PROCEDURES/INSTRUMENTATION FOR DETERMINATION OF CADMIUM IN BIOLOGICAL SAMPLES

Analytical procedure	Limit of detection [ng/(g or ml)]	Specified biological matrix	Reference	Comments
Flame Atomic Absorption Spectroscopy (FAAS).	≥1.0	Any matrix	Perkin-Elmer (1982).	Not sensitive enough for biomonitoring without extensive sample digestion, metal chelation and organic solvent extraction.
Graphite Furnace Atomic Absorption Spectroscopy (GFAAS).	0.04	Urine	Pruszkowska et al. (1983).	Methods of choice for routine cadmium analysis.
	0.20	Blood	Stoepler and Brandt (1980).	
Inductively-Coupled Argon-Plasma Atomic Emission Spectroscopy (ICAPAES).	2.0	Any matrix	NIOSH (1984A)	Requires extensive sample preparation and concentration of metal with chelating resin. Advantage is simultaneous analyses for as many as 10 metals from 1 sample.
Neutron Activation Gamma Spectroscopy (NA).	1.5	In vivo (liver)	Ellis et al. (1983)	Only available in vivo method for direct determination of cadmium body tissue burdens; expensive; absolute determination of cadmium in reference materials.
Isotope Dilution Mass Spectroscopy (IDMS).	<1.0	Any matrix	Michiels and DeBievre (1986).	Suitable for absolute determination of cadmium in reference materials; expensive.
Differential Pulse Anodic Stripping Voltammetry (DPASV).	<1.0	Any matrix	Stoepler and Brandt (1980).	Suitable for absolute determination of cadmium in reference materials; efficient method to check accuracy of analytical method.

To determine the amount of a specific metallic element in a sample using AAS, the sample is dissolved in a solvent and aspirated into a high-temperature flame as an aerosol. At high temperatures, the solvent is rapidly evaporated or decomposed and the solute is initially solidified; the majority of the sample elements then are transformed into an atomic vapor. Next, a light beam is focused above the flame and the amount of metal in the sample can be determined by measuring the degree of absorbance of the atoms of the target element released by the flame at a characteristic wavelength.

A more refined atomic absorption technique, flameless AAS, substitutes an electrothermal, graphite furnace for the flame. An aliquot (10-100 µl) of the sample is pipetted into the cold furnace that is then heated rapidly to generate an atomic vapor of the element.

AAS is a sensitive and specific method for the elemental analysis of metals; its main drawback is nonspecific background absorption and scattering of the light beam by particles of the sample as it decomposes at high temperatures; nonspecific absorbance reduces the sensitivity of the analytical method. The problem of nonspecific absorbance and scattering can be reduced by extensive sample pretreatment, such as ashing and/or acid digestion of the sample to reduce its organic content.

Current AAS instruments employ background correction devices to adjust electronically for background absorption and scattering. A common method to correct for background effects is to use a deuterium arc lamp as a second light source. A continuum light source, such as the deuterium lamp, emits a broad spectrum of wavelengths instead of specific wavelengths characteristic of a particular element, as with the hollow cathode tube. With this system, light from the primary source and the continuum source are passed alternately through the sample cell. The target element effectively absorbs light only from the primary source (that is much brighter than the continuum source at the characteristic wavelengths), while the background matrix absorbs and scatters light from both sources equally. Therefore, when the ratio of the two beams is measured electronically, the effect of nonspecific background absorption and scattering is eliminated. A less common, but more sophisticated, background correction system is based on the Zeeman effect, which uses a magnetically-activated light polarizer to compensate electronically for nonspecific absorption and scattering.

Atomic emission spectroscopy with inductively-coupled argon plasma (AES-ICAP) is widely used to analyze for metals. With this instrument, the sample is aspirated into an extremely hot argon plasma flame, which excites the metal atoms; emission spectra specific for the sample element then are generated. The quanta of emitted light passing through a monochromator are amplified by photomultiplier tubes and measured by a photodetector to determine the amount of metal in the sample. An advantage of AES-ICAP over AAS is that multi-elemental analyses of a sample can be performed by simultaneously measuring specific elemental emission energies. However, AES-ICAP lacks the sensitivity of AAS, exhibiting a limit of detection that is higher than the limit of detection for graphite-furnace AAS (Table 3).

Neutron activation (NA) analysis and isotope dilution mass spectrometry (IDMS) are 2 additional, but highly specialized, methods that have been used for cadmium determinations. These methods are expensive because they require elaborate and sophisticated instrumentation.

NA analysis has the distinct advantage over other analytical methods of being able to determine cadmium body burdens in specific organs (e.g., liver, kidney) in vivo (Ellis et al. 1983). Neutron bombardment of the target transforms cadmium-113 to cadmium-114, that promptly decays ($<10^{-14}$ sec) to its ground state, emitting gamma rays that are measured using large gamma detectors; appropriate shielding and instrumentation are required when using this method.

IDMS analysis, a definitive but laborious method, is based on the change in the ratio of 2 isotopes of cadmium (cadmium 111 and 112) that occurs when a known amount of the element (with an artificially altered ratio of the same isotopes [i.e., a cadmium 111 "spike"] is added to a weighed aliquot of the sample (Michiels and De Bièvre 1986).

5.1.2 Methods Developed for CDB Determinations

A variety of methods have been used for preparing and analyzing CDB samples; most of these methods rely on one of the analytical techniques described above. Among the earliest reports, Princi (1947) and Smith et al. (1955) employed a colorimetric procedure to analyze for CDB and CDU. Samples were dried and digested through several cycles with concentrated mineral acids (HNO_3 and H_2SO_4) and hydrogen peroxide (H_2O_2). The digest was neutralized, and the cadmium was complexed with diphenylthiocarbazon and extracted with chloroform. The dithizone-cadmium complex then was quantified using a spectrometer.

Colorimetric procedures for cadmium analyses were replaced by methods based on atomic absorption spectroscopy (AAS) in the early 1960s, but many of the complex sample preparation procedures were retained. Kjellstrom (1979) reports that in Japanese, American and Swedish laboratories during the early 1970s, blood samples were wet ashed with mineral acids or ashed at high temperature and wetted with nitric acid. The cadmium in the digest was complexed with metal chelators including diethyl dithiocarbamate (DDTC), ammonium

pyrrolidine dithiocarbamate (APDC) or diphenylthiocarbazone (dithizone) in ammonia-citrate buffer and extracted with methyl isobutyl ketone (MIBK). The resulting solution then was analyzed by flame AAS or graphite-furnace AAS for cadmium determinations using deuterium-lamp background correction.

In the late 1970s, researchers began developing simpler preparation procedures. Roels et al. (1978) and Roberts and Clark (1986) developed simplified digestion procedures. Using the Roberts and Clark method, a 0.5 ml aliquot of blood is collected and transferred to a digestion tube containing 1 ml concentrated HNO_3 . The blood is then digested at 110°C for 4 hours. The sample is reduced in volume by continued heating, and 0.5 ml 30% H_2O_2 is added as the sample dries. The residue is dissolved in 5 ml dilute (1%) HNO_3 , and 20 μl of sample is then analyzed by graphite-furnace AAS with deuterium-background correction.

The current trend in the preparation of blood samples is to dilute the sample and add matrix modifiers to reduce background interference, rather than digesting the sample to reduce organic content. The method of Stoeppler and Brandt (1980), and the abbreviated procedure published in the American Public Health Association's (APHA) Methods for Biological Monitoring (1988), are straightforward and are nearly identical. For the APHA method, a small aliquot (50-300 μl) of whole blood that has been stabilized with ethylenediaminetetraacetate (EDTA) is added to 1.0 ml 1M HNO_3 , vigorously shaken and centrifuged. Aliquots (10-25 μl) of the supernatant then are then analyzed by graphite-furnace AAS with appropriate background correction.

Using the method of Stoeppler and Brandt (1980), aliquots (50-200 μl) of whole blood that have been stabilized with EDTA are pipetted into clean polystyrene tubes and mixed with 150-600 μl of 1 M HNO_3 . After vigorous shaking, the solution is centrifuged and a 10-25 μl aliquot of the supernatant then is analyzed by graphite-furnace AAS with appropriate background correction.

Claeys-Thoreau (1982) and DeBenzo et al. (1990) diluted blood samples at a ratio of 1:10 with a matrix modifier (0.2% Triton X-100, a wetting agent) for direct determinations of CDB. DeBenzo et al. also demonstrated that aqueous standards of cadmium, instead of spiked, whole-blood samples, could be used to establish calibration curves if standards and samples are treated with additional small volumes of matrix modifiers (i.e., 1% HNO_3 , 0.2% ammonium hydrogenphosphate and 1 mg/ml magnesium salts).

These direct dilution procedures for CDB analysis are simple and rapid. Laboratories can process more than 100 samples a day using a dedicated graphite-furnace AAS, an auto-sampler, and either a Zeeman- or a deuterium-background correction system. Several authors emphasize using optimum settings for graphite-furnace temperatures during the drying, charring, and atomization processes associated with the flameless AAS method, and the need to run frequent QC samples when performing automated analysis.

5.1.3 Sample Collection and Handling

Sample collection procedures are addressed primarily to identify ways to minimize the degree of variability that may be introduced by sample collection during medical monitoring. It is unclear at this point the extent to that collection procedures contribute to variability among CDB samples. Sources of variation that may result from sampling procedures include time-of-day effects and introduction of external contamination during the collection process. To minimize these sources, strict adherence to a sample collection protocol is recommended. Such a protocol must include provisions for thorough cleaning of the site from that blood will be extracted; also, every effort should be made to collect samples near the same time of day. It is also important to recognize that under the recent OSHA blood-borne pathogens standard (29 CFR 1910.1030), blood samples and certain body fluids must be handled and treated as if they are infectious.

5.1.4 Best Achievable Performance

The best achievable performance using a particular method for CDB determinations is assumed to be equivalent to the performance reported by research laboratories in that the method was developed.

For their method, Roberts and Clark (1986) demonstrated a limit of detection of 0.4 $\mu\text{g Cd/l}$ in whole blood, with a linear response curve from 0.4 to 16.0 $\mu\text{g Cd/l}$. They report a coefficient of variation (CV) of 6.7% at 8.0 $\mu\text{g/l}$.

The APHA (1988) reports a range of 1.0-25 $\mu\text{g/l}$, with a CV of 7.3% (concentration not stated). Insufficient documentation was available to critique this method.

Stoepler and Brandt (1980) achieved a detection limit of 0.2 µg Cd/l whole blood, with a linear range of 0.4-12.0 µg Cd/l, and a CV of 15-30%, for samples at <1.0 µg/l. Improved precision (CV of 3.8%) was reported for CDB concentrations at 9.3 µg/l.

5.1.5 General Method Performance

For any particular method, the performance expected from commercial laboratories may be somewhat lower than that reported by the research laboratory in that the method was developed. With participation in appropriate proficiency programs and use of a proper in-house QA/QC program incorporating provisions for regular corrective actions, the performance of commercial laboratories is expected to approach that reported by research laboratories. Also, the results reported for existing proficiency programs serve as a gauge of the likely level of performance that currently can be expected from commercial laboratories offering these analyses.

Weber (1988) reports on the results of the proficiency program run by the Centre de Toxicologie du Quebec (CTQ). As indicated previously, participants in that program receive 18 blood samples per year having cadmium concentrations ranging from 0.2-20 µg/l. Currently, 76 laboratories are participating in this program. The program is established for several analytes in addition to cadmium, and not all of these laboratories participate in the cadmium proficiency-testing program.

Under the CTQ program, cadmium results from individual laboratories are compared against the consensus mean derived for each sample. Results indicate that after receiving 60 samples (i.e., after participation for approximately three years), 60% of the laboratories in the program are able to report results that fall within ± 1 µg/l or 15% of the mean, whichever is greater. (For this procedure, the 15% criterion was applied to concentrations exceeding 7 µg/l.) On any single sample of the last 20 samples, the percentage of laboratories falling within the specified range is between 55 and 80%.

The CTQ also evaluates the performance of participating laboratories against a less severe standard: ± 2 µg/l or 15% of the mean, whichever is greater (Weber 1988); 90% of participating laboratories are able to satisfy this standard after approximately 3 years in the program. (The 15% criterion is used for concentrations in excess of 13 µg/l.) On any single sample of the last 15 samples, the percentage of laboratories falling within the specified range is between 80 and 95% (except for a single test for that only 60% of the laboratories achieved the desired performance).

Based on the data presented in Weber (1988), the CV for analysis of CDB is nearly constant at 20% for cadmium concentrations exceeding 5 µg/l, and increases for cadmium concentrations below 5 µg/l. At 2 µg/l, the reported CV rises to approximately 40%. At 1 µg/l, the reported CV is approximately 60%.

Participating laboratories also tend to overestimate concentrations for samples exhibiting concentrations less than 2 µg/l (see Figure 11 of Weber 1988). This problem is due in part to the proficiency evaluation criterion that allows reporting a minimum ± 2.0 µg/l for evaluated CDB samples. There is currently little economic or regulatory incentive for laboratories participating in the CTQ program to achieve greater accuracy for CDB samples containing cadmium at concentrations less than 2.0 µg/l, even if the laboratory has the experience and competency to distinguish among lower concentrations in the samples obtained from the CTQ.

The collective experience of international agencies and investigators demonstrate the need for a vigorous QC program to ensure that CDB values reported by participating laboratories are indeed reasonably accurate. As Friberg (1988) stated:

"Information about the quality of published data has often been lacking. This is of concern as assessment of metals in trace concentrations in biological media are fraught with difficulties from the collection, handling, and storage of samples to the chemical analyses. This has been proven over and over again from the results of interlaboratory testing and quality control exercises. Large variations in results were reported even from 'experienced' laboratories."

The UNEP/WHO global study of cadmium biological monitoring set a limit for CDB accuracy using the maximum allowable deviation method at $Y = X \pm (0.1X + 1)$ for a targeted concentration of 10 µg Cd/l (Friberg and Vahter 1983). The performance of participating laboratories over a concentration range of 1.5-12 µg/l was reported by Lind et al. (1987). Of the 3 QC runs conducted during 1982 and 1983, 1 or 2 of the 6 laboratories failed each run. For the years 1983 and 1985, between zero and 2 laboratories failed each of the consecutive QC runs.

In another study (Vahter and Friberg 1988), QC samples consisting of both external (unknown) and internal (stated) concentrations were distributed to laboratories participating in the epidemiology research. In this study, the maximum acceptable deviation between the regression analysis of reported results and reference values was set at $Y=X\pm(0.05X+0.2)$ for a concentration range of 0.3-5.0 $\mu\text{g Cd/l}$. It is reported that only 2 of 5 laboratories had acceptable data after the first QC set, and only 1 of 5 laboratories had acceptable data after the second QC set. By the fourth QC set, however, all 5 laboratories were judged proficient.

The need for high quality CDB monitoring is apparent when the toxicological and biological characteristics of this metal are considered; an increase in CDB from 2 to 4 $\mu\text{g/l}$ could cause a doubling of the cadmium accumulation in the kidney, a critical target tissue for selective cadmium accumulation (Nordberg and Nordberg 1988).

Historically, the CDC's internal QC program for CDB cadmium monitoring program has found achievable accuracy to be $\pm 10\%$ of the true value at CDB concentrations $\leq 5.0 \mu\text{g/l}$ (Paschal 1990). Data on the performance of laboratories participating in this program currently are not available.

5.1.6 Observed CDB Concentrations

As stated in Section 4.3, CDB concentrations are representative of ongoing levels of exposure to cadmium. Among those who have been exposed chronically to cadmium for extended periods, however, CDB may contain a component attributable to the general cadmium body burden.

5.1.6.1 CDB Concentrations Among Unexposed Samples

Numerous studies have been conducted examining CDB concentrations in the general population, and in control groups used for comparison with cadmium-exposed workers. A number of reports have been published that present erroneously high values of CDB (Nordberg and Nordberg 1988). This problem was due to contamination of samples during sampling and analysis, and to errors in analysis. Early AAS methods were not sufficiently sensitive to accurately estimate CDB concentrations.

Table 4 presents results of recent studies reporting CDB levels for the general U.S. population not exposed occupationally to cadmium. Other surveys of tissue cadmium using U.S. samples and conducted as part of a cooperative effort among Japan, Sweden and the U.S., did not collect CDB data because standard analytical methodologies were unavailable, and because of analytic problems (Kjellstrom 1979; SWRI 1978).

Arithmetic and/or geometric means and standard deviations are provided in Table 4 for measurements among the populations defined in each study listed. The range of reported measurements and/or the 95% upper and lower confidence intervals for the means are presented when this information was reported in a study. For studies reporting either an arithmetic or geometric standard deviation along with a mean, the lower and upper 95th percentile for the distribution also were derived and reported in the table.

The data provided in Table 4 from Kowal et al. (1979) are from studies conducted between 1974 and 1976 evaluating CDB levels for the general population in Chicago, and are considered to be representative of the U.S. population. These studies indicate that the average CDB concentration among those not occupationally exposed to cadmium is approximately 1 $\mu\text{g/l}$.

In several other studies presented in Table 4, measurements are reported separately for males and females, and for smokers and nonsmokers. The data in this table indicate that similar CDB levels are observed among males and females in the general population, but that smokers tend to exhibit higher CDB levels than nonsmokers. Based on the Kowal et al. (1979) study, smokers not occupationally exposed to cadmium exhibit an average CDB level of 1.4 $\mu\text{g/l}$.

In general, nonsmokers tend to exhibit levels ranging to 2 $\mu\text{g/l}$, while levels observed among smokers range to 5 $\mu\text{g/l}$. Based on the data presented in Table 4, 95% of those not occupationally exposed to cadmium exhibit CDB levels less than 5 $\mu\text{g/l}$.

TABLE 4.-BLOOD CADMIUM CONCENTRATIONS OF U.S. POPULATION NOT OCCUPATIONALLY EXPOSED TO CADMIUM^a

Study No.	No. in study (n)	Sex	Age	Smoking habits ^b	Arithmetic Mean (\pm S.D.) ^c	Absolute range or (95% CI) ^d	Geometric Mean (\pm GSD) ^e	Lower 95 th percentile of distribution ^f	Upper 95 th percentile of distribution ^f	Reference
1	80	M	4 to 69	NS, S	1.13	0.35-3.3	0.98 \pm 1.71	0.4	2.4	Kowal et al.(1979).
	88	F	4 to 69	NS, S	1.03	0.21-3.3	0.91 \pm 1.63	0.4	2.0	
	115	M/F	4 to 69	NS	0.95	0.21-3.3	0.85 \pm 1.59	0.4	1.8	
	31	M/F	4 to 69	S	1.54	0.4-3.3	1.37 \pm 1.65	0.6	3.2	
2	10	M	Adults	(?)	2.0 \pm 2.1	(0.5-5.0)		^g (0)	^g (5.8)	Ellis et al.(1983).
	24	M	Adults	NS			0.6 \pm 1/87	0.2	1.8	
3	20	M	Adults	S			1.2 \pm 2.13	0.3	4.4	Frieberg and Vahter (1983).
	64	F	Adults	NS			0.5 \pm 1.85	0.2	1.4	
	39	F	Adults	S			0.8 \pm 2.22	0.2	3.1	
	32	M	Adults	S, NS			1.2 \pm 2.0	0.4	3.9	
5	35	M	Adults	(?)	2.1 \pm 2.1	(0.5-7.3)		^g (0)	^g (5.6)	Mueller et al.(1989).

^aConcentrations reported in $\mu\text{g Cd/1}$ blood unless otherwise stated.

^bNS--never smoked; S--current cigarette smoker.

^cS.D.--Arithmetic Standard Deviation.

^dC.I.--Confidence interval.

^eGSD--Geometric Standard Deviation.

^fBased on an assumed lognormal distribution.

^gBased on an assumed normal distribution.

5.1.6.2 CDB concentrations among exposed workers

Table 5 is a summary of results from studies reporting CDB levels among workers exposed to cadmium in the work place. As in Table 4, arithmetic and/or geometric means and standard deviations are provided if reported in the listed studies. The absolute range, or the 95% confidence interval around the mean, of the data in each study are provided when reported. In addition, the lower and upper 95th percentile of the distribution are presented for each study if that a mean and corresponding standard deviation were reported. Table 5 also provides estimates of the duration, and level, of exposure to cadmium in the work place if these data were reported in the listed studies. The data presented in table 5 suggest that CDB levels are dose related. Sukuri et al. (1983) show that higher CDB levels are observed among workers experiencing higher work place exposure. This trend appears to be true of the studies listed in the table.

CDB levels reported in table 5 are higher among those showing signs of cadmium-related kidney damage than those showing no such damage. Lauwerys et al. (1976) report CDB levels among workers with kidney lesions that generally are above the levels reported for workers without kidney lesions. Ellis et al. (1983) report a similar observation comparing workers with and without renal dysfunction, although they found more overlap between the 2 groups than Lauwerys et al.

The data in table 5 also indicate that CDB levels are higher among those experiencing current occupational exposure than those who have been removed from such exposure. Roels et al. (1982) indicate that CDB levels observed among workers experiencing ongoing exposure in the work place are almost entirely above levels observed among workers removed from such exposure. This finding suggests that CDB levels decrease once cadmium exposure has ceased.

A comparison of the data presented in tables 4 and 5 indicates that CDB levels observed among cadmium-exposed workers is significantly higher than levels observed among the unexposed groups. With the exception of 2 studies presented in table 5 (1 of that includes former workers in the sample group tested), the lower 95th percentile for CDB levels among exposed workers are greater than 5 µg/l, that is the value of the upper 95th percentile for CDB levels observed among those who are not occupationally exposed. Therefore, a CDB level of 5 µg/l represents a threshold above that significant work place exposure to cadmium may be occurring.

TABLE 5.--BLOOD CADMIUM IN WORKERS EXPOSED TO CADMIUM IN THE WORKPLACE

Study number	Work environment worker population monitored)	Number in study	Employment in years (mean)	Mean concentration of cadmium in air ($\mu\text{g}/\text{m}^3$)	Concentrations of Cadmium in blood ^a					Reference
					Arithmetic mean (\pm S.D.) ^b	Absolute range or (95% C.I.) ^c	Geometric mean (GSD) ^d	Lower 95 th percentile of range ^e () ^f	Upper 95 th percentile of range ^e () ^f	
1	Ni-Cd battery plant and Cd production plant: (Workers without kidney lesions) (Workers with kidney lesions)	96	3-40	.90	21.4 \pm 1.9	(18)	(25)	Lauwerys et al. 1976.
		25	38.8 \pm 3.8	(32)	(45)	
2	Ni-Cd battery plant: (Smokers) (Nonsmokers)	7	(5)	10.1	22.7	7.3-67.2	Adamsson et al. (1979).
		8	(9)	7.0	7.0	4.9-10.5				
3	Cadmium alloy plant: (High exposure group) (Low exposure group)	7	(10.6)	(1,000 – 5 yrs;	20.8 \pm 7.1	(7.3)	(34)	Sukuri et al. 1982.
		9	(7.3)	40-5 yrs)	7.1 \pm 1.1	(5.1)	(9.1)	
4	Retrospective study of workers with renal problems: (Before removal) (After removal)	19	15-41	39.9 \pm 3.7	11-179	(34)	(46)	Roels et al. 1982.
		(27.2)	14.1 \pm 5.6	5.7-27.4				
5	Cadmium production plant: (Workers without renal dysfunction). (Workers with renal dysfunction)	33	1-34	15 \pm 5.7	7-31	(5.4)	(25)	Ellis et al. 1983.
		18	10-34	24 \pm 8.5	10-34	(9.3)	(39)	
6	Cd-Cu alloy plant	75	Up to 39	8.8 \pm 1.1	7.5	10	Mason et al. 1988.
7	Cadmium recovery operation - Current (19) and former (26) workers.	45	(19.0)	7.9 \pm 2.0	2.5	25	Thun et al. 1989.
8	Cadmium recovery operation	40	10.2 \pm 5.3	2.2-18.8	(1.3)	(19)	Mueller et al. 1989.

^a Concentrations reported in μg Cd/l blood unless otherwise stated.^b S.D.--Standard Deviation.^c C.I.--Confidence Interval.^d GSD--Geometric Standard Deviation.^e Based on an assumed lognormal distribution.^f Based on an assumed normal distribution^g Years following removal.

5.1.7 Conclusions and Recommendations for CDB

Based on the above evaluation, the following recommendations are made for a CDB proficiency program.

5.1.7.1 Recommended method

The method of Stoeppler and Brandt (1980) should be adopted for analyzing CDB. This method was selected over other methods for its straightforward sample-preparation procedures, and because limitations of the method were described adequately. It also is the method used by a plurality of laboratories currently participating in the CTQ proficiency program. In a recent CTQ interlaboratory comparison report (CTQ 1991), analysis of the methods used by laboratories to measure CDB indicates that 46% (11 of 24) of the participating laboratories used the Stoeppler and Brandt methodology (HNO₃ deproteinization of blood followed by analysis of the supernatant by GF-AAS). Other CDB methods employed by participating laboratories identified in the CTQ report include dilution of blood (29%), acid digestion (12%) and miscellaneous methods (12%).

Laboratories may adopt alternate methods, but it is the responsibility of the laboratory to demonstrate that the alternate methods meet the data quality objectives defined for the Stoeppler and Brandt method (see Section 5.1.7.2 below).

5.1.7.2 Data quality objectives

Based on the above evaluation, the following data quality objectives (DQOs) should facilitate interpretation of analytical results.

Limit of Detection. 0.5 µg/l should be achievable using the Stoeppler and Brandt method. Stoeppler and Brandt (1980) report a limit of detection equivalent to 0.2 µg/l in whole blood using 25 µl aliquots of deproteinized, diluted blood samples.

Accuracy. Initially, some of the laboratories performing CDB measurements may be expected to satisfy criteria similar to the less severe criteria specified by the CTQ program, i.e., measurements within 2 µg/l or 15% (whichever is greater) of the target value. About 60% of the laboratories enrolled in the CTQ program could meet this criterion on the first proficiency test (Weber 1988).

Currently, approximately 12 laboratories in the CTQ program are achieving an accuracy for CDB analysis within the more severe constraints of ±1 µg/l or 15% (whichever is greater). Later, as laboratories gain experience, they should achieve the level of accuracy exhibited by these 12 laboratories. The experience in the CTQ program has shown that, even without incentives, laboratories benefit from the feedback of the program; after they have analyzed 40-50 control samples from the program, performance improves to the point where about 60% of the laboratories can meet the stricter criterion of ±1 µg/l or 15% (Weber 1988). Thus, this stricter target accuracy is a reasonable DQO.

Precision. Although Stoeppler and Brandt (1980) suggest that a coefficient of variation (CV) near 1.3% (for a 10 µg/l concentration) is achievable for within-run reproducibility, it is recognized that other factors affecting within- and between-run comparability will increase the achievable CV. Stoeppler and Brandt (1980) observed CVs that were as high as 30% for low concentrations (0.4 µg/l), and CVs of less than 5% for higher concentrations.

For internal QC samples (see Section 3.3.1), laboratories should attain an overall precision near 25%. For CDB samples with concentrations less than 2 µg/l, a target precision of 40% is reasonable, while precisions of 20% should be achievable for concentrations greater than 2 µg/l. Although these values are more strict than values observed in the CTQ interlaboratory program reported by Webber (1988), they are within the achievable limits reported by Stoeppler and Brandt (1980).

5.1.7.3 Quality assurance/quality control

Commercial laboratories providing measurement of CDB should adopt an internal QA/QC program that incorporates the following components: Strict adherence to the selected method, including all calibration requirements; regular incorporation of QC samples during actual runs; a protocol for corrective actions, and documentation of these actions; and, participation in an interlaboratory proficiency program. Note that the non-mandatory QA/QC program presented in Attachment 1 is based on the Stoeppler and Brandt method for CDB analysis. Should an alternate method be adopted, the laboratory should develop a QA/QC program satisfying the provisions of Section 3.3.1.

5.2 Measuring Cadmium in Urine (CDU)

As in the case of CDB measurement, proper determination of CDU requires strict analytical discipline regarding collection and handling of samples. Because cadmium is both

ubiquitous in the environment and employed widely in coloring agents for industrial products that may be used during sample collection, preparation and analysis, care should be exercised to ensure that samples are not contaminated during the sampling procedure.

Methods for CDU determination share many of the same features as those employed for the determination of CDB. Thus, changes and improvements to methods for measuring CDU over the past 40 years parallel those used to monitor CDB. The direction of development has largely been toward the simplification of sample preparation techniques made possible because of improvements in analytic techniques.

5.2.1 Units of CDU Measurement

Procedures adopted for reporting CDU concentrations are not uniform. In fact, the situation for reporting CDU is more complicated than for CDB, where concentrations are normalized against a unit volume of whole blood.

Concentrations of solutes in urine vary with several biological factors (including the time since last voiding and the volume of liquid consumed over the last few hours); as a result, solute concentrations should be normalized against another characteristic of urine that represents changes in solute concentrations. The 2 most common techniques are either to standardize solute concentrations against the concentration of creatinine, or to standardize solute concentrations against the specific gravity of the urine. Thus, CDU concentrations have been reported in the literature as "uncorrected" concentrations of cadmium per volume of urine (i.e., $\mu\text{g Cd/l urine}$), "corrected" concentrations of cadmium per volume of urine at a standard specific gravity (i.e., $\mu\text{g Cd/l urine at a specific gravity of 1.020}$), or "corrected" mass concentration per unit mass of creatinine (i.e., $\mu\text{g Cd/g creatinine}$). (CDU concentrations [whether uncorrected or corrected for specific gravity, or normalized to creatinine] occasionally are reported in nanomoles [i.e., nmoles] of cadmium per unit mass or volume. In this protocol, these values are converted to μg of cadmium per unit mass or volume using $89 \text{ nmoles of cadmium} = 10 \mu\text{g}$.)

While it is agreed generally that urine values of analytes should be normalized for reporting purposes, some debate exists over what correction method should be used. The medical community has long favored normalization based on creatinine concentration, a common urinary constituent. Creatinine is a normal product of tissue catabolism, is excreted at a uniform rate, and the total amount excreted per day is constant on a day-to-day basis (NIOSH 1984b). While this correction method is accepted widely in Europe, and within some occupational health circles, Kowals (1983) argues that the use of specific gravity (i.e., total solids per unit volume) is more straightforward and practical (than creatinine) in adjusting CDU values for populations that vary by age or gender.

Kowals (1983) found that urinary creatinine (CRTU) is lower in females than males, and also varies with age. Creatinine excretion is highest in younger males (20-30 years old), decreases at middle age (50-60 years), and may rise slightly in later years. Thus, cadmium concentrations may be underestimated for some workers with high CRTU levels.

Within a single void urine collection, urine concentration of any analyte will be affected by recent consumption of large volumes of liquids, and by heavy physical labor in hot environments. The absolute amount of analyte excreted may be identical, but concentrations will vary widely so that urine must be corrected for specific gravity (i.e., to normalize concentrations to the quantity of total solute) using a fixed value (e.g., 1.020 or 1.024). However, since heavy-metal exposure may increase urinary protein excretion, there is a tendency to underestimate cadmium concentrations in samples with high specific gravities when specific-gravity corrections are applied.

Despite some shortcomings, reporting solute concentrations as a function of creatinine concentration is accepted generally; OSHA therefore recommends that CDU levels be reported as the mass of cadmium per unit mass of creatinine ($\mu\text{g/g CRTU}$).

Reporting CDU as $\mu\text{g/g CRTU}$ requires an additional analytical process beyond the analysis of cadmium: Samples must be analyzed independently for creatinine so that results may be reported as the ratio of cadmium to creatinine concentrations found in the urine sample. Consequently, the overall quality of the analysis depends on the combined performance by a laboratory on these 2 determinations. The analysis used for CDU determinations is addressed below in terms of $\mu\text{g Cd/l}$, with analysis of creatinine addressed separately. Techniques for assessing creatinine are discussed in Section 5.4.

Techniques for deriving cadmium as a ratio of CRTU, and the confidence limits for independent measurements of cadmium and CRTU, are provided in Section 3.3.3.

5.2.2 Analytical Techniques Used to Monitor CDU

Analytical techniques used for CDU determinations are similar to those employed for CDB determinations; these techniques are summarized in Table 3. As with CDB monitoring, the technique most suitable for CDU determinations is atomic absorption spectroscopy (AAS). AAS methods used for CDU determinations typically employ a graphite furnace, with background correction made using either the deuterium-lamp or Zeeman techniques; Section 5.1.1 provides a detailed description of AAS methods.

5.2.3 Methods Developed for CDU Determinations

Princi (1947), Smith et al. (1955), Smith and Kench (1957), and Tsuchiya (1967) used colorimetric procedures similar to those described in the CDB section above to estimate CDU concentrations. In these methods, urine (50 ml) is reduced to dryness by heating in a sand bath and digested (wet ashed) with mineral acids. Cadmium then is complexed with dithiazone, extracted with chloroform and quantified by spectrophotometry. These early studies typically report reagent blank values equivalent to 0.3 µg Cd/l, and CDU concentrations among non-exposed control groups at maximum levels of 10 µg Cd/l—erroneously high values when compared to more recent surveys of cadmium concentrations in the general population.

By the mid-1970s, most analytical procedures for CDU analysis used either wet ashing (mineral acid) or high temperatures (>400 °C) to digest the organic matrix of urine, followed by cadmium chelation with APDC or DDTC solutions and extraction with MIBK. The resulting aliquots were analyzed by flame or graphite-furnace AAS (Kjellstrom 1979).

Improvements in control over temperature parameters with electrothermal heating devices used in conjunction with flameless AAS techniques, and optimization of temperature programs for controlling the drying, charring, and atomization processes in sample analyses, led to improved analytical detection of diluted urine samples without the need for sample digestion or ashing. Roels et al. (1978) successfully used a simple sample preparation, dilution of 1.0 ml aliquots of urine with 0.1 N HNO₃, to achieve accurate low-level determinations of CDU.

In the method described by Pruszkowska et al. (1983), that has become the preferred method for CDU analysis, urine samples were diluted at a ratio of 1:5 with water; diammonium hydrogenphosphate in dilute HNO₃ was used as a matrix modifier. The matrix modifier allows for a higher charring temperature without loss of cadmium through volatilization during preatomization. This procedure also employs a stabilized temperature platform in a graphite furnace, while nonspecific background absorption is corrected using the Zeeman technique. This method allows for an absolute detection limit of approximately 0.04 µg Cd/l urine.

5.2.4 Sample Collection and Handling

Sample collection procedures for CDU may contribute to variability observed among CDU measurements. Sources of variation attendant to sampling include time-of-day, the interval since ingestion of liquids, and the introduction of external contamination during the collection process. Therefore, to minimize contributions from these variables, strict adherence to a sample-collection protocol is recommended. This protocol should include provisions for normalizing the conditions under that urine is collected. Every effort also should be made to collect samples during the same time of day.

Collection of urine samples from an industrial work force for biological monitoring purposes usually is performed using "spot" (i.e., single-void) urine with the pH of the sample determined immediately. Logistic and sample-integrity problems arise when efforts are made to collect urine over long periods (e.g., 24 hrs). Unless single-void urines are used, there are numerous opportunities for measurement error because of poor control over sample collection, storage and environmental contamination.

To minimize the interval during that sample urine resides in the bladder, the following adaption to the "spot" collection procedure is recommended: The bladder should first be emptied, and then a large glass of water should be consumed; the sample may be collected within an hour after the water is consumed.

5.2.5 Best Achievable Performance

Performance using a particular method for CDU determinations is assumed to be equivalent to the performance reported by the research laboratories in that the method was developed. Pruszkowska et al. (1983) report a detection limit of 0.04 µg/l CDU, with a CV of <4% between 0-5 µg/l. The CDC reports a minimum CDU detection limit of 0.07 µg/l using a modified method based on Pruszkowska et al. (1983). No CV is stated in this protocol; the protocol contains only rejection criteria for internal QC parameters used during accuracy

determinations with known standards (Attachment 8 of exhibit 106 of OSHA docket H057A). Stoeppler and Brandt (1980) report a CDU detection limit of 0.2 µg/l for their methodology.

5.2.6 General Method Performance

For any particular method, the expected initial performance from commercial laboratories may be somewhat lower than that reported by the research laboratory in that the method was developed. With participation in appropriate proficiency programs, and use of a proper in-house QA/QC program incorporating provisions for regular corrective actions, the performance of commercial laboratories may be expected to improve and approach that reported by a research laboratories. The results reported for existing proficiency programs serve to specify the initial level of performance that likely can be expected from commercial laboratories offering analysis using a particular method.

Weber (1988) reports on the results of the CTQ proficiency program, that includes CDU results for laboratories participating in the program. Results indicate that after receiving 60 samples (i.e., after participating in the program for approximately 3 years), approximately 80% of the participating laboratories report CDU results ranging between ± 2 µg/l or 15% of the consensus mean, whichever is greater. On any single sample of the last 15 samples, the proportion of laboratories falling within the specified range is between 75 and 95%, except for a single test for that only 60% of the laboratories reported acceptable results. For each of the last 15 samples, approximately 60% of the laboratories reported results within ± 1 µg or 15% of the mean, whichever is greater. The range of concentrations included in this set of samples was not reported.

Another report from the CTQ (1991) summarizes preliminary CDU results from their 1991 interlaboratory program. According to the report, for 3 CDU samples with values of 9.0, 16.8, 31.5 µg/l, acceptable results (target of ± 2 µg/l or 15% of the consensus mean, whichever is greater) were achieved by only 44-52% of the 34 laboratories participating in the CDU program. The overall CVs for these 3 CDU samples among the 34 participating laboratories were 31%, 25%, and 49%, respectively. The reason for this poor performance has not been determined.

A more recent report from the CTQ (Weber, private communication) indicates that 36% of the laboratories in the program have been able to achieve the target of ± 1 µg/l or 15% for more than 75% of the samples analyzed over the last 5 years, while 45% of participating laboratories achieved a target of ± 2 µg/l or 15% for more than 75% of the samples analyzed over the same period.

Note that results reported in the interlaboratory programs are in terms of µg Cd/l of urine, unadjusted for creatinine. The performance indicated, therefore, is a measure of the performance of the cadmium portion of the analyses, and does not include variation that may be introduced during the analysis of CRTU.

5.2.7 Observed CDU Concentrations

Prior to the onset of renal dysfunction, CDU concentrations provide a general indication of the exposure history (i.e., body burden)(see Section 4.3). Once renal dysfunction occurs, CDU levels appear to increase and are no longer indicative solely of cadmium body burden (Friberg and Elinder 1988).

5.2.7.1 Range of CDU concentrations observed among unexposed samples

Surveys of CDU concentrations in the general population were first reported from cooperative studies among industrial countries (i.e., Japan, U.S. and Sweden) conducted in the mid-1970s. In summarizing these data, Kjellstrom (1979) reported that CDU concentrations among Dallas, Texas men (age range: <9-59 years; smokers and nonsmokers) varied from 0.11-1.12 µg/l (uncorrected for creatinine or specific gravity). These CDU concentrations are intermediate between population values found in Sweden (range: 0.11-0.80 µg/l) and Japan (range: 0.14-2.32 µg/l).

Kowal and Zirkes (1983) reported CDU concentrations for almost 1,000 samples collected during 1978-79 from the general U.S. adult population (i.e., nine states; both genders; ages 20-74 years). They report that CDU concentrations are log normally distributed; low levels predominated, but a small proportion of the population exhibited high levels. These investigators transformed the CDU concentrations values, and reported the same data 3 different ways: µg/l urine (unadjusted), µg/l (specific gravity adjusted to 1.020), and µg/g CRTU. These data are summarized in Tables 6 and 7.

Based on further statistical examination of these data, including the lifestyle characteristics of this group, Kowal (1988) suggested increased cadmium absorption (i.e., body

burden) was correlated with low dietary intakes of calcium and iron, as well as cigarette smoking.

CDU levels presented in Table 6 are adjusted for age and gender. Results suggest that CDU levels may be slightly different among men and women (i.e., higher among men when values are unadjusted, but lower among men when the values are adjusted, for specific gravity or CRTU). Mean differences among men and women are small compared to the standard deviations, and therefore may not be significant. Levels of CDU also appear to increase with age. The data in Table 6 suggest as well that reporting CDU levels adjusted for specific gravity or as a function of CRTU results in reduced variability.

TABLE 6
URINE CADMIUM CONCENTRATIONS IN THE U.S. ADULT POPULATION:
NORMAL AND CONCENTRATION--ADJUSTED VALUES BY AGE AND SEX¹

	Geometric means (and geometric standard deviations)		
	Unadjusted ($\mu\text{g/l}$)	SG-adjusted ² $\mu\text{g/l}$ at 1.020)	Creatine- adjusted ($\mu\text{g/g}$)
Sex:			
Male (n=484)	0.55(2.9)	0.73(2.6)	0.55(2.7)
Female (n=498)	0.49(3.0)	0.86(2.7)	0.78(2.7)
Age:			
20-29 (n=222)	0.32(3.0)	0.43(2.7)	0.32(2.7)
30-39 (n=141)	0.46(3.2)	0.70(2.8)	0.54(2.7)
40-49 (n=142)	0.50(3.0)	0.81(2.6)	0.70(2.7)
50-59 (n=117)	0.61(2.9)	0.99(2.4)	0.90(2.3)
60-69 (n=272)	0.76(2.6)	1.16(2.3)	1.03(2.3)

¹ From Kowal and Zirkes 1983.

² SC-adjusted is adjusted for specific gravity.

TABLE 7
URINE CADMIUM CONCENTRATIONS IN THE U.S. ADULT POPULATION:
CUMULATIVE FREQUENCY DISTRIBUTION OF URINARY CADMIUM (N=982)¹

Range of concentrations	$\mu\text{g/l}$ percent	SG-adjusted ($\mu\text{g/l}$ at 1.020) percent	Creatine- adjusted ($\mu\text{g/g}$) percent
<0.5	43.9	28.0	35.8
0.6-1.0	71.7	56.4	65.6
1.1-1.5	84.4	74.9	81.4
1.6-2.0	91.3	84.7	88.9
2.1-3.0	97.3	94.4	95.8
3.1-4.0	98.8	97.4	97.2
4.1-5.0	99.4	98.2	97.9
5.1-10.0	99.6	99.4	99.3

Range of concentrations	µg/l) percent	SG-adjusted (µg/l at 1.020) percent	Creatine-adjusted (µg/g) percent
10.0-20.0	99.8	99.6	99.6

¹ Source: Kowal and Zirkes (1983).

The data in the Table 6 indicate the geometric mean of CDU levels observed among the general population is 0.52 µg Cd/l urine (unadjusted), with a geometric standard deviation of 3.0. Normalized for creatinine, the geometric mean for the population is 0.66 µg/g CRTU, with a geometric standard deviation of 2.7. Table 7 provides the distributions of CDU concentrations for the general population studied by Kowal and Zirkes. The data in this table indicate that 95% of the CDU levels observed among those not occupationally exposed to cadmium are below 3 µg/g CRTU.

5.2.7.2 Range of CDU concentrations observed among exposed workers

Table 8 is a summary of results from available studies of CDU concentrations observed among cadmium-exposed workers. In this table, arithmetic and/or geometric means and standard deviations are provided if reported in these studies. The absolute range for the data in each study, or the 95% confidence interval around the mean of each study, also are provided when reported. The lower and upper 95th percentile of the distribution are presented for each study in that a mean and corresponding standard deviation were reported. Table 8 also provides estimates of the years of exposure, and the levels of exposure, to cadmium in the work place if reported in these studies. Concentrations reported in this table are in µg/g CRTU, unless otherwise stated.

Data in Table 8 from Lauwerys et al. (1976) and Ellis et al. (1983) indicate that CDU concentrations are higher among those exhibiting kidney lesions or dysfunction than among those lacking these symptoms. Data from the study by Roels et al. (1982) indicate that CDU levels decrease among workers removed from occupational exposure to cadmium in comparison to workers experiencing ongoing exposure. In both cases, however, the distinction between the 2 groups is not as clear as with CDB; there is more overlap in CDU levels observed among each of the paired populations than is true for corresponding CDB levels. As with CDB levels, the data in Table 8 suggest increased CDU concentrations among workers who experienced increased overall exposure.

Although a few occupationally-exposed workers in the studies presented in Table 8 exhibit CDU levels below 3 µg/g CRTU, most of those workers exposed to cadmium levels in excess of the PEL defined in the final cadmium rule exhibit CDU levels above 3 µg/g CRTU; this level represents the upper 95th percentile of the CDU distribution observed among those who are not occupationally exposed to cadmium (Table 7).

The mean CDU levels reported in Table 8 among occupationally-exposed groups studied (except 2) exceed 3 µg/g CRTU. Correspondingly, the level of exposure reported in these studies (with 1 exception) are significantly higher than what workers will experience under the final cadmium rule. The 2 exceptions are from the studies by Mueller et al. (1989) and Kawada et al. (1990); these studies indicate that workers exposed to cadmium during pigment manufacture do not exhibit CDU levels as high as those levels observed among workers exposed to cadmium in other occupations. Exposure levels, however, were lower in the pigment manufacturing plants studied. Significantly, workers removed from occupational cadmium exposure for an average of 4 years still exhibited CDU levels in excess of 3 µg/g CRTU (Roels et al. 1982). In the single-exception study with a reported level of cadmium exposure lower than levels proposed in the final rule (i.e., the study of a pigment manufacturing plant by Kawada et al. 1990), most of the workers exhibited CDU levels less than 3 µg/g CRTU (i.e., the mean value was only 1.3 µg/g CRTU). CDU levels among workers with such limited cadmium exposure are expected to be significantly lower than levels of other studies reported in Table 8.

Based on the above data, a CDU level of 3 µg/g CRTU appear to represent a threshold above that significant work place exposure to cadmium occurs over the work span of those being monitored. Note that this threshold is not as distinct as the corresponding threshold

described for CDB. In general, the variability associated with CDU measurements among exposed workers appears to be higher than the variability associated with CDB measurements among similar workers.

5.2.8 Conclusions and Recommendations for CDU

The above evaluation supports the following recommendations for a CDU proficiency program. These recommendations address only sampling and analysis procedures for CDU determinations specifically, that are to be reported as an unadjusted $\mu\text{g Cd/l}$ urine. Normalizing this result to creatinine requires a second analysis for CRTU so that the ratio of the 2 measurements can be obtained. Creatinine analysis is addressed in Section 5.4. Formal procedures for combining the 2 measurements to derive a value and a confidence limit for CDU in $\mu\text{g/g CRTU}$ are provided in Section 3.3.3.

5.2.8.1 Recommended method

The method of Pruszkowska et al. (1983) should be adopted for CDU analysis. This method is recommended because it is simple, straightforward and reliable (i.e., small variations in experimental conditions do not affect the analytical results).

A synopsis of the methods used by laboratories to determine CDU under the interlaboratory program administered by the CTQ (1991) indicates that more than 78% (24 of 31) of the participating laboratories use a dilution method to prepare urine samples for CDU analysis. Laboratories may adopt alternate methods, but it is the responsibility of the laboratory to demonstrate that the alternate methods provide results of comparable quality to the Pruszkowska method.

5.2.8.2 Data quality objectives

The following data quality objectives should facilitate interpretation of analytical results, and are achievable based on the above evaluation.

Limit of Detection. A level of $0.5 \mu\text{g/l}$ (i.e., corresponding to a detection limit of $0.5 \mu\text{g/g CRTU}$, assuming 1 g CRT/l urine) should be achievable. Pruszkowska et al. (1983) achieved a limit of detection of $0.04 \mu\text{g/l}$ for CDU based on the slope of the curve for their working standards ($0.35 \text{ pg Cd}/0.0044$, $A_{\text{signal}}=1\%$ absorbance using GF-AAS).

TABLE 8.--URINE CADMIUM CONCENTRATIONS IN WORKERS EXPOSED TO CADMIUM IN THE WORKPLACE

Study number	Work environment (worker population monitored)	Number in Study (n)	Employment in years (mean)	Mean Concentration of cadmium in air ($\mu\text{g}/\text{m}^3$)	Concentration of cadmium in urine ^a					Reference
					Arithmetic mean (\pm S.D.) ^b	Absolute range or (95% C.I.) ^c	Geometric mean (GSD) ^d	Lower 95 th percentile of range ^e () ^f	Upper 95 th percentile of range ^e () ^f	
1	Ni-Cd battery plant and Cd production plant. (Workers without kidney lesions). (Workers with kidney lesions)	3-40	.90	Lauwerys et al. 1976.
		96	16.3 \pm 16.7	(0)	(44)	
		25	48.2 \pm 42.6	(0)	(120)	
2	Ni-Cd battery plant (Smokers) (Nonsmokers)	Adamsson et al. (1979).
		7	(5)	10.1	5.5	1.0-14.7	
8		8	(9)	7.0	3.6	0.5-9.3	
3	Cadmium salts production facility.	148	(15.4)	15.8	2-150	Butchet et al. 1980.
4	Retrospective study of workers with renal problems. (Before removal) (After removal)	19	15-41	Roels et al. 1982.
		(27.2)	39.4 \pm 28.1	10.8-117	(0)	(88)	
		(4.2)g	16.4 \pm 9.0	80-42.3	(1.0)	(32)	
5	Cadmium production plant (Workers without renal dysfunction). (Workers with renal dysfunction).	Ellis et al. 1983.
		33	1-34	9.4 \pm 6.9	2-27	(0)	(21)	
18	10-34	22.8 \pm 12.7	8-55	(1)	(45)			
6	Cd-Cu alloy plant	75	Up to 39	Note h	6.9 \pm 9.4	(0)	(23)	Mason et al. 1988.
7	Cadmium recovery operation.	45	(19)	87	9.3 \pm 6.9	(0)	(21)	Thun et al. 1989.
8	Pigment manufacturing plant.	29	(12.8)	0.18-3.0	0.2-9.5	1.1	Mueller et al. 1989.
9	Pigment manufacturing plant.	26	(12.1)	.3.0	1.25 \pm 2.45	0.3	6	Kawada et al. 1990.

^a Concentrations reported in $\mu\text{g}/\text{g}$ Cr.^b S.D.--Standard Deviation.^c C.I.--Confidence Interval.^d GSD--Geometric Standard Deviation.^e Based on an assumed lognormal distribution.^f Based on an assumed normal distribution.^g Years following removal.^h Equivalent to 50 for 20.22 yrs

The CDC reports a minimum detection limit for CDU of 0.07 µg/l using a modified Pruszkowska method. This limit of detection was defined as 3 times the standard deviation calculated from 10 repeated measurements of a "low level" CDU test sample (Attachment 8 of exhibit 106 of OSHA docket H057A).

Stoeppler and Brandt (1980) report a limit of detection for CDU of 0.2 µg/l using an aqueous dilution (1:2) of the urine samples.

Accuracy. A recent report from the CTQ (Weber, private communication) indicates that 36% of the laboratories in the program achieve the target of ± 1 µg/l or 15% for more than 75% of the samples analyzed over the last 5 years, while 45% of participating laboratories achieve a target of ± 2 µg/l or 15% for more than 75% of the samples analyzed over the same period. With time and a strong incentive for improvement, it is expected that the proportion of laboratories successfully achieving the stricter level of accuracy should increase. It should be noted, however, these indices of performance do not include variations resulting from the ancillary measurement of CRTU (that is recommended for the proper recording of results). The low cadmium levels expected to be measured indicate that the analysis of creatinine will contribute relatively little to the overall variability observed among creatinine-normalized CDU levels (see Section 5.4). The initial target value for reporting CDU under this program, therefore, is set at ± 1 µg/g CRTU or 15% (whichever is greater).

Precision. For internal QC samples (that are recommended as part of an internal QA/QC program, Section 3.3.1), laboratories should attain an overall precision of 25%. For CDB samples with concentrations less than 2 µg/l, a target precision of 40% is acceptable, while precisions of 20% should be achievable for CDU concentrations greater than 2 µg/l. Although these values are more stringent than those observed in the CTQ interlaboratory program reported by Webber (1988), they are well within limits expected to be achievable for the method as reported by Stoeppler and Brandt (1980).

5.2.8.3 Quality assurance/quality control

Commercial laboratories providing CDU determinations should adopt an internal QA/QC program that incorporates the following components: Strict adherence to the selected method, including calibration requirements; regular incorporation of QC samples during actual runs; a protocol for corrective actions, and documentation of such actions; and, participation in an interlaboratory proficiency program. Note that the non-mandatory program presented in Attachment 1 as an example of an acceptable QA/QC program, is based on using the Pruszkowska method for CDU analysis. Should an alternate method be adopted by a laboratory, the laboratory should develop a QA/QC program equivalent to the non-mandatory program, and that satisfies the provisions of Section 3.3.1.

5.3 Monitoring β -2-Microglobulin in Urine (B2MU)

As indicated in Section 4.3, B2MU appears to be the best of several small proteins that may be monitored as early indicators of cadmium-induced renal damage. Several analytic techniques are available for measuring B2M.

5.3.1 Units of B2MU Measurement

Procedures adopted for reporting B2MU levels are not uniform. In these guidelines, OSHA recommends that B2MU levels be reported as µg/g CRTU, similar to reporting CDU concentrations. Reporting B2MU normalized to the concentration of CRTU requires an additional analytical process beyond the analysis of B2M: Independent analysis for creatinine so that results may be reported as a ratio of the B2M and creatinine concentrations found in the urine sample. Consequently, the overall quality of the analysis depends on the combined performance on these 2 analyses. The analysis used for B2MU determinations is described in terms of µg B2M/l urine, with analysis of creatinine addressed separately. Techniques used to measure creatinine are provided in Section 5.4. Note that Section 3.3.3 provides techniques for deriving the value of B2M as function of CRTU, and the confidence limits for independent measurements of B2M and CRTU.

5.3.2 Analytical Techniques Used to Monitor B2MU

One of the earliest tests used to measure B2MU was the radial immunodiffusion technique. This technique is a simple and specific method for identification and quantitation of a number of proteins found in human serum and other body fluids when the protein is not readily differentiated by standard electrophoretic procedures. A quantitative relationship exists between the concentration of a protein deposited in a well that is cut into a thin agarose layer containing the corresponding monospecific antiserum, and the distance that the resultant complex diffuses. The wells are filled with an unknown serum and the standard (or control),

and incubated in a moist environment at room temperature. After the optimal point of diffusion has been reached, the diameters of the resulting precipitation rings are measured. The diameter of a ring is related to the concentration of the constituent substance. For B2MU determinations required in the medical monitoring program, this method requires a process that may be insufficient to concentrate the protein to levels that are required for detection.

Radioimmunoassay (RIA) techniques are used widely in immunologic assays to measure the concentration of antigen or antibody in body-fluid samples. RIA procedures are based on competitive-binding techniques. If antigen concentration is being measured, the principle underlying the procedure is that radioactive-labeled antigen competes with the sample's unlabeled antigen for binding sites on a known amount of immobile antibody. When these 3 components are present in the system, an equilibrium exists. This equilibrium is followed by a separation of the free and bound forms of the antigen. Either free or bound radioactive-labeled antigen can be assessed to determine the amount of antigen in the sample. The analysis is performed by measuring the level of radiation emitted either by the bound complex following removal of the solution containing the free antigen, or by the isolated solution containing the residual-free antigen. The main advantage of the RIA method is the extreme sensitivity of detection for emitted radiation and the corresponding ability to detect trace amounts of antigen. Additionally, large numbers of tests can be performed rapidly.

The enzyme-linked immunosorbent assay (ELISA) techniques are similar to RIA techniques except that nonradioactive labels are employed. This technique is safe, specific and rapid, and is nearly as sensitive as RIA techniques. An enzyme-labeled antigen is used in the immunologic assay; the labeled antigen detects the presence and quantity of unlabeled antigen in the sample. In a representative ELISA test, a plastic plate is coated with antibody (e.g., antibody to B2M). The antibody reacts with antigen (B2M) in the urine and forms an antigen-antibody complex on the plate. A second anti-B2M antibody (i.e., labeled with an enzyme) is added to the mixture and forms an antibody-antigen-antibody complex. Enzyme activity is measured spectrophotometrically after the addition of a specific chromogenic substrate that is activated by the bound enzyme. The results of a typical test are calculated by comparing the spectrophotometric reading of a serum sample to that of a control or reference serum. In general, these procedures are faster and require less laboratory work than other methods.

In a fluorescent ELISA technique (such as the one employed in the Pharmacia Delphia test for B2M), the labeled enzyme is bound to a strong fluorescent dye. In the Pharmacia Delphia test, an antigen bound to a fluorescent dye competes with unlabeled antigen in the sample for a predetermined amount of specific, immobile antibody. Once equilibrium is reached, the immobile phase is removed from the labeled antigen in the sample solution and washed; an enhancement solution then is added that liberates the fluorescent dye from the bound antigen-antibody complex. The enhancement solution also contains a chelate that complexes with the fluorescent dye in solution; this complex increases the fluorescent properties of the dye so that it is easier to detect.

To determine the quantity of B2M in a sample using the Pharmacia Delphia test, the intensity of the fluorescence of the enhancement solution is measured. This intensity is proportional to the concentration of labeled antigen that bound to the immobile antibody phase during the initial competition with unlabeled antigen from the sample. Consequently, the intensity of the fluorescence is an inverse function of the concentration of antigen (B2M) in the original sample. The relationship between the fluorescence level and the B2M concentration in the sample is determined using a series of graded standards, and extrapolating these standards to find the concentration of the unknown sample.

5.3.3 Methods Developed for B2MU Determinations

B2MU usually is measured by radioimmunoassay (RIA) or enzyme-linked immunosorbent assay (ELISA); however, other methods (including gel electrophoresis, radial immunodiffusion, and nephelometric assays) also have been described (Schardun and van Epps 1987). RIA and ELISA methods are preferred because they are sensitive at concentrations as low as micrograms per liter, require no concentration processes, are highly reliable and use only a small sample volume.

Based on a survey of the literature, the ELISA technique is recommended for monitoring B2MU. While RIAs provide greater sensitivity (typically about 1 µg/l, Evrin et al. 1971), they depend on the use of radioisotopes; use of radioisotopes requires adherence to rules and regulations established by the Atomic Energy Commission, and necessitates an expensive

radioactivity counter for testing. Radioisotopes also have a relatively short half-life that corresponds to a reduced shelf life, thereby increasing the cost and complexity of testing. In contrast, ELISA testing can be performed on routine laboratory spectrophotometers, do **not** necessitate adherence to additional rules and regulations governing the handling of radioactive substances, and the test kits have long shelf lives. Further, the range of sensitivity commonly achieved by the recommended ELISA test (i.e., the Pharmacia Delphia test) is approximately 100 µg/l (Pharmacia 1990), which is sufficient for monitoring B2MU levels resulting from cadmium exposure. Based on the studies listed in Table 9 (Section 5.3.7), the average range of B2M concentrations among the general, non-exposed population falls between 60 and 300 µg/g CRTU. The upper 95th percentile of distributions, derived from studies in Table 9 that reported standard deviations, range between 180 and 1,140 µg/g CRTU. Also, the Pharmacia Delphia test currently is the most widely used test for assessing B2MU.

5.3.4 Sample Collection and Handling

As with CDB or CDU, sample collection procedures are addressed primarily to identify ways to minimize the degree of variability introduced by sample collection during medical monitoring. It is unclear the extent to that sample collection contributes to B2MU variability. Sources of variation include time-of-day effects, the interval since consuming liquids and the quantity of liquids consumed, and the introduction of external contamination during the collection process. A special problem unique to B2M sampling is the sensitivity of this protein to degradation under acid conditions commonly found in the bladder. To minimize this problem, strict adherence to a sampling protocol is recommended. The protocol should include provisions for normalizing the conditions under that the urine is collected. Clearly, it is important to minimize the interval urine spends in the bladder. It also is recommended that every effort be made to collect samples during the same time of day.

Collection of urine samples for biological monitoring usually is performed using "spot" (i.e., single-void) urine. Logistics and sample integrity become problems when efforts are made to collect urine over extended periods (e.g., 24 hrs). Unless single-void urines are used, numerous opportunities exist for measurement error because of poor control over sample collection, storage and environmental contamination.

To minimize the interval that sample urine resides in the bladder, the following adaption to the "spot" collection procedure is recommended: The bladder should be emptied and then a large glass of water should be consumed; the sample then should be collected within an hour after the water is consumed.

5.3.5 Best Achievable Performance

The best achievable performance is assumed to be equivalent to the performance reported by the manufacturers of the Pharmacia Delphia test kits (Pharmacia 1990). According to the insert that comes with these kits, QC results should be within ± 2 SDs of the mean for each control sample tested; a CV of less than or equal to 5.2% should be maintained. The total CV reported for test kits is less than or equal to 7.2%.

5.3.6 General Method Performance

Unlike analyses for CDB and CDU, the Pharmacia Delphia test is standardized in a commercial kit that controls for many sources of variation. In the absence of data to the contrary, it is assumed that the achievable performance reported by the manufacturer of this test kit will serve as an achievable performance objective. The CTQ proficiency-testing program for B2MU analysis is expected to use the performance parameters defined by the test kit manufacturer as the basis of the B2MU proficiency testing program.

Note that results reported for the test kit are expressed in terms of µg B2M/l of urine, and have not been adjusted for creatinine. The indicated performance, therefore, is a measure of the performance of the B2M portion of the analyses only, and does not include variation that may have been introduced during the analysis of creatinine.

5.3.7 Observed B2MU Concentrations

As indicated in Section 4.3, the concentration of B2MU may serve as an early indicator of the onset of kidney damage associated with cadmium exposure.

5.3.7.1 Range of B2MU Concentrations Among Unexposed Samples

Most of the studies listed in Table 9 report B2MU levels for those who were not occupationally exposed to cadmium. Studies noted in the second column of this table (that contain the footnote "d") reported B2MU concentrations among cadmium-exposed workers who, nonetheless, showed **no** signs of proteinuria. These latter studies are included in this table because, as indicated in Section 4.3, monitoring B2MU is intended to provide advanced

warning of the onset of kidney dysfunction associated with cadmium exposure, rather than to distinguish relative exposure. This table, therefore, indicates the range of B2MU levels observed among those who had no symptoms of renal dysfunction (including cadmium-exposed workers with none of these symptoms).

TABLE 9
B-2-MICROGLOBULIN CONCENTRATIONS OBSERVED IN URINE AMONG THOSE NOT
OCCUPATIONALLY EXPOSED TO CADMIUM

Study No.	No. in study	Geometric mean	Geo-metric standard deviation	Lower 95th percentile of distribution ^a	Upper 95th percentile of distribution ^a	Reference
1	133 m ^b	115 µg/g ^c	4.03	12	1,140 µg/g ^c	Ishizaki et al.1989.
2	161 f ^b	146 µg/g ^c	3.11	23	940 µg/g ^c	Ishizaki et al. 1989.
3	10	84 µg/g.	Ellis et al. 1983.
4	203	76 µg/l	Stewart and Hughes 1981.
5	9	103 µg/g	Chia et al. 1989.
6	47 ^d	86 µg/L.	1.9	30 µg/l.	250 µg/L	Kjellstrom et al. 1977.
7	1,000 ^e	68.1 µg/gr Cr ^f .	3.1 m & f	<10 µg/gr Cr ^h .	320 µg/gr Cr ^h .	Kowal 1983.
8	87	71 µg/g ⁱ	7 ^h	200 ^h	Buchet et al. 1980.
9	10	0.073 mg/24h.	Evrin et al. 1971.
10	59	156 µg/g	1.1 ^j	130	180	Mason et al. 1988.
11	8	118 µg/g	Iwao et al. 1980.
12	34	79 µg/g.	Wibowo et al. 1982.
13	41 m	400 µg/gr Cr ^k .	Falck et al. 1983.
14	35 ⁿ	67	Roels et al. 1991.
15	31 ^d	63	Roels et al. 1991.
16	36 ^d	77 ⁱ	Miksche et al. 1981.
17	18 ⁿ	130	Kawada et al. 1989.
18	32 ^p	122	Kawada et al. 1989.
19	18 ^d	295	1.4	170	510	Thun et al. 1989.

^a Based on an assumed lognormal distribution.

^b m = males, f = females.

^c Aged general population from non-polluted area; 47.9% population aged 50-69; 52.1% 70 years of age; values reported in study.

^d Exposed workers without proteinuria.

^e 492 females, 484 males.

^f Creatinine adjusted; males = 68.1 µg/g Cr. females = 64.3 µg/g Cr.

^h Reported in the study.

ⁱ Arithmetic mean.

^j Geometric standard error.

^k Upper 95% tolerance limits: for Falck this is based on the 24 hour urine sample.

ⁿ Controls.

^p Exposed synthetic resin and pigment workers without proteinuria; Cadmium in urine levels up to 10 µg/g Cr.

To the extent possible, the studies listed in Table 9 provide geometric means and geometric standard deviations for measurements among the groups defined in each study. For studies reporting a geometric standard deviation along with a mean, the lower and upper 95th percentile for these distributions were derived and reported in the table.

The data provided from 15 of the 19 studies listed in Table 9 indicate that the geometric mean concentration of B2M observed among those who were not occupationally exposed to cadmium is 70-170 µg/g CRTU. Data from the 4 remaining studies indicate that exposed workers who exhibit no signs of proteinuria show mean B2MU levels of 60-300 µg/g CRTU. B2MU values in the study by Thun et al. (1989), however, appear high in comparison to the other 3 studies. If this study is removed, B2MU levels for those who are not occupationally exposed to cadmium are similar to B2MU levels found among cadmium-exposed workers who exhibit no signs of kidney dysfunction. Although the mean is high in the study by Thun et al., the range of measurements reported in this study is within the ranges reported for the other studies.

Determining a reasonable upper limit from the range of B2M concentrations observed among those who do not exhibit signs of proteinuria is problematic. Elevated B2MU levels are among the signs used to define the onset of kidney dysfunction. Without access to the raw data from the studies listed in Table 9, it is necessary to rely on reported standard deviations to estimate an upper limit for normal B2MU concentrations (i.e., the upper 95th percentile for the distributions measured). For the 8 studies reporting a geometric standard deviation, the upper 95th percentiles for the distributions are 180-1140 µg/g CRTU. These values are in general agreement with the upper 95th percentile for the distribution (i.e., 631 µg/g CRTU) reported by Buchet et al. (1980). These upper limits also appear to be in general agreement with B2MU values (i.e., 100-690 µg/g CRTU) reported as the normal upper limit by Iwao et al. (1980), Kawada et al. (1989), Wibowo et al. (1982), and Schardun and van Epps (1987). These values must be compared to levels reported among those exhibiting kidney dysfunction to define a threshold level for kidney dysfunction related to cadmium exposure.

5.3.7.2 Range of B2MU Concentrations Among Exposed Workers

Table 10 presents results from studies reporting B2MU determinations among those occupationally exposed to cadmium in the work place; in some of these studies, kidney dysfunction was observed among exposed workers, while other studies did not make an effort to distinguish among exposed workers based on kidney dysfunction. As with Table 9, this table provides geometric means and geometric standard deviations for the groups defined in each study if available. For studies reporting a geometric standard deviation along with a mean, the lower and upper 95th percentiles for the distributions are derived and reported in the table.

TABLE 10
B-2-MICROGLOBULIN CONCENTRATIONS OBSERVED IN URINE AMONG OCCUPATIONALLY EXPOSED WORKERS

Study No.	N	Concentration of B-2 Microglobulin in urine				Reference
		Geo-metric mean ($\mu\text{g/g}$) ^a	Geom std dev	L 95% of range ^b	U 95% of range ^b	
1	1,424	160	6.19	8.1	3,300	Ishizaki et al., 1989.
2	1,754	260	6.50	12	5,600	Ishizaki et al., 1989.
3	33	210	Ellis et al., 1983.
4	65	210	Chia et al., 1989.
5	^c 44	5,700	6.49	^d 300	^d 98,000	Kjellstrom et al., 1977.
6	148	^e 180	^f 110	^f 280	Buchet et al., 1980.
7	37	160	3.90	17	1,500	Kenzaburo et al., 1979.
8	^c 45	3,300	8.7	^d 310	^d 89,000	Mason et al., 1988.
9	^c 10	6,100	5.99	^f 650	^f 57,000	Falck et al., 1983.
10	^c 11	3,900	2.96	^d 710	^d 15,000	Elinder et al., 1985.
11	^c 12	300	Roels et al., 1991.
12	^g 8	7,400	Roels et al., 1991.
13	^c 23	^h 1,800	Roels et al., 1989.
14	10	690	Iwao et al., 1980.
15	34	71	Wibowo et al., 1982.
16	^c 15	4,700	6.49	^d 590	^d 93,000	Thun et al., 1989.

^a Unless otherwise stated.

^b Based on an assumed lognormal distribution.

^c Among workers diagnosed as having renal dysfunction; for Elinder this means β_2 levels greater than 300 micrograms per gram creatinine ($\mu\text{g/gr Cr}$); for Roels, 1991, range = 31-35, 170 $\mu\text{g}\beta_2/\text{gr Cr}$ and geometric mean = 63 among healthy workers; for Mason $\beta_2 > 300 \mu\text{g/gr Cr}$.

^d Based on a detailed review of the data by OSHA.

^e Arithmetic mean.

^f Reported in the study.

^g Retired workers.

^h 1,800 $\mu\text{g}\beta_2/\text{gr Cr}$ for first survey; second survey = 1,600; third survey = 2,600; fourth survey = 2,600; fifth survey = 2,600.

The data provided in Table 10 indicate that the mean B2MU concentration observed among workers experiencing occupational exposure to cadmium (but with undefined levels of

proteinuria) is 160-7400 µg/g CRTU. One of these studies reports geometric means lower than this range (i.e., as low as 71 µg/g CRTU); an explanation for this wide spread in average concentrations is not available.

Seven of the studies listed in Table 10 report a range of B2MU levels among those diagnosed as having renal dysfunction. As indicated in this table, renal dysfunction (proteinuria) is defined in several of these studies by B2MU levels in excess of 300 µg/g CRTU (see footnote "c" of Table 10); therefore, the range of B2MU levels observed in these studies is a function of the operational definition used to identify those with renal dysfunction. Nevertheless, a B2MU level of 300 µg/g CRTU appears to be a meaningful threshold for identifying those having early signs of kidney damage. While levels much higher than 300 µg/g CRTU have been observed among those with renal dysfunction, the vast majority of those not occupationally exposed to cadmium exhibit much lower B2MU concentrations (see Table 9). Similarly, the vast majority of workers not exhibiting renal dysfunction are found to have levels below 300 µg/g CRTU (Table 9).

The 300 µg/g CRTU level for B2MU proposed in the above paragraph has support among researchers as the threshold level that distinguishes between cadmium-exposed workers with and without kidney dysfunction. For example, in the guide for physicians who must evaluate cadmium-exposed workers written for the Cadmium Council by Dr. Lauwerys, levels of B2M greater than 200-300 µg/g CRTU are considered to require additional medical evaluation for kidney dysfunction (exhibit 8-447, OSHA docket H057A). The most widely used test for measuring B2M (i.e., the Pharmacia Delphia test) defines B2MU levels above 300 µg/l as abnormal (exhibit L-140-1, OSHA docket H057A).

Dr. Elinder, chairman of the Department of Nephrology at the Karolinska Institute, testified at the hearings on the proposed cadmium rule. According to Dr. Elinder (exhibit L-140-45, OSHA docket H057A), the normal concentration of B2MU has been well documented (Evrin and Wibell 1972; Kjellstrom et al. 1977a; Elinder et al. 1978, 1983; Buchet et al. 1980; Jawaid et al. 1983; Kowal and Zirkes, 1983). Elinder stated that the upper 95 or 97.5 percentiles for B2MU among those without tubular dysfunction are below 300 µg/g CRTU (Kjellstrom et al. 1977a; Buchet et al. 1980; Kowal and Zirkes, 1983). Elinder defined levels of B2M above 300 µg/g CRTU as "slight" proteinuria.

5.3.8 Conclusions and Recommendations for B2MU

Based on the above evaluation, the following recommendations are made for a B2MU proficiency-testing program. Note that the following discussion addresses only sampling and analysis for B2MU determinations (i.e., to be reported as an unadjusted µg B2M/l urine). Normalizing this result to creatinine requires a second analysis for CRTU (see Section 5.4) so that the ratio of the 2 measurements can be obtained.

5.3.8.1 Recommended method

The Pharmacia Delphia method (Pharmacia 1990) should be adopted as the standard method for B2MU determinations. Laboratories may adopt alternate methods, but it is the responsibility of the laboratory to demonstrate that alternate methods provide results of comparable quality to the Pharmacia Delphia method.

5.3.8.2 Data quality objectives

The following data quality objectives should facilitate interpretation of analytical results, and should be achievable based on the above evaluation.

Limit of Detection. A limit of 100 µg/l urine should be achievable, although the insert to the test kit (Pharmacia 1990) cites a detection limit of 150 µg/l; private conversations with representatives of Pharmacia, however, indicate that the lower limit of 100 µg/l should be achievable provided an additional standard of 100 µg/l B2M is run with the other standards to derive the calibration curve (Section 3.3.1.1). The lower detection limit is desirable due to the proximity of this detection limit to B2MU values defined for the cadmium medical monitoring program.

Accuracy. Because results from an interlaboratory proficiency-testing program are not available currently, it is difficult to define an achievable level of accuracy. Given the general performance parameters defined by the insert to the test kits, however, an accuracy of ±15% of the target value appears achievable.

Due to the low levels of B2MU to be measured generally, it is anticipated that the analysis of creatinine will contribute relatively little to the overall variability observed among

creatinine-normalized B2MU levels (see Section 5.4). The initial level of accuracy for reporting B2MU levels under this program should be set at $\pm 15\%$.

Precision. Based on precision data reported by Pharmacia (1990), a precision value (i.e., CV) of 5% should be achievable over the defined range of the analyte. For internal QC samples (i.e., recommended as part of an internal QA/QC program, Section 3.3.1), laboratories should attain precision near 5% over the range of concentrations measured.

5.3.8.3 Quality assurance/quality control

Commercial laboratories providing measurement of B2MU should adopt an internal QA/QC program that incorporates the following components: Strict adherence to the Pharmacia Delphia method, including calibration requirements; regular use of QC samples during routine runs; a protocol for corrective actions, and documentation of these actions; and, participation in an interlaboratory proficiency program. Procedures that may be used to address internal QC requirements are presented in Attachment 1. Due to differences between analyses for B2MU and CDB/CDU, specific values presented in Attachment 1 may have to be modified. Other components of the program (including characterization runs), however, can be adapted to a program for B2MU.

5.4 Monitoring Creatinine in Urine (CRTU)

Because CDU and B2MU should be reported relative to concentrations of CRTU, these concentrations should be determined in addition CDU and B2MU determinations.

5.4.1 Units of CRTU Measurement

CDU should be reported as $\mu\text{g Cd/g CRTU}$, while B2MU should be reported as $\mu\text{g B2M/g CRTU}$. To derive the ratio of cadmium or B2M to creatinine, CRTU should be reported in units of g crtn/l of urine. Depending on the analytical method, it may be necessary to convert results of creatinine determinations accordingly.

5.4.2 Analytical Techniques Used To Monitor CRTU

Of the techniques available for CRTU determinations, an absorbance spectrophotometric technique and a high-performance liquid chromatography (HPLC) technique are identified as acceptable in this protocol.

5.4.3 Methods Developed for CRTU Determinations

CRTU analysis performed in support of either CDU or B2MU determinations should be performed using either of the following 2 methods:

1. The Du Pont method (i.e., Jaffe method), in that creatinine in a sample reacts with picrate under alkaline conditions, and the resulting red chromophore is monitored (at 510 nm) for a fixed interval to determine the rate of the reaction; this reaction rate is proportional to the concentration of creatinine present in the sample (a copy of this method is provided in Attachment 2 of this protocol); or,
2. The OSHA SLC Technical Center (OSLTC) method, in that creatinine in an aliquot of sample is separated using an HPLC column equipped with a UV detector; the resulting peak is quantified using an electrical integrator (a copy of this method is provided in Attachment 3 of this protocol).

5.4.4 Sample Collection and Handling

CRTU samples should be segregated from samples collected for CDU or B2MU analysis. Sample-collection techniques have been described under Section 5.2.4. Samples should be preserved either to stabilize CDU (with HNO_3) or B2MU (with NaOH). Neither of these procedures should adversely affect CRTU analysis (see Attachment 3).

5.4.5 General Method Performance

Data from the OSLTC indicate that a CV of 5% should be achievable using the OSLTC method (Septon, L private communication). The achievable accuracy of this method has not been determined.

Results reported in surveys conducted by the CAP (CAP 1991a, 1991b and 1992) indicate that a CV of 5% is achievable. The accuracy achievable for CRTU determinations has not been reported.

Laboratories performing creatinine analysis under this protocol should be CAP accredited and should be active participants in the CAP surveys.

5.4.6 Observed CRTU Concentrations

Published data suggest the range of CRTU concentrations is 1.0-1.6 g in 24-hour urine samples (Harrison 1987). These values are equivalent to about 1 g/l urine.

5.4.7 Conclusions and Recommendations for CRTU

5.4.7.1 Recommended method

Use either the Jaffe method (Attachment 2) or the OSLTC method (Attachment 3). Alternate methods may be acceptable provided adequate performance is demonstrated in the CAP program.

5.4.7.2 Data quality objectives

Limit of Detection. This value has not been formally defined; however, a value of 0.1 g/l urine should be readily achievable.

Accuracy. This value has not been defined formally; accuracy should be sufficient to retain accreditation from the CAP.

Precision. A CV of 5% should be achievable using the recommended methods.

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Attachment 1: Nonmandatory Protocol for an Internal Quality Assurance/Quality Control Program

The following is an example of the type of internal quality assurance/quality control program that assures adequate control to satisfy OSHA requirements under this protocol. However, other approaches may also be acceptable.

As indicated in Section 3.3.1 of the protocol, the QA/QC program for CDB and CDU should address, at a minimum, the following:

- Calibration;
- Establishment of control limits;
- Internal QC analyses and maintaining control; and
- Corrective action protocols.

This illustrative program includes both initial characterization runs to establish the performance of the method and ongoing analysis of quality control samples intermixed with compliance samples to maintain control.

Calibration

Before any analytical runs are conducted, the analytic instrument must be calibrated. This is to be done at the beginning of each day on that quality control samples and/or compliance samples are run. Once calibration is established, quality control samples or compliance samples may be run. Regardless of the type of samples run, every fifth sample must be a standard to assure that the calibration is holding.

Calibration is defined as holding if every standard is within plus or minus (\pm) 15% of its theoretical value. If a standard is more than plus or minus 15% of its theoretical value, then the run is out of control due to calibration error and the entire set of samples must either be reanalyzed after recalibrating or results should be recalculated based on a statistical curve derived from the measurement of all standards.

It is essential that the highest standard run is higher than the highest sample run. To assure that this is the case, it may be necessary to run a high standard at the end of the run, that is selected based on the results obtained over the course of the run.

All standards should be kept fresh, and as they get old, they should be compared with new standards and replaced if they exceed the new standards by $\pm 15\%$.

Initial Characterization Runs and Establishing Control

A participating laboratory should establish four pools of quality control samples for each of the analytes for which determinations will be made. The concentrations of quality control samples within each pool are to be centered around each of the four target levels for the particular analyte identified in Section 4.4 of the protocol.

Within each pool, at least 4 quality control samples need to be established with varying concentrations ranging between plus or minus 50% of the target value of that pool. Thus for the medium-high cadmium in blood pool, the theoretical values of the quality control samples may range from 5 to 15 $\mu\text{g/l}$, (the target value is 10 $\mu\text{g/l}$). At least 4 unique theoretical values must be represented in this pool.

The range of theoretical values of plus or minus 50% of the target value of a pool means that there will be overlap of the pools. For example, the range of values for the medium-low pool for cadmium in blood is 3.5 to 10.5 µg/l while the range of values for the medium-high pool is 5 to 15 µg/l. Therefore, it is possible for a quality control sample from the medium-low pool to have a higher concentration of cadmium than a quality control sample from the medium-high pool.

Quality control samples may be obtained as commercially available reference materials, internally prepared, or both. Internally prepared samples should be well characterized and traced or compared to a reference material for that a consensus value for concentration is available. Levels of analyte in the quality control samples must be concealed from the analyst prior to the reporting of analytical results. Potential sources of materials that may be used to construct quality control samples are listed in Section 3.3.1 of the protocol.

Before any compliance samples are analyzed, control limits must be established. Control limits should be calculated for every pool of each analyte for that determinations will be made and control charts should be kept for each pool of each analyte. A separate set of control charts and control limits should be established for each analytical instrument in a laboratory that will be used for analysis of compliance samples.

At the beginning of this QA/QC program, control limits should be based on the results of the analysis of 20 quality control samples from each pool of each analyte. For any given pool, the 20 quality control samples should be run on 20 different days. Although no more than one sample should be run from any single pool on a particular day, a laboratory may run quality control samples from different pools on the same day. This constitutes a set of initial characterization runs.

For each quality control sample analyzed, the value F/T (defined in the glossary) should be calculated. To calculate the control limits for a pool of an analyte, it is first necessary to calculate the mean, \bar{X} , of the F/T values for each quality control sample in a pool and then to calculate its standard deviation $\hat{\sigma}$. Thus, for the control limit for a pool, \bar{X} is calculated as:

$$\frac{\left(\sum \frac{F}{T} \right)}{N}$$

and $\hat{\sigma}$ is calculated as

$$\left[\frac{\sum \left(\frac{F}{T} - \bar{X} \right)^2}{(N-1)} \right]^{\frac{1}{2}}$$

Where N is the number of quality control samples run for a pool.

The control limit for a particular pool is then given by the mean plus or minus 2 standard deviations ($\bar{X} \pm 2\hat{\sigma}$).

The control limits may be no greater than 40% of the mean F/T value. If three standard deviations are greater than 40% of the mean F/T value, then analysis of compliance samples may not begin.¹ Instead, an investigation into the causes of the large standard deviation should begin, and the inadequacies must be remedied. Then, control limits must be reestablished that will mean repeating the running 20 quality control samples from each pool over 20 days.

Internal Quality Control Analyses and Maintaining Control

Once control limits have been established for each pool of an analyte, analysis of compliance samples may begin. During any run of compliance samples, quality control samples are to be interspersed at a rate of no less than 5% of the compliance sample workload. When quality control samples are run, however, they should be run in sets consisting of one quality control sample from each

¹Note that the value, "40%" may change over time as experience is gained with the program.

pool. Therefore, it may be necessary, at times, to intersperse quality control samples at a rate greater than 5%.

There should be at least one set of quality control samples run with any analysis of compliance samples. At a minimum, for example, 4 quality control samples should be run even if only 1 compliance sample is run. Generally, the number of quality control samples that should be run are a multiple of four with the minimum equal to the smallest multiple of four that is greater than 5% of the total number of samples to be run. For example, if 300 compliance samples of an analyte are run, then at least 16 quality control samples should be run (16 is the smallest multiple of four that is greater than 15, that is 5% of 300).

Control charts for each pool of an analyte (and for each instrument in the laboratory to be used for analysis of compliance samples) should be established by plotting F/T versus date as the quality control sample results are reported. On the graph there should be lines representing the control limits for the pool, the mean F/T limits for the pool, and the theoretical F/T of 1.000. Lines representing plus or minus (\pm) 2σ should also be represented on the charts. A theoretical example of a control chart is presented in Figure 1.

"FIGURE 1.--THEORETICAL EXAMPLE OF A CONTROL CHART FOR A POOL OF AN ANALYTE

												1.162 (Upper Control Limit)
						X						
												1.096 (Upper 2σ Line)
		X										
		...										1.000 (Theoretical Mean)
	X											
				X	X							0.964 (Mean)
							X				X	
								X				
												0.832 (Lower 2σ Line)
			X									
									X			
												0.766 (Lower Control Limit)
March	2	2	3	5	6	9	10	13	16	17		

All quality control samples should be plotted on the chart, and the charts should be checked for visual trends. If a quality control sample falls above or below the control limits for its pool, then corrective steps must be taken (see the section on corrective actions below). Once a laboratory's program has been established, control limits should be updated every 2 months.

The updated control limits should be calculated from the results of the last 100 quality control samples run for each pool. If 100 quality control samples from a pool have not been run at the time of the update, then the limits should be based on as many as have been run provided at least 20 quality control samples from each pool have been run over 20 different days.

The trends that should be looked for on the control charts are:

1. 10 consecutive quality control samples falling above or below the mean;
2. 3 consecutive quality control samples falling more than 2σ from the mean (above or below the 2σ lines of the chart); or
3. The mean calculated to update the control limits falls more than 10% above or below the theoretical mean of 1.000.

If any of these trends is observed, then all analysis must be stopped, and an investigation into the causes of the errors must begin. Before the analysis of compliance samples may resume, the inadequacies must be remedied and the control limits must be reestablished for that pool of an analyte. Reestablishment of control limits will entail running 20 sets of quality control samples over 20 days.

Note that alternative procedures for defining internal quality control limits may also be acceptable. Limits may be based, for example, on proficiency testing, such as $\pm 1\mu\text{g}$ or 15% of the mean (whichever is greater). These should be clearly defined.

Corrective actions

Corrective action is the term used to describe the identification and remediation of errors occurring within an analysis. Corrective action is necessary whenever the result of the analysis of any quality control sample falls outside of the established control limits. The steps involved may include simple things like checking calculations of basic instrument maintenance, or it may involve more complicated actions like major instrument repair. Whatever the source of error, it must be identified and corrected

(and a Corrective Action Report (CAR) must be completed. CARs should be kept on file by the laboratory.

ATTACHMENT 2--CREATININE IN URINE (JAFJE PROCEDURE)

Intended use: The CREA pack is used in the Du Pont ACA® discrete clinical analyzer to quantitatively measure creatinine in serum and urine.

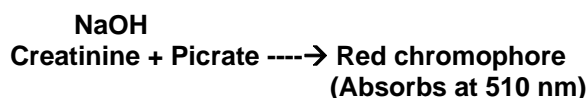
Summary: The CREA method employs a modification of the kinetic Jaffe reaction reported by Larsen. This method has been reported to be less susceptible than conventional methods to interference from non-creatinine, Jaffe-positive compounds.¹

A split sample comparison between the CREA method and a conventional Jaffe procedure on Autoanalyzer® showed a good correlation. (See Specific Performance Characteristics).

***Note:** Numbered subscripts refer to the bibliography and lettered subscripts refer to footnotes.

Autoanalyzer®, is a registered trademark of Technicon Corp., Tarrytown, NY.

Principles of Procedure: In the presence of a strong base such as NaOH, picrate reacts with creatinine to form a red chromophore. The rate of increasing absorbance at 510 nm due to the formation of this chromophore during a 17.07-second measurement period is directly proportional to the creatinine concentration in the sample.



Reagents:

Compartment ^a	Form	Ingredient	Quantity ^b
No. 2, 3, & 4.	Liquid	Picrate	0.11 mmol.
6	Liquid	NaOH (for pH adjustment) ^c .	

- a. Compartments are numbered 1-7, with compartment #7 located closest to pack fill position #2.
- b. Nominal value at manufacture.
- c. See Precautions.

Precautions: Compartment #6 contains 75µL of 10 N NaOH; avoid contact; skin irritant; rinse contacted area with water. Comply with OSHA'S Bloodborne Pathogens Standard while handling biological samples (29 CFR 1910.1039).

Used packs contain human body fluids; handle with appropriate care.

FOR IN VITRO DIAGNOSTIC USE

Mixing and Diluting:

Mixing and diluting are automatically performed by the ACA® discrete clinical analyzer. The sample cup must contain sufficient quantity to accommodate the sample volume plus the "dead volume"; precise cup filling is not required.

SAMPLE CUP VOLUMES(µL)

Analyzer	Standard		Microsystem	
	Dead	Total	Dead	Total
II, III	120	3000	10	500
IV, SX	120	3000	30	500
V	90	3000	10	500

Storage of Unprocessed Packs: Store at 2-8⁰C. Do not freeze. Do not expose to temperatures above 35⁰C or to direct sunlight.

Expiration: Refer to EXPIRATION DATE on the tray label.

Specimen Collection: Serum or urine can be collected and stored by normal procedures.²

Known Interfering Substances³

- Serum Protein Influence--Serum protein levels exert a direct influence on the CREA assay. The following should be taken into account when this method is used for urine samples and when it is calibrated:
Aqueous creatinine standards or urine specimens will give CREA results depressed by approximately 0.7 mg/dL [62 µmol/L]^d and will be less precise than samples containing more than 3 g/dL [30 g/L] protein.
All urine specimens should be diluted with an albumin solution to give a final protein concentration of at least 3 g/dL [30 g/L]. Du Pont Enzyme Diluent (Cat. #790035-901) may be used for this purpose.
- High concentration of endogenous bilirubin (>20 mg/dL [>342 µmol/L]) will give depressed CREA results (average depression 0.8 mg/dL [71 µmol/L]).⁴
- Grossly hemolyzed (hemoglobin >100 mg/dL [>62 µmol/L]) or visibly lipemic specimens may cause falsely elevated CREA results.^{5,6}
- The following cephalosporin antibiotics do not interfere with the CREA method when present at the concentrations indicated. Systematic inaccuracies (bias) due to these substances are less than or equal to 0.1 mg/dL [8.84 µmol/L] at CREA concentrations of approximately 1 mg/dL [88 µmol/L].

Antibiotic	Peak serum level ^{7,8,9}		Drug concentration	
	mg/dL	[mmol/L]	mg/dL	[mmol/L]
Cephaloridine	1.4	0.3	25	6.0
Cephalexin	0.6-2.0	0.2-0.6	25	7.2
Cephmandole	1.3-2.5	0.3-0.5	25	4.9
Cephapirin	2.0	0.4	25	5.6
Cephadrine	1.5-2.0	0.4-0.6	25	7.1
Cefazolin	2.5-5.0	0.55-1.1	50	11.0

- The following cephalosporin antibiotics have been shown to affect CREA results when present at the indicated concentrations. System inaccuracies (bias) due to these substances are greater than 0.1 mg/dL [8.84 µmol/L] at CREA concentrations of:

Antibiotic	Peak serum level ^{8,10}		Drug concentration		
	mg/dL	[mmol/L]	mg/dL	[mmol/L]	Effect
Cephalothin	1-6	0.2-1.5	100	25.2	↓20-25%
Cephoxitin	2.0	0.5	5.0	1.2	↑35-40%

- The single wavelength measurement used in this method eliminates interference from chromophores whose 510 nm absorbance is constant throughout the measurement period.
- Each laboratory should determine the acceptability of its own blood collection tubes and serum separation products. Variations in these products may exist between manufacturers and, at times, from lot to lot.

- d. Systeme International d'unites (S.I. Units) are in brackets.
Procedure:

TEST MATERIALS

Item	II, III Du Pont Cat. No.	IV, SX Du Pont Cat. No.	V Du Pont Cat. No.
ACA® CREA Analytical Test Pack	701976901	701976901	701976901
Sample System Kit or	710642901	710642901	713697901
Micro Sample System Kit and	702694901	710356901	NA
Micro Sample System Holders	702785000	NA	NA
DYLUX® Photosensitive
Printer Paper	700036000	NA	NA
Thermal Printer Paper	NA	710639901	713645901
Du Pont Purified Water	704209901	710615901	710815901
Cell Wash Solution	701864901	710664901	710864901

Test Steps: The operator need only load the sample kit and appropriate test pack(s) into a properly prepared ACA® discrete clinical analyzer. It automatically advances the pack(s) through the test steps and prints a result(s). See the Instrument Manual of the ACA® analyzer for details of mechanical travel of the test pack(s).

Preset Creatinine (CREA)--Test Conditions

- Sample Volume: 200µL
- Diluent: Purified Water
- Temperature: 37.0 ±0.1°C
- Reaction Period: 29 seconds
- Type of Measurement: Rate
- Measurement Period: 17.07 seconds
- Wavelength: 510 nm
- Units: mg/dL [µmol/L]

CALIBRATION: The general calibration procedure is described in the Calibration/Verification chapter of the Manuals.

The following information should be considered when calibrating the CREA method.

- Assay Range: 0-20 mg/mL [0-1768 µmol/L]e.
- Reference Material: Protein containing primary standards for secondary calibrators such as Du Pont Elevated Chemistry Control (Cat. #790035903) and Normal Chemistry Control (Cat. #790035905)g.
- Suggested Calibration Levels: 1,5,20, mg/mL [88, 442, 1768 µmol/L].
- Calibration Scheme: 3 levels, 3 packs per level.
- Frequency: Each new pack lot. Every 3 months for any one pack lot.
 - e. For the results in S.I. units [µmol/L] the conversion factory is 88.4.
 - f. Refer to the Creatinine Standard Preparation and Calibration Procedure available on request from a DuPont Representative.
 - g. If the DuPont Chemistry Controls are being used, prepare them according to the instructions on the product insert sheets.

PRESET CREATININE (CREA) TEST CONDITIONS

Item	ACA®II analyzer	ACA®III, IV, SX, V analyzer
Count by.....	One(1).....	NA
	[Five(5)]....	
Decimal Point.	0.0 mg/dL....	000.0 mg/dL
Location.....	[000.0 µmol/L]	[000 µmol/L]
Assigned Starting.	999.8.....	-1.000 E1
Point or Off-set C ₀ .	[9823.].....	[-8.840 E2]
Scale Factor or Assigned.	0.2000..... mg/dL/count ^h .	2.004 E-1 ^h
Linear Term C ₁ ^h .	[0.3536 µmol/ L/count].	[1.772E1]

- h. The preset scale factor (linear term) was derived from the molar absorptivity of the indicator and is based on an absorbance to activity relationship (sensitivity) of 0.596 (mA/min)/(U/L). Due to small differences in filters and electronic components between instruments, the actual scale factor (linear term) may differ slightly from that given above.

Quality Control: Two types of quality control procedures are recommended:

- General Instrument Check. Refer to the Filter Balance Procedure and the Absorbance Test Method described in the ACA Analyzer Instrument Manual. Refer also to the ABS Test Methodology literature.
- Creatinine Method Check. At least once daily run a CREA test on a solution of known creatinine activity such as an assayed control or calibration standard other than that used to calibrate the CREA method. For further details review the Quality Assurance Section of the Chemistry Manual. The result obtained should fall within acceptable limits defined by the day-to-day variability of the system as measured in the user's laboratory. (See SPECIFIC PERFORMANCE CHARACTERISTICS for guidance.) If the result falls outside the laboratory's acceptable limits, follow the procedure outlined in the Chemistry Troubleshooting Section of the Chemistry Manual.

A possible system malfunction is indicated when analysis of a sample with five consecutive test packs gives the following results:

Level	SD
1 mg/dL	>0.15 mg/dL
[88 µmol/L]	[>13 µmol/L]
20 mg/dL	>0.68 mg/dL
[1768 µmol/L]	[>60 µmol/L]

Refer to the procedure outlined in the Trouble Shooting Section of the Manual.

Results: The ACA® analyzer automatically calculates and prints the CREA result in mg/dL [µmol/L].

Limitation of Procedure: Results >20 mg/dL [1768 µmol/L]:

- Dilute with suitable protein base diluent. Reassay. Correct for diluting before reporting. The reporting system contains error messages to warn the operator of specific malfunctions. Any report slip containing a letter code or word immediately following the numerical value should not be reported. Refer to the Manual for the definition of error codes.

Reference Interval

Serum: ^{11, i}	
Males	0.8-1.3 md/dL [71-115 µmol/L]
Females	0.6-1.0 md/dL [53-88 µmol/L]
Urine: ¹²	
Males	0.6-2.5 g/24 hr [53-221 mmol/24 hr]
Females	0.6-1.5 g/24 hr [53-133 mmol/24 hr]

- i. Reference interval data obtained from 200 apparently healthy individuals (71 males, 129 females) between the ages of 19 and 72.

Each laboratory should establish its own reference intervals for CREA as performed on the analyzer.

Specific Performance Characteristics^jREPRODUCIBILITY^k

Material	Mean	Standard deviation (%CV)	
		Within-run	Between-day
Lyophilized	1.3	0.05 (3.7)	0.05 (3.7)
Control	[115]	[4.4]	[4.4]
Lyophilized	20.6	0.12 (0.6)	0.37 (1.8)
Control	[1821]	[10.6]	[32.7]

CORRELATION--REGRESSION STATISTICS^l

Comparative method	Slope	Intercept	Correlation coefficient	n
Autoanalyzer®	1.03	0.03[2.7]	0.997	260

- j. All specific performance characteristics tests were run after normal recommended equipment quality control checks were performed (see Instrument Manual).
- k. Specimens at each level were analyzed in duplicate for twenty days. The within-run and between-day standard deviations were calculated by the analysis of variance method.
- l. Model equation for regression statistics is:

$$\text{Result of ACA® Analyzer} = \text{Slope (Comparative method result)} + \text{intercept}$$

Assay Range^m
0.0-20.0 mg/dl
[0-1768 µmol]

- m. See REPRODUCIBILITY for method performance within the assay range.

Analytical Specificity
See KNOWN INTERFERING SUBSTANCES section for details.

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ATTACHMENT 3 ANALYSIS OF CREATININE FOR THE NORMALIZATION OF CADMIUM AND BETA-2- MICROGLOBULIN CONCENTRATIONS IN URINE (OSLTC PROCEDURE).

Matrix: Urine.

Target concentration: 1.1 g/L (this amount is representative of creatinine concentrations found in urine).

Procedure: A 1.0 mL aliquot of urine is passed through a C18 SEP-PAK® (Waters Associates). Approximately 30 mL of HPLC (high performance liquid chromatography) grade water is then run through the SEP-PAK. The resulting solution is diluted to volume in a 100-mL volumetric flask and analyzed by HPLC using an ultraviolet (UV) detector.

Special requirements: After collection, samples should be appropriately stabilized for cadmium (Cd) analysis by using 10% high purity (with low Cd background levels) nitric acid (exactly 1.0 mL of 10% nitric acid per 10 mL of urine) or stabilized for Beta-2-Microglobulin (B2M) by taking to pH 7 with dilute NaOH (exactly 1.0 mL of 0.11 N NaOH per 10 mL of urine). If not immediately analyzed, the samples should be frozen and shipped by overnight mail in an insulated container.

Dated: January 1992.

David B. Armitage,
Duane Lee,

Chemists.

Organic Service Branch II, OSHA Technical Center, Salt Lake City, Utah

1. General Discussion

1.1 Background

1.1.1 History of procedure

Creatinine has been analyzed by several methods in the past. The earliest methods were of the wet chemical type. As an example, creatinine reacts with sodium picrate in basic solution to form a red complex, which is then analyzed colorimetrically (Refs. 5.1. and 5.2.).

Since industrial hygiene laboratories will be analyzing for Cd and B2M in urine, they will be normalizing those concentrations to the concentration of creatinine in urine. A literature search revealed several HPLC methods (Refs. 5.3., 5.4., 5.5. and 5.6.) for creatinine in urine and because many industrial hygiene laboratories have HPLC equipment, it was desirable to develop an industrial hygiene HPLC method for creatinine in urine. The method of Hausen, Fuchs, and Wachter was chosen as the starting point for method development. SEP-PAKs were used for sample clarification and cleanup in this method to protect the analytical column. The urine aliquot that has been passed through the SEP-PAK is then analyzed by reverse-phase HPLC using ion-pair techniques.

This method is very similar to that of Ogata and Taguchi (Ref. 5.6.), except they used centrifugation for sample cleanup. It is also of note that they did a comparison of their HPLC results to those of the Jaffe method (a picric acid method commonly used in the health care industry) and found a linear relationship of close to 1:1. This indicates that either HPLC or colorimetric methods may be used to measure creatinine concentrations in urine.

1.1.2. Physical properties (Ref. 5.7.)

Molecular weight: 113.12

Molecular formula: $C_4H_7N_3O$

Chemical name: 2-amino-1,5-dihydro-1-methyl-4H-imidazol-4-one

CAS No.: 60-27-5

Melting point: 300°C (decomposes)

Appearance: white powder

Solubility: soluble in water; slightly soluble in alcohol; practically insoluble in acetone, ether, and chloroform

Synonyms: 1-methylglycocyanidine, 1-methylhydantoin-2-imide

Structure: see Figure #1

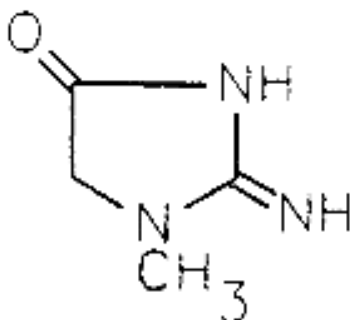


Figure #1

1.2. Advantages

1.2.1. This method offers a simple, straight-forward, and specific alternative method to the Jaffe method.

1.2.2. HPLC instrumentation is commonly found in many industrial hygiene laboratories.

2. Sample stabilization procedure

2.1. Apparatus

Metal-free plastic container for urine sample.

2.2. Reagents

2.2.1. Stabilizing Solution--

- (1) Nitric acid (10%, high purity with low Cd background levels) for stabilizing urine for Cd analysis or
- (2) NaOH, 0.11 N, for stabilizing urine for B2M analysis.
- 2.2.2. HPLC grade water
- 2.3. Technique
- 2.3.1. Stabilizing solution is added to the urine sample (see section 2.2.1.). The stabilizing solution should be such that for each 10 mL of urine, add exactly 1.0 mL of stabilizer solution. (Never add water or urine to acid or base. Always add acid or base to water or urine.) Exactly 1.0 mL of 0.11 N NaOH added to 10 mL of urine should result in a pH of 7. Or add 1.0 mL of 10% nitric acid to 10 mL of urine.
- 2.3.2. After sample collection seal the plastic bottle securely and wrap it with an appropriate seal. Urine samples should be frozen and then shipped by overnight mail (if shipping is necessary) in an insulated container. (Do not fill plastic bottle too full. This will allow for expansion of contents during the freezing process.)
- 2.4. The Effect of Preparation and Stabilization Techniques on Creatinine Concentrations
- Three urine samples were prepared by making one sample acidic, not treating a second sample, and adjusting a third sample to pH 7. The samples were analyzed in duplicate by two different procedures. For the first procedure a 1.0 mL aliquot of urine was put in a 100-mL volumetric flask, diluted to volume with HPLC grade water, and then analyzed directly on an HPLC. The other procedure used SEP-PAKs. The SEP-PAK was rinsed with approximately 5 mL of methanol followed by approximately 10 mL of HPLC grade water and both rinses were discarded. Then, 1.0 mL of the urine sample was put through the SEP-PAK, followed by 30 mL of HPLC grade water. The urine and water were transferred to a 100-mL volumetric flask, diluted to volume with HPLC grade water, and analyzed by HPLC. These three urine samples were analyzed on the day they were obtained and then frozen. The results show that whether the urine is acidic, untreated or adjusted to pH 7, the resulting answer for creatinine is essentially unchanged. The purpose of stabilizing the urine by making it acidic or neutral is for the analysis of Cd or B2M respectively.

COMPARISON OF PREPARATION & STABILIZATION TECHNIQUES

Sample	w/o SEP-PAK g/L creatinine	with SEP-PAK g/L creatinine
Acid	1.10	1.10
Acid	1.11	1.10
Untreated	1.12	1.11
Untreated	1.11	1.12
pH 7	1.08	1.02
pH 7	1.11	1.08

2.5. Storage

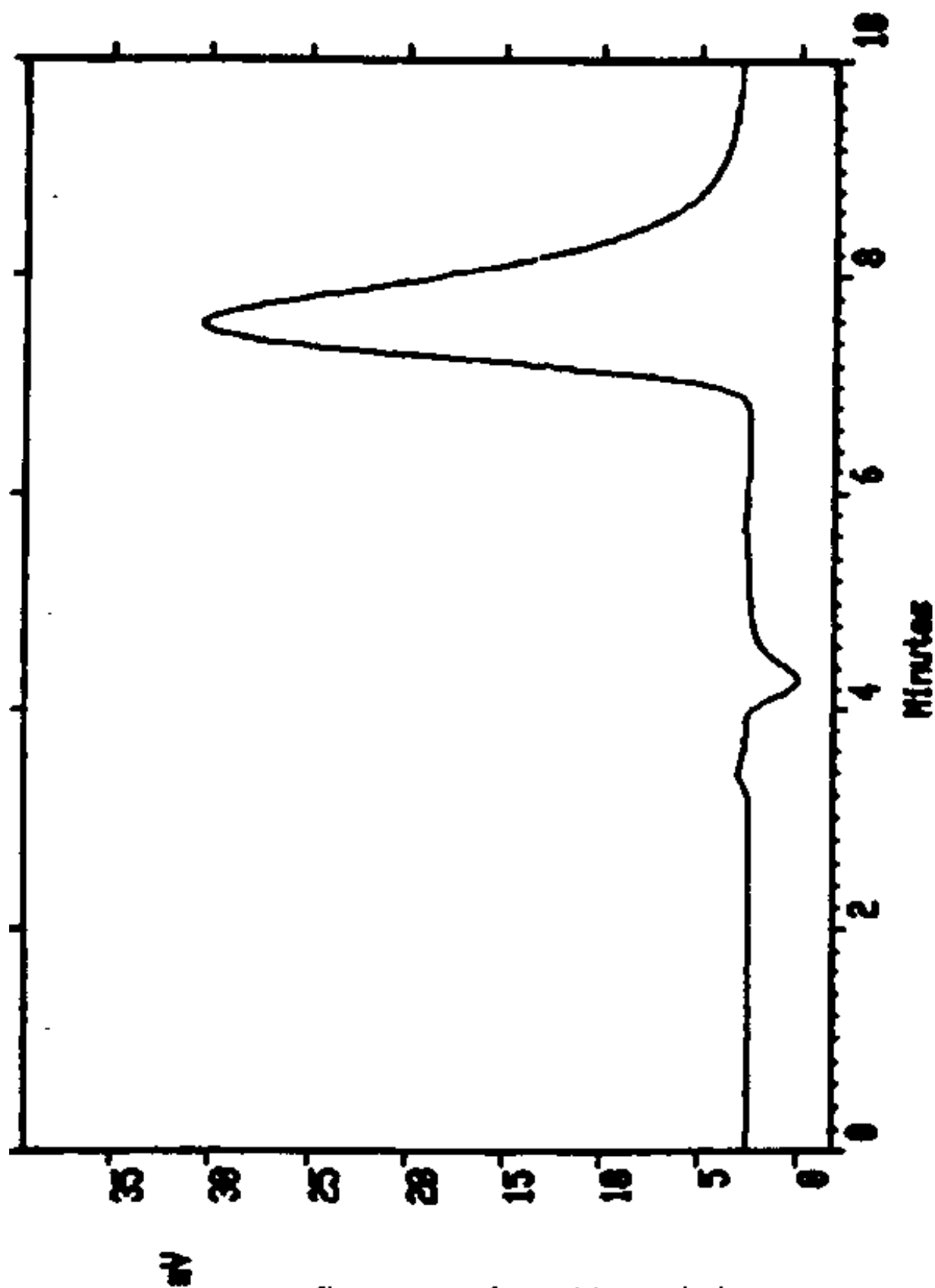
After 4 days and 54 days of storage in a freezer, the samples were thawed, brought to room temperature and analyzed using the same procedures as in section 2.4. The results of several days of storage show that the resulting answer of creatinine is essentially unchanged.

STORAGE DATA

Sample	4 days		54 days	
	w/o SEP-Pak g/L creatinine	with SEP-PAK g/L creatinine	w/o SEP-PAK g/L creatinine	with SEP-PAK g/L creatinine
Acid	1.09	1.09	1.08	1.09
Acid	1.10	1.10	1.09	1.10
Acid	1.09	1.09
Untreated	1.13	1.14	1.09	1.11
Untreated	1.15	1.14	1.10	1.10
Untreated	1.09	1.10
pH 7	1.14	1.13	1.12	1.12
pH 7	1.14	1.13	1.12	1.12
pH 7	1.12	1.12

- 2.6. Interferences
None.
- 2.7. Safety precautions
- 2.7.1. Make sure samples are properly sealed and frozen before shipment to avoid leakage.
- 2.7.2. Follow the appropriate shipping procedures.
The following modified special safety precautions are based on those recommended by the Centers for Disease Control (CDC) (Ref. 5.8.) and OSHA'S Bloodborne Pathogens standard (29 CFR 1910.1039).
- 2.7.3. Wear gloves, lab coat, and safety glasses while handling all human urine products. Disposable plastic, glass, and paper (pipet tips, gloves, etc.) that contact urine should be placed in a biohazard autoclave bag. These bags should be kept in appropriate containers until sealed and autoclaved. Wipe down all work surfaces with 10% sodium hypochlorite solution when work is finished.
- 2.7.4. Dispose of all biological samples and diluted specimens in a biohazard autoclave bag at the end of the analytical run.
- 2.7.5. Special care should be taken when handling and dispensing nitric acid. Always remember to add acid to water (or urine). Nitric acid is a corrosive chemical capable of severe eye and skin damage. Wear metal-free gloves, a lab coat, and safety glasses. If the nitric acid comes in contact with any part of the body, quickly wash with copious quantities of water for at least 15 minutes.
- 2.7.6. Special care should be taken when handling and dispensing NaOH. Always remember to add base to water (or urine). NaOH can cause severe eye and skin damage. Always wear the appropriate gloves, a lab coat, and safety glasses. If the NaOH comes in contact with any part of the body, quickly wash with copious quantities of water for at least 15 minutes.
3. Analytical procedure
- 3.1. Apparatus
- 3.1.1. A high performance liquid chromatograph equipped with pump, sample injector and UV detector.
- 3.1.2. A C18 HPLC column; 25 cm x 4.6 mm I.D.
- 3.1.3. An electronic integrator, or some other suitable means of determining analyte response.
- 3.1.4. Stripchart recorder.
- 3.1.5. C18 SEP-PAKs (Waters Associates) or equivalent.
- 3.1.6. Luer-lock syringe for sample preparation (5 mL or 10 mL).

- 3.1.7. Volumetric pipettes and flasks for standard and sample preparation.
- 3.1.8. Vacuum system to aid sample preparation (optional).
- 3.2. Reagents
 - 3.2.1. Water, HPLC grade.
 - 3.2.2. Methanol, HPLC grade.
 - 3.2.3. PIC B-7® (Waters Associates) in small vials.
 - 3.2.4. Creatinine, anhydrous, Sigma Chemical Corp., purity not listed.
 - 3.2.5. 1-Heptanesulfonic acid, sodium salt monohydrate.
 - 3.2.6. Phosphoric acid.
 - 3.2.7. Mobile phase. It can be prepared by mixing one vial of PIC B-7 into a 1 L solution of 50% methanol and 50% water. The mobile phase can also be made by preparing a solution that is 50% methanol and 50% water with 0.005M heptanesulfonic acid and adjusting the pH of the solution to 3.5 with phosphoric acid.
- 3.3. Standard preparation
 - 3.3.1. Stock standards are prepared by weighing 10 to 15 mg of creatinine. This is transferred to a 25-mL volumetric flask and diluted to volume with HPLC grade water.
 - 3.3.2. Dilutions to a working range of 3 to 35 µg/mL are made in either HPLC grade water or HPLC mobile phase (standards give the same detector response in either solution).
- 3.4. Sample preparation
 - 3.4.1. The C18 SEP-PAK is connected to a Luer-lock syringe. It is rinsed with 5 mL HPLC grade methanol and then 10 mL of HPLC grade water. These rinses are discarded.
 - 3.4.2. Exactly 1.0 mL of urine is pipetted into the syringe. The urine is put through the SEP-PAK into a suitable container using a vacuum system.
 - 3.4.3. The walls of the syringe are rinsed in several stages with a total of approximately 30 mL of HPLC grade water. These rinses are put through the SEP-PAK into the same container. The resulting solution is transferred to a 100-mL volumetric flask and then brought to volume with HPLC grade water.
- 3.5. Analysis (conditions and hardware are those used in this evaluation.)
 - 3.5.1. Instrument conditions
 - Column: Zorbax® ODS, 5-6 µm particle size; 25 cm x 4.6 mm I.D.
 - Mobile phase: See Section 3.2.7.
 - Detector: Dual wavelength UV; 229 nm (primary) 254 nm (secondary)
 - Flow rate: 0.7 mL/minute
 - Retention time: 7.2 minutes
 - Sensitivity: 0.05 AUFS
 - Injection volume: 20µl
 - 3.5.2. Chromatogram (see Figure #2)



Chromatogram of a creatinine standard
Figure #2 (mV versus minutes)

- 3.6. Interferences
- 3.6.1. Any compound that has the same retention time as creatinine and absorbs at 229 nm is an interference.
- 3.6.2. HPLC conditions may be varied to circumvent interferences. In addition, analysis at another UV wavelength (i.e. 254 nm) would allow a comparison of the ratio of response of a standard to that of a sample. Any deviations would indicate an interference.
- 3.7. Calculations
- 3.7.1. A calibration curve is constructed by plotting detector response versus standard concentration (See Figure #3).
- 3.7.2. The concentration of creatinine in a sample is determined by finding the concentration corresponding to its detector response. (See Figure #3).
- 3.7.3. The $\mu\text{g/mL}$ creatinine from section 3.7.2. is then multiplied by 100 (the dilution factor). This value is equivalent to the micrograms of creatinine in the 1.0 mL stabilized urine aliquot or the milligrams of creatinine per liter of urine. The desired units, g/L, is determined by the following relationship:

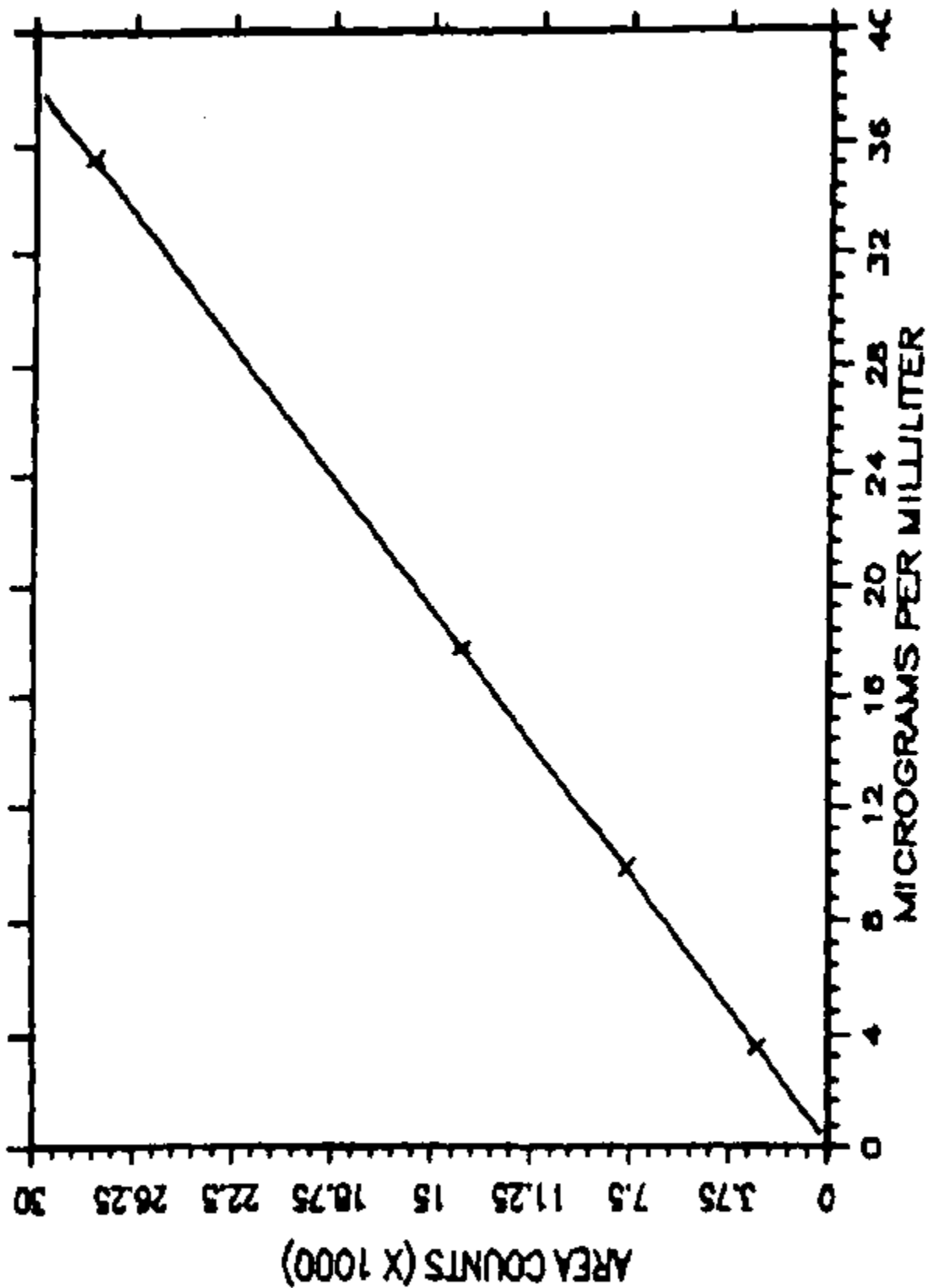
$$\text{g/L} = \frac{\text{ug/mL}}{1000} = \frac{\text{mg/L}}{1000}$$

- 3.7.4. The resulting value for creatinine is used to normalize the urinary concentration of the desired analyte (A) (Cd or B2M) by using the following formula.

$$\text{ug A/g creatinine} = \frac{\text{ug A/g creatinine}}{\text{g/L creatinine}}$$

Where A is the desired analyte. The protocol of reporting such normalized results is $\mu\text{g A/g creatinine}$.

- 3.8. Safety precautions See section 2.7.



Calibration curve for creatinine

Figure #3

4. Conclusions

The determination of creatinine in urine by HPLC is a good alternative to the Jaffe method for industrial hygiene laboratories. Sample clarification with SEP-PAKs did not change the amount of creatinine found in urine samples. However, it does protect the analytical column. The results of this creatinine in urine procedure are unaffected by the pH of the urine sample under the conditions tested by this procedure. Therefore, no special measures are required for creatinine analysis whether the urine sample has been stabilized with 10% nitric acid for the Cd analysis or brought to a pH of 7 with 0.11 N NaOH for the B2M analysis.

5. References

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(b) Definitions. As used in 29 CFR 1910.1027 and applied to this chapter:

"Assistant Secretary" means the director of the department of labor and industrial relations, State of Hawaii.

"Effective date" means March 14, 1993.

"OSHA" means occupational safety and health division, State of Hawaii.

"OSH Act" means chapter 396, Hawaii Revised Statutes.

"Startup dates" means six months following the dates listed in paragraph

(p) of 29 CFR 1910.1027.

"29 CFR 1910.20" means section 1910.1020 in section 12-202-3.1.

"29 CFR 1910.133" means section 1910.133 in chapter 12-64.1.

"29 CFR 1910.134" means section 1910.134 in chapter 12-64.1.

"29 CFR 1910.141" means chapter 12-67.

"29 CFR 1910.1200" means chapter 12-203.1. [Eff 2/26/93; am 11/5/93; am 9/21/96; am 7/6/98; am 3/31/06; am 12/21/06; am 4/19/07] (Auth: HRS §396-4) (Imp: HRS §396-4)

§12-202-40 1,3-Butadiene. (a) Incorporation of federal standard. Title 29, Code of Federal Regulations, section 1910.1051, entitled "1,3-Butadiene", published by the Office of the Federal Register, National Archives and Records Administration, on November 4, 1996, and the amendments published by the Office of the Federal Register, National Archives and Records Administration, on January 8, 1998; November 7, 2002; January 5, 2005; and April 3, 2006, are made a part of this section, except as provided in subsection (b).

§1910.1051 1,3-Butadiene.**(a) Scope and application.**

- (1) This section applies to all occupational exposures to 1,3-Butadiene (BD), Chemical Abstracts Service Registry No. 106-99-0, except as provided in paragraph (a)(2) of this section.
- (2) (i) Except for the record keeping provisions in paragraph (m)(1) of this section, this section does not apply to the processing, use, or handling of products containing BD or to other work operations and streams in that BD is present where objective data are reasonably relied upon that demonstrate the work operation or the product or the group of products or operations to that it belongs may not reasonably be foreseen to release BD in airborne concentrations at or above the action level or in excess of the STEL under the expected conditions of processing, use, or handling that will cause the greatest possible release or in any plausible accident.
- (ii) This section also does not apply to work operations, products or streams where the

only exposure to BD is from liquid mixtures containing 0.1% or less of BD by volume or the vapors released from such liquids, unless objective data become available that show that airborne concentrations generated by such mixtures can exceed the action level or STEL under reasonably predictable conditions of processing, use or handling that will cause the greatest possible release.

- (iii) Except for labeling requirements and requirements for emergency response, this section does not apply to the storage, transportation, distribution or sale of BD or liquid mixtures in intact containers or in transportation pipelines sealed in such a manner as to fully contain BD vapors or liquid.
- (3) Where products or processes containing BD are exempted under paragraph (a)(2) of this section, the employer shall maintain records of the objective data supporting that exemption and the basis for the employer's reliance on the data, as provided in paragraph (m)(1) of this section.
- (b) Definitions: For the purpose of this section, the following definitions shall apply:
 - Action level** means a concentration of airborne BD of 0.5 ppm calculated as an eight (8)-hour time-weighted average.
 - Assistant Secretary** means the Assistant Secretary of Labor for Occupational Safety and Health, U.S. Department of Labor, or designee.
 - Authorized person** means any person specifically designated by the employer, whose duties require entrance into a regulated area, or a person entering such an area as a designated representative of employees to exercise the right to observe monitoring and measuring procedures under paragraph (d)(8) of this section, or a person designated under the Act or regulations issued under the Act to enter a regulated area.
 - 1,3-Butadiene** means an organic compound with chemical formula $\text{CH}_2=\text{CH}-\text{CH}=\text{CH}_2$ that has a molecular weight of approximately 54.15 gm/mole.
 - Business day** means any Monday through Friday, except those days designated as federal, state, local or company specific holidays.
 - Complete Blood Count (CBC)** means laboratory tests performed on whole blood specimens and includes the following: White blood cell count (WBC), hematocrit (Hct), red blood cell count (RBC), hemoglobin (Hgb), differential count of white blood cells, red blood cell morphology, red blood cell indices, and platelet count.
 - Day** means any part of a calendar day.
 - Director** means the Director of the National Institute for Occupational Safety and Health (NIOSH), U.S. Department of Health and Human Services, or designee.
 - Emergency situation** means any occurrence such as, but not limited to, equipment failure, rupture of containers, or failure of control equipment that may or does result in an uncontrolled significant release of BD.
 - Employee exposure** means exposure of a worker to airborne concentrations of BD that would occur if the employee were not using and physical properties of a material, stream or product.
 - Permissible Exposure Limits, PELs** means either the 8-hour Time Weighted Average (8-hr TWA) exposure or the Short-Term Exposure Limit (STEL).
 - Physician or other licensed health care professional** is an individual whose legally permitted scope of practice (i.e., license, registration, or certification) allows him or her to independently provide or be delegated the responsibility to provide one or more of the specific health care services required by paragraph (k) of this section.
 - Regulated area** means any area where airborne concentrations of BD exceed or can reasonably be expected to exceed the 8-hour time weighted average (8-hr TWA) exposure of 1 ppm or the short-term exposure limit (STEL) of 5 ppm for 15 minutes.
 - This section** means this 1,3-butadiene standard.
- (c) Permissible exposure limits (PELs).
 - (1) Time-weighted average (TWA) limit. The employer shall ensure that no employee is exposed to an airborne concentration of BD in excess of one (1) part BD per million parts of air (ppm) measured as an eight (8)-hour time-weighted average.
 - (2) Short-term exposure limit (STEL). The employer shall ensure that no employee is exposed to an airborne concentration of BD in excess of five parts of BD per million parts of air (5 ppm) as determined over a sampling period of fifteen (15) minutes.
- (d) Exposure monitoring
 - (1) General.

- (i) Determinations of employee exposure shall be made from breathing zone air samples that are representative of the 8-hour TWA and 15-minute short-term exposures of each employee.
 - (ii) Representative 8-hour TWA employee exposure shall be determined on the basis of one or more samples representing full-shift exposure for each shift and for each job classification in each work area.
 - (ii) Representative 15-minute short-term employee exposures shall be determined on the basis of one or more samples representing 15-minute exposures associated with operations that are most likely to produce exposures above the STEL for each shift and for each job classification in each work area.
 - (iii) Except for the initial monitoring required under paragraph (d)(2) of this section, where the employer can document that exposure levels are equivalent for similar operations on different work shifts, the employer need only determine representative employee exposure for that operation from the shift during that the highest exposure is expected.
- (2) Initial monitoring.
- (i) Each employer who has a workplace or work operation covered by this section, shall perform initial monitoring to determine accurately the airborne concentrations of BD to which employees may be exposed, or shall rely on objective data pursuant to paragraph (a)(2)(i) of this section to fulfill this requirement. The initial monitoring required under this paragraph shall be completed within 60 days of the introduction of BD into the workplace.
 - (ii) Where the employer has monitored within two years prior to the effective date of this section and the monitoring satisfies all other requirements of this section, the employer may rely on such earlier monitoring results to satisfy the requirements of paragraph (d)(2)(i) of this section, provided that the conditions under that the initial monitoring was conducted have not changed in a manner that may result in new or additional exposures.
- (3) Periodic monitoring and its frequency.
- (i) If the initial monitoring required by paragraph (d)(2) of this section reveals employee exposure to be at or above the action level but at or below both the 8-hour TWA limit and the STEL, the employer shall repeat the representative monitoring required by paragraph (d)(1) of this section every twelve months.
 - (ii) If the initial monitoring required by paragraph (d)(2) of this section reveals employee exposure to be above the 8-hour TWA limit, the employer shall repeat the representative monitoring required by paragraph (d)(1)(ii) of this section at least every three months until the employer has collected two samples per quarter (each at least 7 days apart) within a two-year period, after that such monitoring must occur at least every six months.
 - (iii) If the initial monitoring required by paragraph (d)(2) of this section reveals employee exposure to be above the STEL, the employer shall repeat the representative monitoring required by paragraph (d)(1)(iii) of this section at least every three months until the employer has collected two samples per quarter (each at least 7 days apart) within a two-year period, after that such monitoring must occur at least every six months.
 - (iv) The employer may alter the monitoring schedule from every six months to annually for any required representative monitoring for that two consecutive measurements taken at least 7 days apart indicate that employee exposure has decreased to or below the 8-hour TWA, but is at or above the action level.
- (4) Termination of monitoring.
- (i) If the initial monitoring required by paragraph (d)(2) of this section reveals employee exposure to be below the action level and at or below the STEL, the employer may discontinue the monitoring for employees whose exposures are represented by the initial monitoring.
 - (ii) If the periodic monitoring required by paragraph (d)(3) of this section reveals that employee exposures, as indicated by at least two consecutive measurements taken at least 7 days apart, are below the action level and at or below the STEL, the employer may discontinue the monitoring for those employees who are represented by such monitoring.
- (5) Additional monitoring.

- (i) The employer shall institute the exposure monitoring required under paragraph (d) of this section whenever there has been a change in the production, process, control equipment, personnel or work practices that may result in new or additional exposures to BD or when the employer has any reason to suspect that a change may result in new or additional exposures.
- (ii) Whenever spills, leaks, ruptures or other breakdowns occur that may lead to employee exposure above the 8-hr TWA limit or above the STEL, the employer shall monitor (using leak source, such as direct reading instruments, area or personal monitoring), after the cleanup of the spill or repair of the leak, rupture or other breakdown, to ensure that exposures have returned to the level that existed prior to the incident.
- (6) Accuracy of monitoring. Monitoring shall be accurate, at a confidence level of 95 percent, to within plus or minus 25 percent for airborne concentrations of BD at or above the 1 ppm TWA limit and to within plus or minus 35 percent for airborne concentrations of BD at or above the action level of 0.5 ppm and below the 1 ppm TWA limit.
- (7) Employee notification of monitoring results.
 - (i) The employer must, within 15 working days after the receipt of the results of any monitoring performed under this section, notify each affected employee of these results either individually in writing or by posting the results in an appropriate location that is accessible to employees.
 - (ii) The employer shall, within 15 business days after receipt of any monitoring performed under this section indicating the 8-hour TWA or STEL has been exceeded, provide the affected employees, in writing, with information on the corrective action being taken by the employer to reduce employee exposure to or below the 8-hour TWA or STEL and the schedule for completion of this action.
- (8) Observation of monitoring.
 - (i) Employee observation. The employer shall provide affected employees or their designated representatives an opportunity to observe any monitoring of employee exposure to BD conducted in accordance with paragraph (d) of this section.
 - (ii) Observation procedures. When observation of the monitoring of employee exposure to BD requires entry into an area where the use of protective clothing or equipment is required, the employer shall provide the observer at no cost with protective clothing and equipment, and shall ensure that the observer uses this equipment and complies with all other applicable safety and health procedures.
- (e) Regulated areas.**
 - (1) The employer shall establish a regulated area wherever occupational exposures to airborne concentrations of BD exceed or can reasonably be expected to exceed the permissible exposure limits, either the 8-hr TWA or the STEL.
 - (2) Access to regulated areas shall be limited to authorized persons.
 - (3) Regulated areas shall be demarcated from the rest of the workplace in any manner that minimizes the number of employees exposed to BD within the regulated area.
 - (4) An employer at a multi-employer worksite who establishes a regulated area shall communicate the access restrictions and locations of these areas to other employers with work operations at that worksite whose employees may have access to these areas.
- (f) Methods of compliance.**
 - (1) Engineering controls and work practices.
 - (i) The employer shall institute engineering controls and work practices to reduce and maintain employee exposure to or below the PELs, except to the extent that the employer can establish that these controls are not feasible or where paragraph (h)(1)(i) of this section applies.
 - (ii) Wherever the feasible engineering controls and work practices that can be instituted are not sufficient to reduce employee exposure to or below the 8-hour TWA or STEL, the employer shall use them to reduce employee exposure to the lowest levels achievable by these controls and shall supplement them by the use of respiratory protection that complies with the requirements of paragraph (h) of this section.
 - (2) Compliance plan.
 - (i) Where any exposures are over the PELs, the employer shall establish and implement a written plan to reduce employee exposure to or below the PELs primarily by means of engineering and work practice controls, as required by paragraph (f)(1) of this section, and by the use of respiratory protection where required or permitted under this section.

No compliance plan is required if all exposures are under the PELs.

- (ii) The written compliance plan shall include a schedule for the development and implementation of the engineering controls and work practice controls including periodic leak detection surveys.
 - (iii) Copies of the compliance plan required in paragraph (f)(2) of this section shall be furnished upon request for examination and copying to the Assistant Secretary, the Director, affected employees and designated employee representatives. Such plans shall be reviewed at least every 12 months, and shall be updated as necessary to reflect significant changes in the status of the employer's compliance program.
 - (iv) The employer shall not implement a schedule of employee rotation as a means of compliance with the PELs.
- (g) Exposure Goal Program.**
- (1) For those operations and job classifications where employee exposures are greater than the action level, in addition to compliance with the PELs, the employer shall have an exposure goal program that is intended to limit employee exposures to below the action level during normal operations.
 - (2) Written plans for the exposure goal program shall be furnished upon request for examination and copying to the Assistant Secretary, the Director, affected employees and designated employee representatives.
 - (3) Such plans shall be updated as necessary to reflect significant changes in the status of the exposure goal program.
 - (4) Respirator use is not required in the exposure goal program.
 - (5) The exposure goal program shall include the following items unless the employer can demonstrate that the item is not feasible, will have no significant effect in reducing employee exposures, or is not necessary to achieve exposures below the action level:
 - (i) A leak prevention, detection, and repair program.
 - (ii) A program for maintaining the effectiveness of local exhaust ventilation systems.
 - (iii) The use of pump exposure control technology such as, but not limited to, mechanical double-sealed or seal-less pumps.
 - (iv) Gauging devices designed to limit employee exposure, such as magnetic gauges on rail cars.
 - (v) Unloading devices designed to limit employee exposure, such as a vapor return system.
 - (vi) A program to maintain BD concentration below the action level in control rooms by use of engineering controls.
- (h) Respiratory protection.**
- (1) General. For employees who use respirators required by this section, the employer must provide respirators that comply with the requirements of this paragraph. Respirators must be used during:
 - (i) Periods necessary to install or implement feasible engineering and work-practice controls.
 - (ii) Non-routine work operations that are performed infrequently and for that employee exposures are limited in duration.
 - (iii) Work operations for that feasible engineering and work-practice controls are not yet sufficient to reduce employee exposures to or below the PELs.
 - (iv) Emergencies.
 - (2) Respirator program.
 - (i) The employer must implement a respiratory protection program in accordance with 29 CFR 1910.134 (b) through (d) (except (d)(1)(iii), (d)(3)(iii)(B)(1), and (2)), and (f) through (m).
 - (ii) If air-purifying respirators are used, the employer must replace the air-purifying filter elements according to the replacement schedule set for the class of respirators listed in Table 1 of this section, and the beginning of each work shift.
 - (iii) Instead of using the replacement schedule listed in Table 1 of this section, the employer may replace cartridges or canisters at 90% of their expiration service life, provided the employer:
 - (A) Demonstrates that employees will be adequately protected by this procedure.
 - (B) Uses BD breakthrough data for this purpose that have been derived from tests conducted under work-case conditions of humidity, temperature, and air-flow rate

- through the filter element, and the employer also describes the data supporting the cartridge-or canister-change schedule, as well as the basis for using the data in the employer's respirator program.
- (iv) A label must be attached to each filter element to indicate the date and time it is first installed on the respirator.
 - (v) If NIOSH approves and end-of-service-life indicator (ESLI) for an air-purifying filter element, the element may be used until the ESLI shows no further useful service life or until the element is replaced at the beginning of the next work shift, whatever occurs first.
 - (vi) Regardless of the air-purifying element used, if an employee detects the odor of BD, the employer must replace the air-purifying element immediately.
- (3) Respirator selection.
- (i) The employer must select appropriate respirators from Table 1 of this section.

TABLE 1. - MINIMUM REQUIREMENTS FOR RESPIRATORY PROTECTION FOR AIRBORNE BD

Concentration of airborne BD (ppm) or condition of use	Minimum required respirator
Less than or equal to 5 ppm (5 times PEL)	(a) Air-purifying half mask or full facepiece respirator equipped with approved BD or organic vapor cartridges or canisters. Cartridges or canisters shall be replaced every 4 hours.
Less than or equal to 10 ppm (10 times PEL)	(a) Air-purifying half mask or full facepiece respirator equipped with approved BD or organic vapor cartridges or canisters. Cartridges or canisters shall be replaced every 3 hours.
Less than or equal to 25 ppm (25 times PEL)	(a) Air-purifying full facepiece respirator equipped with approved BD or organic vapor cartridges or canisters. Cartridges or canisters shall be replaced every 2 hours. (b) Any powered air-purifying respirator equipped with approved BD or organic vapor cartridges. PAPR cartridges shall be replaced every 2 hours. (c) Continuous flow supplied air respirator equipped with a hood or helmet.
Less than or equal to 50 ppm (50 times PEL)	(a) Air-purifying facepiece respirator equipped with approved BD or organic vapor cartridges or canisters. Cartridges or canisters shall be replaced every (1) hour. (b) Powered air-purifying respirator equipped with a tight fitting facepiece and an approved BD or organic vapor cartridges. PAPR cartridges shall be replaced every (1) hour.
Less than or equal to 1,000 ppm (1,000 times PEL)	(a) Supplied air respirator equipped with a half mask or full facepiece and operated in a pressure demand or other positive pressure mode.
Greater than 1000 ppm unknown concentration, or firefighting	(a) Self-contained breathing unknown concentration, or apparatus equipped with a firefighting full facepiece and operated in a pressure demand or other positive pressure mode. (b) Any supplied air respirator equipped with a full facepiece and operated in a pressure demand or other self-contained breathing apparatus operated in a pressure demand or other positive pressure mode.
Escape from IDLH conditions	(a) Any positive pressure self-contained breathing apparatus with an appropriate service life. (b) A air-purifying full facepiece respirator equipped with a front or back mounted BD or organic vapor canister.

NOTES: Respirators approved for use in higher concentrations are permitted to be used in lower

concentrations. Full facepiece is required when eye irritation is anticipated.

- (ii) Air-purifying respirators must have filter elements approved by NIOSH for organic vapors or BD.
- (iii) When an employee whose job required the use of a respirator cannot use a negative-pressure respirator, the employer must provide the employee with a respirator that has less breathing resistance than the negative-pressure respirator, such as a powered air-purifying respirator or supplied-air respirator, when the employee is able to use it and if it provides the employee adequate protection.
- (i) Protective clothing and equipment. Where appropriate to prevent eye contact and limit dermal exposure to BD, the employer shall provide protective clothing and equipment at no cost to the employee and shall ensure its use. Eye and face protection shall meet the requirements of 29 CFR 1910.133.
- (j) Emergency situations. Written plan. A written plan for emergency situations shall be developed, or an existing plan shall be modified, to contain the applicable elements specified in 29 CFR 1910.38 and 29 CFR 1910.39, "Emergency action plans" and "Fire prevention plans," respectively, and in 29 CFR 1910.120, "Hazardous Waste Operations and Emergency Response," for each workplace where there is the possibility of an emergency.
- (k) Medical screening and surveillance.
 - (1) Employees covered. The employer shall institute a medical screening and surveillance program as specified in this paragraph for:
 - (i) Each employee with exposure to BD at concentrations at or above the action level on 30 or more days or for employees who have or may have exposure to BD at or above the PELs on 10 or more days a year;
 - (ii) Employers (including successor owners) shall continue to provide medical screening and surveillance for employees, even after transfer to a non-BD exposed job and regardless of when the employee is transferred, whose work histories suggest exposure to BD:
 - (A) At or above the PELs on 30 or more days a year for 10 or more years;
 - (B) At or above the action level on 60 or more days a year for 10 or more years; or
 - (C) Above 10 ppm on 30 or more days in any past year; and
 - (iii) Each employee exposed to BD following an emergency situation.
 - (2) Program administration.
 - (i) The employer shall ensure that the health questionnaire, physical examination and medical procedures are provided without cost to the employee, without loss of pay, and at a reasonable time and place.
 - (ii) Physical examinations, health questionnaires, and medical procedures shall be performed or administered by a physician or other licensed health care professional.
 - (iii) Laboratory tests shall be conducted by an accredited laboratory.
 - (3) Frequency of medical screening activities. The employer shall make medical screening available on the following schedule:
 - (i) For each employee covered under paragraphs (j)(1) (i)-(ii) of this section, a health questionnaire and complete blood count with differential and platelet count (CBC) every year, and a physical examination as specified below:
 - (A) An initial physical examination that meets the requirements of this rule, if twelve months or more have elapsed since the last physical examination conducted as part of a medical screening program for BD exposure;
 - (B) Before assumption of duties by the employee in a job with BD exposure;
 - (C) Every 3 years after the initial physical examination;
 - (D) At the discretion of the physician or other licensed health care professional reviewing the annual health questionnaire and CBC;
 - (E) At the time of employee reassignment to an area where exposure to BD is below the action level, if the employee's past exposure history does not meet the criteria of paragraph (j)(1)(ii) of this section for continued coverage in the screening and surveillance program, and if twelve months or more have elapsed since the last physical examination; and
 - (F) At termination of employment if twelve months or more have elapsed since the last physical examination.
 - (ii) Following an emergency situation, medical screening shall be conducted as quickly as

- possible, but not later than 48 hours after the exposure.
- (iii) For each employee who must wear a respirator, physical ability to perform the work and use the respirator must be determined as required by 29 CFR 1910.134.
- (4) Content of medical screening.
- (i) Medical screening for employees covered by paragraphs (j)(1) (i)-(ii) of this section shall include:
 - (A) A baseline health questionnaire that includes a comprehensive occupational and health history and is updated annually. Particular emphasis shall be placed on the hematopoietic and reticuloendothelial systems, including exposure to chemicals, in addition to BD, that may have an adverse effect on these systems, the presence of signs and symptoms that might be related to disorders of these systems, and any other information determined by the examining physician or other licensed health care professional to be necessary to evaluate whether the employee is at increased risk of material impairment of health from BD exposure. Health questionnaires shall consist of the sample forms in Appendix C to this section, or be equivalent to those samples;
 - (B) A complete physical examination, with special emphasis on the liver, spleen, lymph nodes, and skin;
 - (C) A CBC; and
 - (D) Any other test that the examining physician or other licensed health care professional deems necessary to evaluate whether the employee may be at increased risk from exposure to BD.
 - (ii) Medical screening for employees exposed to BD in an emergency situation shall focus on the acute effects of BD exposure and at a minimum include: A CBC within 48 hours of the exposure and then monthly for three months; and a physical examination if the employee reports irritation of the eyes, nose throat, lungs, or skin, blurred vision, coughing, drowsiness, nausea, or headache. Continued employee participation in the medical screening and surveillance program, beyond these minimum requirements, shall be at the discretion of the physician or other licensed health care professional.
- (5) Additional medical evaluations and referrals.
- (i) Where the results of medical screening indicate abnormalities of the hematopoietic or reticuloendothelial systems, for that a non-occupational cause is not readily apparent, the examining physician or other licensed health care professional shall refer the employee to an appropriate specialist for further evaluation and shall make available to the specialist the results of the medical screening.
 - (ii) The specialist to whom the employee is referred under this paragraph shall determine the appropriate content for the medical evaluation, e.g., examinations, diagnostic tests and procedures, etc.
- (6) Information provided to the physician or other licensed health care professional. The employer shall provide the following information to the examining physician or other licensed health care professional involved in the evaluation:
- (i) A copy of this section including its appendices;
 - (ii) A description of the affected employee's duties as they relate to the employee's BD exposure;
 - (iii) The employee's actual or representative BD exposure level during employment tenure, including exposure incurred in an emergency situation;
 - (iv) A description of pertinent personal protective equipment used or to be used; and
 - (v) Information, when available, from previous employment-related medical evaluations of the affected employee that is not otherwise available to the physician or other licensed health care professional or the specialist.
- (7) The written medical opinion.
- (i) For each medical evaluation required by this section, the employer shall ensure that the physician or other licensed health care professional produces a written opinion and provides a copy to the employer and the employee within 15 business days of the evaluation. The written opinion shall be limited to the following information:
 - (A) The occupationally pertinent results of the medical evaluation;
 - (B) A medical opinion concerning whether the employee has any detected medical conditions that would place the employee's health at increased risk of material impairment from exposure to BD;

- (C) Any recommended limitations upon the employee's exposure to BD; and
 - (D) A statement that the employee has been informed of the results of the medical evaluation and any medical conditions resulting from BD exposure that require further explanation or treatment.
 - (ii) The written medical opinion provided to the employer shall not reveal specific records, findings, and diagnoses that have no bearing on the employee's ability to work with BD.
- Note:** However, this provision does not negate the ethical obligation of the physician or other licensed health care professional to transmit any other adverse findings directly to the employee.
- (8) Medical surveillance.
 - (i) The employer shall ensure that information obtained from the medical screening program activities is aggregated (with all personal identifiers removed) and periodically reviewed, to ascertain whether the health of the employee population of that employer is adversely affected by exposure to BD.
 - (ii) Information learned from medical surveillance activities must be disseminated to covered employees, as defined in paragraph (k)(1) of this section, in a manner that ensures the confidentiality of individual medical information.
 - (1) Communication of BD hazards to employees.
 - (1) Hazard communication. The employer shall communicate the hazards associated with BD exposure in accordance with the requirements of the Hazard Communication Standard, 29 CFR 1910.1200, 29 CFR 1915.1200, and 29 CFR 1926.59.
 - (2) Employee information and training.
 - (i) The employer shall provide all employees exposed to BD with information and training in accordance with the requirements of the Hazard Communication Standard, 29 CFR 1910.1200, 29 CFR 1915.1200, and 29 CFR 1926.59.
 - (ii) The employer shall institute a training program for all employees who are potentially exposed to BD at or above the action level or the STEL, ensure employee participation in the program and maintain a record of the contents of such program.
 - (iii) Training shall be provided prior to or at the time of initial assignment to a job potentially involving exposure to BD at or above the action level or STEL and at least annually thereafter.
 - (iv) The training program shall be conducted in a manner that the employee is able to understand. The employer shall ensure that each employee exposed to BD over the action level or STEL is informed of the following:
 - (A) The health hazards associated with BD exposure, and the purpose and a description of the medical screening and surveillance program required by this section;
 - (B) The quantity, location, manner of use, release, and storage of BD and the specific operations that could result in exposure to BD, especially exposures above the PEL or STEL;
 - (C) The engineering controls and work practices associated with the employee's job assignment, and emergency procedures and personal protective equipment;
 - (D) The measures employees can take to protect themselves from exposure to BD.
 - (E) The contents of this standard and its appendices, and
 - (F) The right of each employee exposed to BD at or above the action level or STEL to obtain:
 - (1) medical examinations as required by paragraph (j) of this section at no cost to the employee;
 - (2) the employee's medical records required to be maintained by paragraph (m)(4) of this section; and
 - (3) all air monitoring results representing the employee's exposure to BD and required to be kept by paragraph (m)(2) of this section.
 - (3) Access to information and training materials.
 - (i) The employer shall make a copy of this standard and its appendices readily available without cost to all affected employees and their designated representatives and shall provide a copy if requested.
 - (ii) The employer shall provide to the Assistant Secretary or the Director, or the designated employee representatives, upon request, all materials relating to the employee information and the training program.

(m) Record Keeping.

- (1) Objective data for exemption from initial monitoring.
 - (i) Where the processing, use, or handling of products or streams made from or containing BD are exempted from other requirements of this section under paragraph (a)(2) of this section, or where objective data have been relied on in lieu of initial monitoring under paragraph (d)(2)(ii) of this section, the employer shall establish and maintain a record of the objective data reasonably relied upon in support of the exemption.
 - (ii) This record shall include at least the following information:
 - (A) The product or activity qualifying for exemption;
 - (B) The source of the objective data;
 - (C) The testing protocol, results of testing, and analysis of the material for the release of BD;
 - (D) A description of the operation exempted and how the data support the exemption; and
 - (E) Other data relevant to the operations, materials, processing, or employee exposures covered by the exemption.
 - (iii) The employer shall maintain this record for the duration of the employer's reliance upon such objective data.
- (2) Exposure measurements.
 - (i) The employer shall establish and maintain an accurate record of all measurements taken to monitor employee exposure to BD as prescribed in paragraph (d) of this section.
 - (ii) The record shall include at least the following information:
 - (A) The date of measurement;
 - (B) The operation involving exposure to BD that is being monitored;
 - (C) Sampling and analytical methods used and evidence of their accuracy;
 - (D) Number, duration, and results of samples taken;
 - (E) Type of protective devices worn, if any; and
 - (F) Name, social security number and exposure of the employees whose exposures are represented.
 - (G) The written corrective action and the schedule for completion of this action required by paragraph (d)(7)(ii) of this section.
 - (iii) The employer shall maintain this record for at least 30 years in accordance with 29 CFR 1910.1020.
- (3) Respirator Fit-test.
 - (i) The employer shall establish a record of the fit tests administered to an employee including:
 - (A) The name of the employee,
 - (B) Type of respirator,
 - (C) Brand and size of respirator,
 - (D) Date of test, and
 - (E) Where QNFT is used, the fit factor, strip chart recording or other recording of the results of the test.
 - (ii) Fit test records shall be maintained for respirator users until the next fit test is administered.
- (4) Medical screening and surveillance.
 - (i) The employer shall establish and maintain an accurate record for each employee subject to medical screening and surveillance under this section.
 - (ii) The record shall include at least the following information:
 - (A) The name and social security number of the employee;
 - (B) Physician's or other licensed health care professional's written opinions as described in paragraph (k)(7) of this section;
 - (C) A copy of the information provided to the physician or other licensed health care professional as required by paragraphs (k)(7)(ii)-(iv) of this section.
 - (iii) Medical screening and surveillance records shall be maintained for each employee for the duration of employment plus 30 years, in accordance with 29 CFR 1910.1020.
- (5) Availability.
 - (i) The employer, upon written request, shall make all records required to be maintained by this section available for examination and copying to the Assistant Secretary and the

- Director.
- (ii) Access to records required to be maintained by paragraphs (l)(1)-(3) of this section shall be granted in accordance with 29 CFR 1910.1020(e).
- (6) Transfer of records.
 - (i) Whenever the employer ceases to do business, the employer shall transfer records required by this section to the successor employer. The successor employer shall receive and maintain these records. If there is no successor employer, the employer shall notify the Director, at least three (3) months prior to disposal, and transmit them to the Director if requested by the Director within that period.
 - (ii) The employer shall transfer medical and exposure records as set forth in 29 CFR 1910.1020(h).
- (n) [Reserved]
- (o) Appendices.
 - (1) Appendix E to this section is mandatory.
 - (2) Appendices A, B, C, D, and F to this section are informational and are not intended to create any additional obligations not otherwise imposed or to detract from any existing obligations.

Appendix A

Substance Safety Data Sheet For 1,3-Butadiene (Non-Mandatory)

I. Substance Identification

- A. Substance: 1,3-Butadiene ($\text{CH}_2=\text{CH}-\text{CH}=\text{CH}_2$).
- B. Synonyms: 1,3-Butadiene (BD); butadiene; biethylene; bi-vinyl; divinyl; butadiene-1,3; buta-1,3-diene; erythrene; NCI-C50602; CAS-106-99-0.
- C. BD can be found as a gas or liquid.
- D. BD is used in production of styrene-butadiene rubber and polybutadiene rubber for the tire industry. Other uses include copolymer latexes for carpet backing and paper coating, as well as resins and polymers for pipes and automobile and appliance parts. It is also used as an intermediate in the production of such chemicals as fungicides.
- E. Appearance and odor: BD is a colorless, non-corrosive, flammable gas with a mild aromatic odor at standard ambient temperature and pressure.
- F. Permissible exposure: Exposure may not exceed 1 part BD per million parts of air averaged over the 8-hour workday, nor may short-term exposure exceed 5 parts of BD per million parts of air averaged over any 15-minute period in the 8-hour workday.

II. Health Hazard Data

- A. BD can affect the body if the gas is inhaled or if the liquid form, that is very cold (cryogenic), comes in contact with the eyes or skin.
- B. Effects of overexposure: Breathing very high levels of BD for a short time can cause central nervous system effects, blurred vision, nausea, fatigue, headache, decreased blood pressure and pulse rate, and unconsciousness. There are no recorded cases of accidental exposures at high levels that have caused death in humans, but this could occur. Breathing lower levels of BD may cause irritation of the eyes, nose, and throat. Skin contact with liquefied BD can cause irritation and frostbite.
- C. Long-term (chronic) exposure: BD has been found to be a potent carcinogen in rodents, inducing neoplastic lesions at multiple target sites in mice and rats. A recent study of BD-exposed workers showed that exposed workers have an increased risk of developing leukemia. The risk of leukemia increases with increased exposure to BD. OSHA has concluded that there is strong evidence that workplace exposure to BD poses an increased risk of death from cancers of the lymphohematopoietic system.
- D. Reporting signs and symptoms: You should inform your supervisor if you develop any of these signs or symptoms and suspect that they are caused by exposure to BD.

III. Emergency First Aid Procedures

In the event of an emergency, follow the emergency plan and procedures designated for your work

area. If you have been trained in first aid procedures, provide the necessary first aid measures. If necessary, call for additional assistance from co-workers and emergency medical personnel.

- A. Eye and Skin Exposures: If there is a potential that liquefied BD can come in contact with eye or skin, face shields and skin protective equipment must be provided and used. If liquefied BD comes in contact with the eye, immediately flush the eyes with large amounts of water, occasionally lifting the lower and the upper lids. Flush repeatedly. Get medical attention immediately. Contact lenses should not be worn when working with this chemical. In the event of skin contact, that can cause frostbite, remove any contaminated clothing and flush the affected area repeatedly with large amounts of tepid water.
- B. Breathing: If a person breathes in large amounts of BD, move the exposed person to fresh air at once. If breathing has stopped, begin cardiopulmonary resuscitation (CPR) if you have been trained in this procedure. Keep the affected person warm and at rest. Get medical attention immediately.
- C. Rescue: Move the affected person from the hazardous exposure. If the exposed person has been overcome, call for help and begin emergency rescue procedures. Use extreme caution so that you do not become a casualty. Understand the plant's emergency rescue procedures and know the locations of rescue equipment before the need arises.

IV. Respirators and Protective Clothing

- A. Respirators: Good industrial hygiene practices recommend that engineering and work practice controls be used to reduce environmental concentrations to the permissible exposure level. However, there are some exceptions where respirators may be used to control exposure. Respirators may be used when engineering and work practice controls are not technically feasible, when such controls are in the process of being installed, or when these controls fail and need to be supplemented or during brief, non-routine, intermittent exposure. Respirators may also be used in situations involving non-routine work operations that are performed infrequently and in that exposures are limited in duration, and in emergency situations. In some instances cartridge respirator use is allowed, but only with strict time constraints. For example, at exposure below 5 ppm BD, a cartridge (or canister) respirator, either full or half face, may be used, but the cartridge must be replaced at least every 4 hours, and it must be replaced every 3 hours when the exposure is between and 10 ppm. If the use of respirators is necessary, the only respirators permitted are those that have been approved by the National Institute for Occupational Safety and Health (NIOSH). In addition to respirator selection, a complete respiratory protection program must be instituted that includes regular training, maintenance, fit testing, inspection, cleaning, and evaluation of respirators. If you can smell BD while wearing a respirator, proceed immediately to fresh air, and change cartridge (or canister) before re-entering an area where there is BD exposure. If you experience difficulty in breathing while wearing a respirator, tell your supervisor.
- B. Protective Clothing: Employees should be provided with and required to use impervious clothing, gloves, face shields (eight-inch minimum), and other appropriate protective clothing necessary to prevent the skin from becoming frozen by contact with liquefied BD (or a vessel containing liquid BD). Employees should be provided with and required to use splash-proof safety goggles where liquefied BD may contact the eyes.

V. Precautions for Safe Use, Handling, and Storage

- A. Fire and Explosion Hazards: BD is a flammable gas and can easily form explosive mixtures in air. It has a lower explosive limit of 2%, and an upper explosive limit of 11.5%. It has an autoignition temperature of 420° C (788° F). Its vapor is heavier than air (vapor density, 1.9) and may travel a considerable distance to a source of ignition and flash back. Usually it contains inhibitors to prevent self-polymerization (that is accompanied by evolution of heat) and to prevent formation of explosive peroxides. At elevated temperatures, such as in fire conditions, polymerization may take place. If the polymerization takes place in a container, there is a possibility of violent rupture of the container.
- B. Hazard: Slightly toxic. Slight respiratory irritant. Direct contact of liquefied BD on skin may cause freeze burns and frostbite.
- C. Storage: Protect against physical damage to BD containers. Outside or detached storage of BD containers is preferred. Inside storage should be in a cool, dry, well-ventilated,

noncombustible location, away from all possible sources of ignition. Store cylinders vertically and do not stack. Do not store with oxidizing material.

- D. Usual Shipping Containers: Liquefied BD is contained in steel pressure apparatus.
- E. Electrical Equipment: Electrical installations in Class I hazardous locations, as defined in Article 500 of the National Electrical Code, should be in accordance with Article 501 of the Code. If explosion-proof electrical equipment is necessary, it shall be suitable for use in Group B. Group D equipment may be used if such equipment is isolated in accordance with Section 501-5(a) by sealing all conduit 1/2-inch size or larger. See Venting of Deflagrations (NFPA No. 68, 1994), National Electrical Code (NFPA No. 70, 1996), Static Electricity (NFPA No. 77, 1993), Lightning Protection Systems (NFPA No. 780, 1995), and Fire Hazard Properties of Flammable Liquids, Gases and Volatile Solids (NFPA No. 325, 1994).
- F. Fire Fighting: Stop flow of gas. Use water to keep fire-exposed containers cool. Fire extinguishers and quick drenching facilities must be readily available, and you should know where they are and how to operate them.
- G. Spill and Leak: Persons not wearing protective equipment and clothing should be restricted from areas of spills or leaks until clean-up has been completed. If BD is spilled or leaked, the following steps should be taken:
 1. Eliminate all ignition sources.
 2. Ventilate area of spill or leak.
 3. If in liquid form, for small quantities, allow to evaporate in a safe manner.
 4. Stop or control the leak if this can be done without risk. If source of leak is a cylinder and the leak cannot be stopped in place, remove the leaking cylinder to a safe place and repair the leak or allow the cylinder to empty.
- H. Disposal: This substance, when discarded or disposed of, is a hazardous waste according to Federal regulations (40 CFR part 261). It is listed as hazardous waste number D001 due to its ignitability. The transportation, storage, treatment, and disposal of this waste material must be conducted in compliance with 40 CFR parts 262, 263, 264, 268 and 270. Disposal can occur only in properly permitted facilities. Check state and local regulation of any additional requirements as these may be more restrictive than federal laws and regulation.
- I. You should not keep food, beverages, or smoking materials in areas where there is BD exposure, nor should you eat or drink in such areas.
- J. Ask your supervisor where BD is used in your work area and ask for any additional plant safety and health rules.

VI. Medical Requirements

Your employer is required to offer you the opportunity to participate in a medical screening and surveillance program if you are exposed to BD at concentrations exceeding the action level (0.5 ppm BD as an 8-hour TWA) on 30 days or more a year, or at or above the 8 hr TWA (1 ppm) or STEL (5 ppm for 15 minutes) on 10 days or more a year. Exposure for any part of a day counts. If you have had exposure to BD in the past, but have been transferred to another job, you may still be eligible to participate in the medical screening and surveillance program. The OSHA rule specifies the past exposures that would qualify you for participation in the program. These past exposure are work histories that suggest the following: (1) That you have been exposed at or above the PELs on 30 days a year for 10 or more years; (2) that you have been exposed at or above the action level on 60 days a year for 10 or more years; or (3) that you have been exposed above 10 ppm on 30 days in any past year. Additionally, if you are exposed to BD in an emergency situation, you are eligible for a medical examination within 48 hours. The basic medical screening program includes a health questionnaire, physical examination, and blood test. These medical evaluations must be offered to you at a reasonable time and place, and without cost or loss of pay.

VII. Observation of Monitoring

Your employer is required to perform measurements that are representative of your exposure to BD and you or your designated representative are entitled to observe the monitoring procedure. You are entitled to observe the steps taken in the measurement procedure, and to record the results obtained. When the monitoring procedure is taking place in an area where respirators or personal protective clothing and equipment are required to be worn, you or your representative must also be provided with, and must wear, the protective clothing and equipment.

VIII. Access to Information

- A. Each year, your employer is required to inform you of the information contained in this appendix. In addition, your employer must instruct you in the proper work practices for using BD, emergency procedures, and the correct use of protective equipment.
- B. Your employer is required to determine whether you are being exposed to BD. You or your representative has the right to observe employee measurements and to record the results obtained. Your employer is required to inform you of your exposure. If your employer determines that you are being overexposed, he or she is required to inform you of the actions that are being taken to reduce your exposure to within permissible exposure limits and of the schedule to implement these actions.
- C. Your employer is required to keep records of your exposures and medical examinations. These records must be kept by the employer for at least thirty (30) years.
- D. Your employer is required to release your exposure and medical records to you or your representative upon your request.

Appendix B
Substance Technical Guidelines for 1,3-Butadiene
(Non-Mandatory)

I. Physical and Chemical Data

A. Substance identification:

1. Synonyms: 1,3-Butadiene (BD); butadiene; biethylene; bivinyll; divinyl; butadiene-1,3; buta-1,3-diene; erythrene; NCI-C50620; CAS-106-99-0.
2. Formula: $\text{CH}_2=\text{CH}-\text{CH}=\text{CH}_2$.
3. Molecular weight: 54.1.

B. Physical data:

1. Boiling point (760 mm Hg): -4.7°C (23.5°F).
2. Specific gravity (water=1): 0.62 at 20°C (68°F).
3. Vapor density (air=1 at boiling point of BD): 1.87.
4. Vapor pressure at 20°C (68°F): 910 mm Hg.
5. Solubility in water, g/100 g water at 20°C (68°F): 0.05.
6. Appearance and odor: Colorless, flammable gas with a mildly aromatic odor. Liquefied BD is a colorless liquid with a mildly aromatic odor.

II. Fire, Explosion, and Reactivity Hazard Data

A. Fire:

1. Flash point: -76°C (-105°F) for take out; liquefied BD; Not applicable to BD gas.
2. Stability: A stabilizer is added to the monomer to inhibit formation of polymer during storage. Forms explosive peroxides in air in absence of inhibitor.
3. Flammable limits in air, percent by volume: Lower: 2.0; Upper: 11.5.
4. Extinguishing media: Carbon dioxide for small fires, polymer or alcohol foams for large fires.
5. Special fire fighting procedures: Fight fire from protected location or maximum possible distance. Stop flow of gas before extinguishing fire. Use water spray to keep fire-exposed cylinders cool.
6. Unusual fire and explosion hazards: BD vapors are heavier than air and may travel to a source of ignition and flash back. Closed containers may rupture violently when heated.
7. For purposes of compliance with the requirements of 29 CFR 1910.106, BD is classified as a flammable gas. For example, 7,500 ppm, approximately one-fourth of the lower flammable limit, would be considered to pose a potential fire and explosion hazard.
8. For purposes of compliance with 29 CFR 1910.155, BD is classified as a Class B fire hazard.
9. For purposes of compliance with 29 CFR 1910.307, locations classified as hazardous due

to the presence of BD shall be Class I.

- B. Reactivity:
1. Conditions contributing to instability: Heat. Peroxides are formed when inhibitor concentration is not maintained at proper level. At elevated temperatures, such as in fire conditions, polymerization may take place.
 2. Incompatibilities: Contact with strong oxidizing agents may cause fires and explosions. The contacting of crude BD (not BD monomer) with copper and copper alloys may cause formations of explosive copper compounds.
 3. Hazardous decomposition products: Toxic gases (such as carbon monoxide) may be released in a fire involving BD.
 4. Special precautions: BD will attack some forms of plastics, rubber, and coatings. BD in storage should be checked for proper inhibitor content, for self-polymerization, and for formation of peroxides when in contact with air and iron. Piping carrying BD may become plugged by formation of rubbery polymer.
- C. Warning Properties:
1. Odor Threshold: An odor threshold of 0.45 ppm has been reported in The American Industrial Hygiene Association (AIHA) Report, Odor Thresholds for Chemicals with Established Occupational Health Standards. (Ex. 32-28C)
 2. Eye Irritation Level: Workers exposed to vapors of BD (concentration or purity unspecified) have complained of irritation of eyes, nasal passages, throat, and lungs. Dogs and rabbits exposed experimentally to as much as 6700 ppm for 7 1/2 hours a day for 8 months have developed no histologically demonstrable abnormality of the eyes.
 3. Evaluation of Warning Properties: Since the mean odor threshold is about half of the 1 ppm PEL, and more than 10-fold below the 5 ppm STEL, most wearers of air purifying respirators should still be able to detect breakthrough before a significant overexposure to BD occurs.

III. Spill, Leak, and Disposal Procedures

- A. Persons not wearing protective equipment and clothing should be restricted from areas of spills or leaks until cleanup has been completed. If BD is spilled or leaked, the following steps should be taken:
1. Eliminate all ignition sources.
 2. Ventilate areas of spill or leak.
 3. If in liquid form, for small quantities, allow to evaporate in a safe manner.
 4. Stop or control the leak if this can be done without risk. If source of leak is a cylinder and the leak cannot be stopped in place, remove the leaking cylinder to a safe place and repair the leak or allow the cylinder to empty.
- B. Disposal: This substance, when discarded or disposed of, is a hazardous waste according to Federal regulations (40 CFR part 261). It is listed by the EPA as hazardous waste number D001 due to its ignitability. The transportation, storage, treatment, and disposal of this waste material must be conducted in compliance with 40 CFR parts 262, 263, 264, 268 and 270. Disposal can occur only in properly permitted facilities. Check state and local regulations for any additional requirements because these may be more restrictive than federal laws and regulations.

IV. Monitoring and Measurement Procedures

- A. Exposure above the Permissible Exposure Limit (8-hr TWA) or Short-Term Exposure Limit (STEL):
1. 8-hr TWA exposure evaluation: Measurements taken for the purpose of determining employee exposure under this standard are best taken with consecutive samples covering the full shift. Air samples must be taken in the employee's breathing zone (air that would most nearly represent that inhaled by the employee).
 2. STEL exposure evaluation: Measurements must represent 15-minute exposures associated with operations most likely to exceed the STEL in each job and on each shift.
 3. Monitoring frequencies: Table 1 gives various exposure scenarios and their required monitoring frequencies, as required by the final standard for occupational exposure to butadiene.

TABLE 1. FIVE EXPOSURE SCENARIOS AND THEIR ASSOCIATED MONITORING FREQUENCIES

Action level	8-hr TWA	STEL	Required monitoring activity
-*	-	-	No 8-hr TWA or STEL monitoring required.
+*	-	-	NO STEL monitoring required. Monitor 8-hr TWA annually.
+	+	-	No STEL monitoring 8-hr TWA, in accordance with (d)(3)(II)**. Periodic monitoring STEL, in accordance with (d)(3)(iii).
+	+	+	Periodic monitoring 8-hr TWA, in accordance with (d)(3)(ii)**. Periodic monitoring STEL, in accordance with (d)(3)(iii).
+	-	+	Periodic monitoring STEL, in accordance with (d)(3)(iii). Monitor 8-hr TWA, annually.

* Exposure Scenario, Limit Exceeded: + = Yes. - = No.

** The employer may decrease the frequency of exposure monitoring to annually when at least 2 consecutive measurements taken at least 7 days apart show exposures to be below the 8 hr TWA, but at or above the action level.

4. Monitoring techniques: Appendix D describes the validated method of sampling and analysis that has been tested by OSHA for use with BD. The employer has the obligation of selecting a monitoring method that meets the accuracy and precision requirements of the standard under his or her unique field conditions. The standard required that the method of monitoring must be accurate, to a 95 percent confidence level, to plus or minus 25 percent for concentrations of BD at or above ppm, and to plus or minus 35 percent for concentrations below 1 ppm.
- V. Personal Protective Equipment
 - A. Employees should be provide with and required to use impervious clothing, gloves, face shields (eight-inch minimum), and other appropriate protective clothing necessary to prevent the skin from becoming frozen from contact with liquid BD.
 - B. Any clothing that becomes wet with liquid BD should be removed immediately and not re-worm until the butadiene has evaporated.
 - C. Employees should be provided with and required to use splash proof safety goggles where liquid BD may contact the eyes.
 - VI. Housekeeping and Hygiene Facilities

For purposes of complying with 29 CFR 1910.141, the following items should be emphasized:

 - A. The workplace should be kept clean, orderly, and in a sanitary condition.
 - B. Adequate washing facilities with hot and cold water are to be provided and maintained in a sanitary condition.
 - VII. Additional Precautions
 - A. Store BD in tightly closed containers in a cool, well-ventilated area and take all necessary precautions to avoid any explosion hazard.
 - B. Non-sparking tools must be used to open and close metal containers. These containers must be effectively grounded.
 - C. Do not incinerate BD cartridges, tanks or other containers.
 - D. Employers must advice employees of all areas and operations where exposure to BD might occur.

Medical Screening and Surveillance for 1,3-Butadiene (Non-Mandatory)

I. Basis for Medical Screening and Surveillance Requirements

A. Route of Entry Inhalation

B. Toxicology

Inhalation of BD has been linked to an increased risk of cancer, damage to the reproductive organs, and fetotoxicity. Butadiene can be converted via oxidation to epoxybutene and diepoxybutane, two genotoxic metabolites that may play a role in the expression of BD's toxic effects. BD has been tested for carcinogenicity in mice and rats. Both species responded to BD exposure by developing cancer at multiple primary organ sites. Early deaths in mice were caused by malignant lymphomas, primarily lymphocytic type, originating in the thymus.

Mice exposed to BD have developed ovarian or testicular atrophy. Sperm head morphology tests also revealed abnormal sperm in mice exposed to BD; lethal mutations were found in a dominant lethal test. In light of these results in animals, the possibility that BD may adversely affect the reproductive systems of male and female workers must be considered.

Additionally, anemia has been observed in animals exposed to butadiene. In some cases, this anemia appeared to be a primary response to exposure; in other cases, it may have been secondary to a neoplastic response.

C. Epidemiology

Epidemiologic evidence demonstrates that BD exposure poses an increased risk of leukemia. Mild alterations of hematologic parameters have also been observed in synthetic rubber workers exposed to BD.

II. Potential Adverse Health Effects

A. Acute

Skin contact with liquid BD causes characteristic burns or frostbite. BD in gaseous form can irritate the eyes, nasal passages, throat, and lungs. Blurred vision, coughing, and drowsiness may also occur. Effects are mild at 2,000 ppm and pronounced at 8,000 ppm for exposures occurring over the full work shift.

At very high concentrations in air, BD is an anesthetic, causing narcosis, respiratory paralysis, unconsciousness, and death. Such concentrations are unlikely, however, except in an extreme emergency because BD poses an explosion hazard at these levels.

B. Chronic

The principal adverse health effects of concern are BD-induced lymphoma, leukemia and potential reproductive toxicity. Anemia and other changes in the peripheral blood cells may be indicators of excessive exposure to BD.

C. Reproductive

Workers may be concerned about the possibility that their BD exposure may be affecting their ability to procreate a healthy child. For workers with high exposures to BD, especially those who have experienced difficulties in conceiving, miscarriages, or stillbirths, appropriate medical and laboratory evaluation of fertility may be necessary to determine if BD is having any adverse effect on the reproductive system or on the health of the fetus.

III. Medical Screening Components At-A-Glance

A. Health Questionnaire

The most important goal of the health questionnaire is to elicit information from the worker regarding potential signs or symptoms generally related to leukemia or other blood abnormalities. Therefore, physicians or other licensed health care professionals should be aware of the presenting symptoms and signs of lymphohematopoietic disorders and cancers, as well as the procedures necessary to confirm or exclude such diagnoses. Additionally, the health questionnaire will assist with the identification of workers at greatest risk of developing leukemia or adverse reproductive effects from their exposures to BD.

Workers with a history of reproductive difficulties or a personal or family history of immune deficiency syndromes, blood dyscrasias, lymphoma, or leukemia, and those who are or have been exposed to medicinal drugs or chemicals known to affect the hematopoietic or lymphatic systems may be at higher risk from their exposure to BD. After the initial administration, the health questionnaire must be updated annually.

B. Complete Blood Count (CBC)

The medical screening and surveillance program requires an annual CBC, with differential and platelet count, to be provided for each employee with BD exposure. This test is to be performed on a blood sample obtained by phlebotomy of the venous system or, if technically feasible, from a fingerstick sample of capillary blood. The sample is to be analyzed by an accredited laboratory.

Abnormalities in a CBC may be due to a number of different etiologies. The concern for workers exposed to BD includes, but is not limited to, timely identification of lymphohematopoietic cancers, such as leukemia and non-Hodgkin's lymphoma. Abnormalities of portions of the CBC are identified by comparing an individual's results to those of an established range of normal values for males and females. A substantial change in any individual employee's CBC may also be viewed as "abnormal" for that individual even if all measurements fall within the population-based range of normal values. It is suggested that a flowsheet for laboratory values be included in each employee's medical record so that comparisons and trends in annual CBCs can be easily made.

A determination of the clinical significance of an abnormal CBC shall be the responsibility of the examining physician, other licensed health care professional, or medical specialist to whom the employee is referred. Ideally, an abnormal CBC should be compared to previous CBC measurements for the same employee, when available. Clinical common sense may dictate that a CBC value that is very slightly outside the normal range does not warrant medical concern. A CBC abnormality may also be the result of a temporary physical stressor, such as a transient viral illness, blood donation, or menorrhagia, or laboratory error. In these cases, the CBC should be repeated in a timely fashion, i.e., within 6 weeks, to verify that return to the normal range has occurred. A clinically significant abnormal CBC should result in removal of the employee from further exposure to BD. Transfer of the employee to other work duties in a BD-free environment would be the preferred recommendation.

C. Physical Examination

The medical screening and surveillance program requires an initial physical examination for workers exposed to BD; this examination is repeated once every three years. The initial physical examination should assess each worker's baseline general health and rule out clinical signs of medical conditions that may be caused by or aggravated by occupational BD exposure. The physical examination should be directed at identification of signs of lymphohematopoietic disorders, including lymph node enlargement, splenomegaly, and hepatomegaly.

Repeated physical examinations should update objective clinical findings that could be indicative of interim development of a lymphohematopoietic disorder, such as lymphoma, leukemia, or other blood abnormality. Physical examinations may also be provided on an as needed basis in order to follow up on a positive answer on the health questionnaire, or in response to an abnormal CBC. Physical examination of workers who will no longer be working in jobs with BD exposure are intended to rule out lymphohematopoietic disorders.

The need for physical examinations for workers concerned about adverse reproductive effects from their exposure to BD should be identified by the physician or other licensed health care professional and provided accordingly. For these workers, such consultations and examinations may relate to developmental toxicity and reproductive capacity.

Physical examination of workers acutely exposed to significant levels of BD should be especially directed at the respiratory system, eyes, sinuses, skin, nervous system, and any region

associated with particular complaints. If the worker has received a severe acute exposure, hospitalization may be required to assure proper medical management. Since this type of exposure may place workers at greater risk of blood abnormalities, a CBC must be obtained within 48 hours and repeated at one, two, and three months.

Appendix D Sampling and Analytical Method for 1,3-Butadiene (Non-Mandatory)

OSHA Method No.: 56.

Matrix: Air.

Target concentration: 1 ppm (2.21 mg/m³)

Procedure: Air samples are collected by drawing known volumes of air through sampling tubes containing charcoal adsorbent that has been coated with 4-tert-butylcatechol. The samples are desorbed with carbon disulfide and then analyzed by gas chromatography using a flame ionization detector.

Recommended sampling rate and air volume: 0.05 L/min and 3 L.

Detection limit of the overall procedure: 90 ppb (200 ug/m³) (based on 3 L air volume).

Reliable quantitation limit: 155 ppb (343 ug/m³) (based on 3 L air volume).

Standard error of estimate at the target concentration: 6.5%.

Special requirements: The sampling tubes must be coated with 4-tert-butylcatechol. Collected samples should be stored in a freezer.

Status of method: A sampling and analytical method has been subjected to the established evaluation procedures of the Organic Methods Evaluation Branch, OSHA Analytical Laboratory, Salt Lake City, Utah 84165.

1. Background

This work was undertaken to develop a sampling and analytical procedure for BD at 1 ppm. The current method recommended by OSHA for collecting BD uses activated coconut shell charcoal as the sampling medium (Ref. 5.2). This method was found to be inadequate for use at low BD levels because of sample instability.

The stability of samples has been significantly improved through the use of a specially cleaned charcoal that is coated with 4-tert-butylcatechol (TBC). TBC is a polymerization inhibitor for BD (Ref. 5.3).

1.1.1 Toxic effects

Symptoms of human exposure to BD include irritation of the eyes, nose and throat. It can also cause coughing, drowsiness and fatigue. Dermatitis and frostbite can result from skin exposure to liquid BD. (Ref. 5.1)

NIOSH recommends that BD be handled in the workplace as a potential occupational carcinogen. This recommendation is based on two inhalation studies that resulted in cancers at multiple sites in rats and in mice. BD has also demonstrated mutagenic activity in the presence of a liver microsomal activating system. It has also been reported to have adverse reproductive effects. (Ref. 5.1)

1.1.2. Potential workplace exposure

About 90% of the annual production of BD is used to manufacture styrene-butadiene rubber and Polybutadiene rubber. Other uses include: Polychloroprene rubber, acrylonitrile butadiene-styrene resins, nylon intermediates, styrene-butadiene latexes, butadiene polymers, thermoplastic elastomers, nitrile resins, methyl methacrylate-butadiene styrene resins and chemical intermediates. (Ref. 5.1)

1.1.3. Physical properties (Ref. 5.1)

CAS No.: 106-99-0

Molecular weight: 54.1

Appearance: Colorless gas

Boiling point: -4.41 °C (760 mm Hg)

Freezing point: -108.9 °C

Vapor pressure: 2 atm @ 15.3 °C; 5 atm (@) 47 °C

Explosive limits: 2 to 11.5% (by volume in air)

Odor threshold: 0.45 ppm

Structural formula: $\text{H}_2\text{C}=\text{CHCH}=\text{CH}_2$

Synonyms: BD; biethylene; bivinyl; butadiene; divinyl; buta-1,3-diene; alpha-gamma-butadiene; erythrene; NCI-C50602; pyrrolylene; vinylethylene.

1.2. Limit defining parameters

The analyte air concentrations listed throughout this method are based on an air volume of 3 L and a desorption volume of 1 mL. Air concentrations listed in ppm are referenced to 25 °C and 760 mm Hg.

1.2.1. Detection limit of the analytical procedure

The detection limit of the analytical procedure was 304 pg per injection. This was the amount of BD that gave a response relative to the interferences present in a standard.

1.2.2. Detection limit of the overall procedure

The detection limit of the overall procedure was 0.60 µg per sample (90 ppb or 200 µg/m³). This amount was determined graphically. It was the amount of analyte that, when spiked on the sampling device, would allow recovery approximately equal to the detection limit of the analytical procedure.

1.2.3. Reliable quantitation limit

The reliable quantitation limit was 1.03 µg per sample (155 ppb or 343 µg/m³). This was the smallest amount of analyte that could be quantitated within the limits of a recovery of at least 75% and a precision ($\pm 1.96 \text{ SD}$) of $\pm 25\%$ or better.

1.2.4. Sensitivity¹

The sensitivity of the analytical procedure over a concentration range representing 0.6 to 2 times the target concentration, based on the recommended air volume, was 387 area units per µg/mL. This value was determined from the slope of the calibration curve. The sensitivity may vary with the particular instrument used in the analysis.

1.2.5. Recovery

The recovery of BD from samples used in storage tests remained above 77% when the samples were stored at ambient temperature and above 94% when the samples were stored at refrigerated temperature. These values were determined from regression lines that were calculated from the storage data. The recovery of the analyte from the collection device must be at least 75% following storage.

1.2.6. Precision (analytical method only)

The pooled coefficient of variation obtained from replicate determinations of analytical standards over the range of 0.6 to 2 times the target concentration was 0.011.

1.2.7. Precision (overall procedure)

The precision at the 95% confidence level for the refrigerated temperature storage test was $\pm 12.7\%$. This value includes an additional $\pm 5\%$ for sampling error. The overall procedure must provide results at the target concentrations that are $\pm 25\%$ at the 95% confidence level.

1.2.8. Reproducibility

Samples collected from a controlled test atmosphere and a draft copy of this procedure were given to a chemist unassociated with this evaluation. The average recovery was 97.2% and the standard deviation was 6.2%.

2. Sampling procedure

2.1. Apparatus

2.1.1. Samples are collected by use of a personal sampling pump that can be calibrated to within $\pm 5\%$ of the recommended 0.05 L/min sampling rate with the sampling tube in line.

2.1.2. Samples are collected with laboratory prepared sampling tubes. The sampling tube is constructed of silane-treated glass and is about 5-cm long. The ID is 4 mm and the OD is 6 mm. One end of the tube is tapered so that a glass wool end plug will hold the contents of the tube in place during sampling. The opening in the tapered end of the sampling tube is at least one-half the ID of the tube (2 mm). The other end of the sampling tube is open to its full 4-mm ID to facilitate packing of the tube. Both ends of the tube are fire-polished for safety. The tube is packed with 2 sections of pretreated charcoal that has been coated with TBC. The tube is packed with a 50-mg backup section, located nearest the tapered end, and with a 100-mg sampling section of charcoal. The two sections of coated adsorbent are separated and retained with small plugs of silanized glass wool. Following packing, the sampling tubes are sealed with two 7/32-inch OD plastic end caps. Instructions for the pretreatment and coating of the charcoal are presented in Section 4.1 of this method.

- 2.2. Reagents
None required.
- 2.3. Technique
- 2.3.1. Properly label the sampling tube before sampling and then remove the plastic end caps.
 - 2.3.2. Attach the sampling tube to the pump using a section of flexible plastic tubing such that the larger front section of the sampling tube is exposed directly to the atmosphere. Do not place any tubing ahead of the sampling tube. The sampling tube should be attached in the worker's breathing zone in a vertical manner such that it does not impede work performance.
 - 2.3.3. After sampling for the appropriate time, remove the sampling tube from the pump and then seal the tube with plastic end caps. Wrap the tube lengthwise.
 - 2.3.4. Include at least one blank for each sampling set. The blank should be handled in the same manner as the samples with the exception that air is not drawn through it.
 - 2.3.5. List any potential interferences on the sample data sheet.
 - 2.3.6. The samples require no special shipping precautions under normal conditions. The samples should be refrigerated if they are to be exposed to higher than normal ambient temperatures. If the samples are to be stored before they are shipped to the laboratory, they should be kept in a freezer. The samples should be placed in a freezer upon receipt at the laboratory.
- 2.4. Breakthrough
(Breakthrough was defined as the relative amount of analyte found on the backup section of the tube in relation to the total amount of analyte collected on the sampling tube. Five-percent breakthrough occurred after sampling a test atmosphere containing 2.0 ppm BD for 90 min at 0.05 L/min. At the end of this time 4.5 L of air had been sampled and 20.1 μg of the analyte was collected. The relative humidity of the sampled air was 80% at 23 °C.)
Breakthrough studies have shown that the recommended sampling procedure can be used at air concentrations higher than the target concentration. The sampling time, however, should be reduced to 45 min if both the expected BD level and the relative humidity of the sampled air are high.
- 2.5. Desorption efficiency
The average desorption efficiency for BD from TBC coated charcoal over the range from 0.6 to 2 times the target concentration was 96.4%. The efficiency was essentially constant over the range studied.
- 2.6. Recommended air volume and sampling rate
- 2.6.1. The recommended air volume is 3L.
 - 2.6.2. The recommended sampling rate is 0.05 L/min for 1 hour.
- 2.7. Interferences
There are no known interferences to the sampling method.
- 2.8. Safety precautions
- 2.8.1. Attach the sampling equipment to the worker in such a manner that it will not interfere with work performance or safety.
 - 2.8.2. Follow all safety practices that apply to the work area being sampled.
3. Analytical procedure
- 3.1. Apparatus
- 3.1.1. A gas chromatograph (GC), equipped with a flame ionization detector (FID)².
 - 3.1.2. A GC column capable of resolving the analytes from any interference³.
 - 3.1.3. Vials, glass 2-mL with Teflon-lined caps.
 - 3.1.4. Disposable Pasteur-type pipets, volumetric flasks, pipets and syringes for preparing samples and standards, making dilutions and performing injections.
- 3.2. Reagents
- 3.2.1. Carbon disulfide⁴.
The benzene contaminant that was present in the carbon disulfide was used as an internal standard (ISTD) in this evaluation.
 - 3.2.2. Nitrogen, hydrogen and air, GC grade.
 - 3.2.3. BD of known high purity⁵.
- 3.3. Standard preparation
- 3.3.1. Prepare standards by diluting known volumes of BD gas with carbon disulfide. This can be accomplished by injecting the appropriate volume of BD into the headspace

above the 1-mL of carbon disulfide contained in sealed 2-mL vial. Shake the vial after the needle is removed from the septum⁶.

- 3.3.2. The mass of BD gas used to prepare standards can be determined by use of the following equations:

$$MV=(760/BP)(273+t)/(273)(22.41)$$

Where:

MV = ambient molar volume

BP = ambient barometric pressure

T = ambient temperature

$\mu\text{g}/\mu\text{L} = 54.09/MV$

$\mu\text{g}/\text{standard} = (\mu\text{g}/\mu\text{L})(\mu\text{L})$ BD used to prepare the standard

3.4. Sample preparation

- 3.4.1. Transfer the 100-mg section of the sampling tube to a 2-mL vial. Place the 50-mg section in a separate vial. If the glass wool plugs contain a significant amount of charcoal, place them with the appropriate sampling tube section.
- 3.4.2. Add 1-mL of carbon disulfide to each vial.
- 3.4.3. Seal the vials with Teflon-lined caps and then allow them to desorb for one hour. Shake the vials by hand vigorously several times during the desorption period.
- 3.4.4. If it is not possible to analyze the samples within 4 hours, separate the carbon disulfide from the charcoal, using a disposable Pasteur-type pipet, following the one hour. This separation will improve the stability of desorbed samples.
- 3.4.5. Save the used sampling tubes to be cleaned and repacked with fresh adsorbent.

3.5. Analysis

- 3.5.1. GC Conditions
 Column temperature: 95 °C
 Injector temperature: 180 °C
 Detector temperature: 275 °C
 Carrier gas flow rate: 30 mL/min
 Injection volume: 0.80 μL
 GC column: 20-ft x 1/8-in OD stainless steel GC column containing 20% FFAP on 80/100 Chromabsorb W-AW-DMCS.
- 3.5.2. Chromatogram. See Section 4.2.
- 3.5.3. Use a suitable method, such as electronic or peak heights, to measure detector response.
- 3.5.4. Prepare a calibration curve using several standard solutions of different concentrations. Prepare the calibration curve daily. Program the integrator to report the results in $\mu\text{g}/\text{mL}$.
- 3.5.5. Bracket sample concentrations with standards.

3.6. Interferences (analytical)

- 3.6.1. Any compound with the same general retention time as the analyte and that also gives a detector response is a potential interference. Possible interferences should be reported by the industrial hygienist to the laboratory with submitted samples.
- 3.6.2. GC parameters (temperature, column, etc.) may be changed to circumvent interferences.
- 3.6.3. A useful means of structure designation is GC/MS. It is recommended that this procedure be used to confirm samples whenever possible.

3.7. Calculations

- 3.7.1. Results are obtained by use of calibration curves. Calibration curves are prepared by plotting detector response against concentration for each standard. The best line through the data points is determined by curve fitting.
- 3.7.2. The concentration, in $\mu\text{g}/\text{mL}$, for a particular sample is determined by comparing its detector response to the calibration curve. If any analyte is found on the backup section, this amount is added to the amount found on the front section. Blank corrections should be performed before adding the results together.
- 3.7.3. The BD air concentration can be expressed using the following equation:

$$\text{mg/m}^3 = (\text{A})(\text{B})/(\text{C})(\text{D})$$

Where:

A = $\mu\text{g/mL}$ from Section 3.7.2
 B = volume
 C = L of air sampled
 D = efficiency

3.7.4. The following equation can be used to convert results in mg/m^3 to ppm:

$$\text{ppm} = (\text{mg/m}^3)(24.46)/54.09$$

Where:

mg/m^3 = result from Section 3.7.3.
 24.46 = molar volume of an ideal gas at 760 mm Hg and 25 °C.

3.8. Safety precautions (analytical)

- 3.8.1. Avoid skin contact and inhalation of all chemicals.
- 3.8.2. Restrict the use of all chemicals to a fume hood whenever possible.
- 3.8.3. Wear safety glasses and a lab coat in all laboratory areas.
4. Additional Information
 - 4.1. A procedure to prepare specially cleaned charcoal coated with TBC
 - 4.1.1. Apparatus.
 - 4.1.1.1. Magnetic stirrer and stir bar.
 - 4.1.1.2. Tube furnace capable of maintaining a temperature of 700 °C and equipped with a quartz tube that can hold 30 g of charcoal⁸.
 - 4.1.1.3. A means to purge nitrogen gas through the charcoal inside the quartz tube.
 - 4.1.1.4. Water bath capable of maintaining a temperature of 60 °C.
 - 4.1.1.5. Miscellaneous laboratory equipment: One-liter vacuum flask, 1-L Erlenmeyer flask, 350-M1 Buchner funnel with a coarse fitted disc, 4-oz brown bottle, rubber stopper, Teflon tape etc.
 - 4.1.2. Reagents
 - 4.1.2.1. Phosphoric acid, 10% by weight, in water⁹.
 - 4.1.2.2. 4-tert-Butylcatechol (TBC)¹⁰.
 - 4.1.2.3. Specially cleaned coconut shell charcoal, 20/40 mesh¹¹.
 - 4.1.2.4. Nitrogen gas, GC grade.
 - 4.1.3. Procedure.

Weigh 30g of charcoal into a 500-mL Erlenmeyer flask. Add about 250 mL of 10% phosphoric acid to the flask and then swirl the mixture. Stir the mixture for 1 hour using a magnetic stirrer. Filter the mixture using a fitted Buchner funnel. Wash the charcoal several times with 250-mL portions of deionized water to remove all traces of the acid. Transfer the washed charcoal to the tube furnace quartz tube. Place the quartz tube in the furnace and then connect the nitrogen gas purge to the tube. Fire the charcoal to 700 °C. Maintain that temperature for at least 1 hour. After the charcoal has cooled to room temperature, transfer it to a tared beaker. Determine the weight of the charcoal and then add an amount of TBC that is 10% of the charcoal, by weight.

CAUTION-TBC is toxic and should only be handled in a fume hood while wearing gloves.

Carefully mix the contents of the beaker and then transfer the mixture to a 4-oz bottle. Stopper the bottle with a clean rubber stopper that has been wrapped with Teflon tape. Clamp the bottle in a water bath so that the water level is above the charcoal level. Gently heat the bath to 60 °C and then maintain that temperature for 1 hour. Cool the charcoal to room temperature and then transfer the coated charcoal to a suitable container.

The coated charcoal is now ready to be packed into sampling tubes. The sampling tubes should be stored in a sealed container to prevent contamination. Sampling tubes should be stored in the dark at room temperature. The sampling tubes should be segregated by coated adsorbent lot number.

4.2 Chromatograms

The chromatograms were obtained using the recommended analytical method. The chart speed was set at 1 cm/min for the first three min and then at 0.2 cm/min for the time remaining in the analysis.

The peak that elutes just before BD is a reaction product between an impurity on the charcoal and TBC. This peak is always present, but it is easily resolved from the analyte. The peak that elutes immediately before benzene is an oxidation product of TBC.

5. References

- 5.1. "Current Intelligence Bulletin 41, 1,3-Butadiene", U.S. Dept. of Health and Human Services, Public Health Service, Center for Disease Control, NIOSH.
- 5.2. "NIOSH Manual of Analytical Methods", 2nd ed; U.S. Dept. of Health Education and Welfare, National Institute for Occupational Safety and Health: Cincinnati, OH. 1977, Vol. 2, Method No. S91 DHEW (NIOSH) Publ. (US), No. 77-157-B.
- 5.3. Hawley, G.C., Ed. "The Condensed Chemical Dictionary", 8th ed.; Van Nostrand Rienhold Company: New York, 1971; 139.5.4. Chem. Eng. News (June 10, 1985), (63), 22-66.

Appendix E [Removed and Reserved]

¹ The reliable quantitation limit and detection limits reported in the method are based upon optimization of the instrument for the smallest possible amount of analyte. When the target concentration of an analyte is exceptionally higher than these limits, they may not be attainable at the routine operation parameters.

² A Hewlett-Packard Model 5840A GC was used for this evaluation. Injections were performed using a Hewlett-Packard Model 7671A automatic sampler.

³ A 20-ft x 1/8-inch OD stainless steel GC column containing 20% FFAP on 80/100 mesh Chromabsorb W-AW-DMCS was used for this evaluation.

⁴ Fisher Scientific Company A.C.S. Reagent Grade solvent was used in this evaluation.

⁵ Matheson Gas Products, CP Grade 1,3-butadiene was used in this study.

⁶ A standard containing 7.71 µg/mL (at ambient temperature and pressure) was prepared by diluting 4 µL of the gas with 1-mL of carbon disulfide.

⁸ A Lindberg Type 55035 Tube furnace was used in this evaluation.

⁹ Baker Analyzed" Reagent grade was diluted with water for use in this evaluation.

¹⁰ The Aldrich Chemical Company 99% grade was used in this evaluation.

¹¹ Specially cleaned charcoal was obtained from Supelco, Inc. for use in this evaluation. The cleaning process used by Supelco is proprietary.

**APPENDIX F
MEDICAL QUESTIONNAIRES
(Non-mandatory)**

1,3-Butadiene (BD) Initial Health Questionnaire

DIRECTIONS:

You have been asked to answer the questions on this form because you work with BD (butadiene). These questions are about your work, medical history, and health concerns. Please do your best to answer all of the questions. If you need help, please tell the doctor or health care professional who reviews this form.

This form is a confidential medical record. Only information directly related to your health and safety on the job may be given to your employer. Personal health information will not be given to anyone without your consent.

Date: _____

Name: _____ SSN ____/____/____
 Last First MI

Job Title: _____

Company's Name: _____

Supervisor's Name: _____ Supervisor's Phone No.: () _____

Work History

- Please list all jobs you have had in the past, starting with the job you have now and moving back in time to your first job. (For more space, write on the back of this page.)

Main Job Duty	Years	Company Name City, State	Chemicals
1			
2			
3			
4			
5			
6			
7			
8			

- Please describe what you do during a typical work day. Be sure to tell about you work with BD.

- Please check any of these chemicals that you work with now or have worked with in the past:

- benzene _____
- glues _____
- toluene _____
- inks, dyes _____

- other solvents, grease cutters _____
- insecticides (like DDT, lindane, etc.) _____
- paints, varnishes, thinners, strippers _____
- dusts _____
- carbon tetrachloride ("carbon tet") _____
- arsine _____
- carbon disulfide _____
- lead _____
- cement _____
- petroleum products _____
- nitrites _____

4. Please check the protective clothing or equipment you use at the job you have now:

- gloves _____
- coveralls _____
- respirator _____
- dust mask _____
- safety glasses, goggles _____

Please circle your answer of yes or no.

- 5. Does your protective clothing or equipment fit you properly? Yes no
- 6. Have you ever made changes in your protective clothing or equipment to make it fit better?
Yes No
- 7. Have you been exposed to BD when you were not wearing protective clothing or equipment?
Yes No
- 8. Where do you eat, drink and/or smoke when you are at work?
(Please check all that apply.)
 - Cafeteria/restaurant/snack bar _____
 - Break room/employee lounge _____
 - Smoking lounge _____
 - At my work station _____

Please circle your answer.

- 9. Have you been exposed to radiation (like x-rays or nuclear material) at the job you have now or at past jobs? Yes No
- 10. Do you have any hobbies that expose you to dusts or chemicals (including paints, glues, etc.)?
Yes No
- 11. Do you have any second or side jobs? Yes No

If yes, what are your duties there?

12. Were you in the military? Yes No

If yes, what did you do in the military?

Family Health History

1. In the FAMILY MEMBER column, across from the disease name, write that family member, if any, had the disease.

DISEASE	FAMILY MEMBER
Cancer	
Lymphoma	
Sickle Cell Disease or Trait	
Immune Disease	
Leukemia	
Anemia	

2. Please fill in the following information about family health:

Relative	Alive?	Age at death?	Cause of death?
Father			
Mother			
Brother/Sister			
Brother/Sister			
Brother/Sister			

PERSONAL HEALTH HISTORY

Birth Date ___/___/___ Age ___ Sex ___ Height ___ Weight ___

Please circle your answer.

1. Do you smoke any tobacco products? Yes No
2. Have you ever had any kind of surgery or operation? Yes No

If yes, what type of surgery:

3. Have you ever been in the hospital for any other reasons? Yes No

If yes, please describe the reason:

4. Do you have any on-going or current medical problems or conditions? Yes No

If yes, please describe:

5. Do you now have or have you ever had any of the following?

Please check all that apply to you.

unexplained fever	___	bruising easily	___	still birth	___
anemia ("low blood")	___	lupus	___	eye redness	___
HIV/AIDS	___	weight loss	___	lumps you can feel	___
weakness	___	kidney problems	___	child with birth defect	___
sickle cell	___	enlarged lymph nodes	___	autoimmune disease	___
miscarriage	___	liver disease	___	overly tired	___
skin rash	___	cancer	___	lung problems	___
bloody stools	___	infertility	___	rheumatoid arthritis	___
leukemia/lymphoma	___	drinking problems	___	mononucleosis ("mono")	___
neck mass/swelling	___	thyroid problems	___	nagging cough	___
wheezing	___	night sweats	___	Yellowing of skin	___
chest pain	___				

Please circle your answer.

6. Do you have any symptoms or health problems that you think may be related to your work with BD?
Yes No

If yes, please describe:

7. Have any of your co-workers had similar symptoms or problems? Yes No don't know

If yes, please describe:

8. Do you notice any irritation of your eyes, nose, throat, lungs, or skin when working with BD?
Yes No

9. Do you notice any blurred vision, coughing, drowsiness, nausea, or headache when working with BD? Yes No

10. Do you take any medications (including birth control or over-the-counter)? Yes No

If yes, please list:

11. Are you allergic to any medication, food, or chemicals? Yes No

If yes, please list:

12. Do you have any health conditions not covered by this questionnaire that you think are affected by your work with BD? Yes No

If yes, please explain:

13. Did you understand all the questions? Yes No

Signature

1,3-Butadiene (BD) Update Health Questionnaire

DIRECTIONS:

You have been asked to answer the questions on this form because you work with BD (butadiene). These questions ask about changes in your work, medical history, and health concerns since the last time you were evaluated. Please do your best to answer all of the questions. If you need help, please tell the doctor or health care professional who reviews this form.

This form is a confidential medical record. Only information directly related to your health and safety on the job may be given to your employer. Personal health information will not be given to anyone without your consent.

Date: _____

Name: _____ SSN ____/____/____
Last First MI

Job Title: _____

Company's Name: _____

Supervisor's Name: _____ Supervisor's Phone No.: () _____

Present Work History

1. Please describe any NEW duties that you have at your job:

2. Please list any additional job titles you have:

Please circle your answer.

3. Are you exposed to any other chemicals in your work since the last time you were evaluated for exposure to BD? Yes No

If yes, please list what they are:

4. Does your personal protective equipment and clothing fit you properly? Yes No
5. Have you made changes in this equipment or clothing to make it fit better? Yes No
6. Have you been exposed to BD when you were not wearing protective equipment or clothing?
Yes No
7. Are you exposed to any NEW chemicals at home or while working on hobbies? Yes No

If yes, please list what they are:

8. Since your last BD health evaluation, have you started working any new second or side jobs?
Yes No

If yes, what are your duties there?

Personal Health History

1. What is your current weight? _____ pounds
2. Have you been diagnosed with any new medical conditions or illness since your last evaluation?
Yes No

If yes, please tell what they are:

3. Since your last evaluation, have you been in the hospital for any illnesses, injuries, or surgery?
Yes No

If yes, please describe:

4. Do you have any of the following?

Please place a check for all that apply to you.

unexplained fever	<input type="checkbox"/>	bruising easily	<input type="checkbox"/>	still birth	<input type="checkbox"/>
anemia ("low blood")	<input type="checkbox"/>	lupus	<input type="checkbox"/>	eye redness	<input type="checkbox"/>
HIV/AIDS	<input type="checkbox"/>	weight loss	<input type="checkbox"/>	lumps you can feel	<input type="checkbox"/>
weakness	<input type="checkbox"/>	kidney problems	<input type="checkbox"/>	child with birth defect	<input type="checkbox"/>
sickle cell	<input type="checkbox"/>	enlarged lymph nodes	<input type="checkbox"/>	autoimmune disease	<input type="checkbox"/>
miscarriage	<input type="checkbox"/>	liver disease	<input type="checkbox"/>	overly tired	<input type="checkbox"/>
skin rash	<input type="checkbox"/>	cancer	<input type="checkbox"/>	lung problems	<input type="checkbox"/>
bloody stools	<input type="checkbox"/>	infertility	<input type="checkbox"/>	rheumatoid arthritis	<input type="checkbox"/>
leukemia/lymphoma	<input type="checkbox"/>	drinking problems	<input type="checkbox"/>	mononucleosis ("mono")	<input type="checkbox"/>
neck mass/swelling	<input type="checkbox"/>	thyroid problems	<input type="checkbox"/>	nagging cough	<input type="checkbox"/>
wheezing	<input type="checkbox"/>	night sweats	<input type="checkbox"/>	Yellowing of skin	<input type="checkbox"/>
chest pain	<input type="checkbox"/>				

Please circle your answer.

5. Do you have any symptoms or health problems that you think may be related to your work with BD? Yes No

If yes, please describe

6. Have any of your co-workers had similar symptoms or problems? Yes No Don't know

If yes, please describe:

7. Do you notice any irritation of your eyes, nose, throat, lungs, or skin when working with BD? Yes No

8. Do you notice any blurred vision, coughing, drowsiness, nausea, or headache when working with BD? Yes No

9. Have you been taking any NEW medications (including birth control or over-the-counter)? Yes No

If yes, please list:

10. Have you developed any NEW allergies to medications, food, or chemicals? Yes No

If yes, please explain:

11. Did you have any health conditions not covered by this questionnaire that you think are affected by your work with BD? Yes No

If yes, please explain:

12. Did you understand all the questions? Yes No

Signature

(b) Definitions. As used in 29 CFR 1910.1051 and applied to this section:

"29 CFR 1910.20" means section 12-202-3.

"29 CFR 1910.38" means chapter 12-71.1.

"29 CFR 1910.106" means chapter 12-74.1.

"29 CFR 1910.120" means chapter 12-74.1.

"29 CFR 1910.133" means section 1910.133 in chapter 12-64.1.

"29 CRF 1910.134" means section 1910.134 in chapter 12-64.1.

"29 CFR 1910.1200" means section 1910.1200 in chapter 12-203.1.

"29 CFR 1926.59" means section 1910.1200 in chapter 12-203.1.

"Assistant Secretary" means the director of the department of labor.

[Eff 5/2/97; am 7/6/98; am 5/21/04; am 3/31/06; am 12/21/06] (Auth: HRS §396-4) (Imp: HRS §396-4)

§12-202-41 Methylene Chloride. (a) Incorporation of federal standard.

Title 29, Code of Federal Regulations, section 1910.1052, entitled "Methylene Chloride", published by the Office of the Federal Register, National Archives and Records Administration, on January 10, 1997; and the amendments published on August 8, 1997; September 15, 1997; October 20, 1997; December 18, 1997; January 8, 1998; April 23, 1998; September 22, 1998; April 3, 2006; and August 24, 2006, are made a part of this section, except as provided in subsection (b).

§1910.1052 Methylene Chloride.

This occupational health standard establishes requirements for employers to control occupational exposure to methylene chloride (MC). Employees exposed to MC are at increased risk of developing cancer, adverse effects on the heart, central nervous system and liver, and skin or eye irritation. Exposure may occur through inhalation, by absorption through the skin, or through contact with the skin. MC is a solvent that is used in many different types of work activities, such as paint stripping, polyurethane foam manufacturing, and cleaning and degreasing. Under the requirements of paragraph (d) of this section, each covered employer must make an initial determination of each employee's exposure to MC. If the employer determines that employees are exposed below the action level, the only other provisions of this section that apply are that a record must be made of the determination, the employees must receive information and training under paragraph (l) of this section and, where appropriate, employees must be protected from contact with liquid MC under paragraph (h) of this section. The provisions of the MC standard are as follows:

- (a) Scope and application. This section applies to all occupational exposures to methylene chloride (MC), Chemical Abstracts Service Registry Number 75-09-2, in general industry, construction and shipyard employment.
- (b) Definitions. For the purposes of this section, the following definitions shall apply:
- Action level** means a concentration of airborne MC of 12.5 parts per million (ppm) calculated as an eight (8)-hour time-weighted average (TWA).
- Assistant Secretary** means the Assistant Secretary of Labor for Occupational Safety and Health, U.S. Department of Labor, or designee.
- Authorized person** means any person specifically authorized by the employer and required by work duties to be present in regulated areas, or any person entering such an area as a designated representative of employees for the purpose of exercising the right to observe monitoring and measuring procedures under paragraph (d) of this section, or any other person authorized by the OSH Act or regulations issued under the Act.
- Director** means the Director of the National Institute for Occupational Safety and Health, U.S. Department of Health and Human Services, or designee.
- Emergency** means any occurrence, such as, but not limited to, equipment failure, rupture of containers, or failure of control equipment, that results, or is likely to result in an uncontrolled release of MC. If an incidental release of MC can be controlled by employees such as maintenance personnel at the time of release and in accordance with the leak/spill provisions required by paragraph (f) of this section, it is not considered an emergency as defined by this standard.
- Employee exposure** means exposure to airborne MC that occurs or would occur if the employee were not using respiratory protection.
- Methylene chloride (MC)** means an organic compound with chemical formula, CH₂CL₂. Its Chemical Abstracts Service Registry Number is 75-09-2. Its molecular weight is 84.9 g/mole.
- Physician or other licensed health care professional** is an individual whose legally permitted scope of practice (i.e., license, registration, or certification) allows him or her to independently provide or be delegated the responsibility to provide some or all of the health care services required by paragraph (j) of this section.
- Regulated area** means an area, demarcated by the employer, where an employee's exposure to airborne concentrations of MC exceeds or can reasonably be expected to exceed either the 8-hour TWA PEL or the STEL.
- Symptom** means central nervous system effects such as headaches, disorientation, dizziness, fatigue, and decreased attention span; skin effects such as chapping, erythema, cracked skin, or skin burns; and cardiac effects such as chest pain or shortness of breath.
- This section** means this methylene chloride standard.
- (c) Permissible exposure limits (PELs).
- (1) Eight-hour time-weighted average (TWA) PEL. The employer shall ensure that no employee is exposed to an airborne concentration of MC in excess of twenty-five parts of MC per million parts of air (25 ppm) as an 8-hour TWA.

- (2) Short-term exposure limit (STEL). The employer shall ensure that no employee is exposed to an airborne concentration of MC in excess of one hundred and twenty-five parts of MC per million parts of air (125 ppm) as determined over a sampling period of fifteen minutes.
- (d) Exposure monitoring.
- (1) Characterization of employee exposure.
- (i) Where MC is present in the workplace, the employer shall determine each employee's exposure by either:
- (A) Taking a personal breathing zone air sample of each employee's exposure; or
 - (B) Taking personal breathing zone air samples that are representative of each employee's exposure.
- (ii) Representative samples. The employer may consider personal breathing zone air samples to be representative of employee exposures when they are taken as follows:
- (A) 8-hour TWA PEL. The employer has taken one or more personal breathing zone air samples for at least one employee in each job classification in a work area during every work shift, and the employee sampled is expected to have the highest MC exposure.
 - (B) Short-term exposure limits. The employer has taken one or more personal breathing zone air samples that indicate the highest likely 15-minute exposures during such operations for at least one employee in each job classification in the work area during every work shift, and the employee sampled is expected to have the highest MC exposure.
 - (C) Exception. Personal breathing zone air samples taken during one work shift may be used to represent employee exposures on other work shifts where the employer can document that the tasks performed and conditions in the workplace are similar across shifts.
- (iii) Accuracy of monitoring. The employer shall ensure that the methods used to perform exposure monitoring produce results that are accurate to a confidence level of 95 percent, and are:
- (A) Within plus or minus 25 percent for airborne concentrations of MC above the 8-hour TWA PEL or the STEL; or
 - (B) Within plus or minus 35 percent for airborne concentrations of MC at or above the action level but at or below the 8-hour TWA PEL.
- (2) Initial determination. Each employer whose employees are exposed to MC shall perform initial exposure monitoring to determine each affected employee's exposure, except under the following conditions:
- (i) Where objective data demonstrate that MC cannot be released in the workplace in airborne concentrations at or above the action level or above the STEL. The objective data shall represent the highest MC exposures likely to occur under reasonably foreseeable conditions of processing, use, or handling. The employer shall document the objective data exemption as specified in paragraph (m) of this section;
 - (ii) Where the employer has performed exposure monitoring within 12 months prior to April 10, 1997 and that exposure monitoring meets all other requirements of this section, and was conducted under conditions substantially equivalent to existing conditions; or
 - (iii) Where employees are exposed to MC on fewer than 30 days per year (e.g., on a construction site), and the employer has measurements by direct-reading instruments that give immediate results (such as a detector tube) and that provide sufficient information regarding employee exposures to determine what control measures are necessary to reduce exposures to acceptable levels.
- (3) Periodic monitoring. Where the initial determination shows employee exposures at or above the action level or above the STEL, the employer shall establish an exposure monitoring program for periodic monitoring of employee exposure to MC in accordance with Table 1:

Table 1.--Six Initial Determination Exposure Scenarios and Their Associated Monitoring Frequencies

Exposure scenario	Required monitoring activity
Below the action level and at or below the STEL	No 8-hour TWA or STEL monitoring required.
Below the action level and above the STEL	No 8-hour TWA monitoring required; monitor STEL exposures every three months.
At or above the action level, at or below the TWA, and at or below the STEL	Monitor 8-hour TWA exposures every six months.
At or above the action level, at or below the TWA, and above the STEL	Monitor 8-hour TWA exposures every six months and monitor STEL exposures every three months.
Above the TWA and at or below the STEL	Monitor 8-hour TWA exposures every three months. In addition, without regard to the last sentence of the note to paragraph (d)(3), the following employers must monitor STEL exposures every three months until either the date by that they must achieve the 8-hour TWA PEL under paragraph (n) of this section or the date by that they in fact achieve the 8-hour TWA PEL, whichever comes first; employers engaged in polyurethane foam manufacturing; foam fabrication; furniture refinishing; general aviation aircraft stripping, product formulation; use of MC-based adhesives for boat building and repair, recreational vehicle manufacture, van conversion, or upholstery; and use of MC in construction work for restoration and preservation of buildings, painting and paint removal, cabinet making, or floor refinishing and resurfacing.
Above the TWA and above the STEL	Monitor 8-hour TWA exposures and STEL exposures every three months.

[Note to paragraph (d)(3): The employer may decrease the frequency of 8-hour TWA exposure monitoring to every six months when at least 2 consecutive measurements taken at least seven days apart show exposures to be at or below the 8-hour TWA PEL. The employer may discontinue the periodic 8-hour TWA monitoring for employees where at least two consecutive measurements taken at least seven days apart are below the action level. The employer may discontinue the periodic STEL monitoring for employees where at least two consecutive measurements taken at least 7 days apart are at or below the STEL.]

- (4) Additional monitoring.
- (i) The employer shall perform exposure monitoring when a change in workplace conditions indicates that employee exposure may have increased. Examples of situations that may require additional monitoring include changes in production, process, control equipment, or work practices, or a leak, rupture, or other breakdown.
 - (ii) Where exposure monitoring is performed due to a spill, leak, rupture or equipment breakdown, the employer shall clean-up the MC and perform the appropriate repairs before monitoring.
- (5) Employee notification of monitoring results.
- (i) The employer shall, within 15 working days after the receipt of the results of any monitoring performed under this section, notify each affected employee of these results in writing, either individually or by posting of results in an appropriate location that is accessible to affected employees.
 - (ii) Whenever monitoring results indicate that employee exposure is above the 8-hour TWA PEL or the STEL, the employer shall describe in the written notification the corrective action being taken to reduce employee exposure to or below the 8-hour TWA PEL or STEL and the schedule for completion of this action.
- (6) Observation of monitoring.
- (i) Employee observation. The employer shall provide affected employees or their

designated representatives an opportunity to observe any monitoring of employee exposure to MC conducted in accordance with this section.

- (ii) Observation procedures. When observation of the monitoring of employee exposure to MC requires entry into an area where the use of protective clothing or equipment is required, the employer shall provide, at no cost to the observer(s), and the observer(s) shall be required to use such clothing and equipment and shall comply with all other applicable safety and health procedures.
- (e) Regulated areas.
- (1) The employer shall establish a regulated area wherever an employee's exposure to airborne concentrations of MC exceeds or can reasonably be expected to exceed either the 8-hour TWA PEL or the STEL.
 - (2) The employer shall limit access to regulated areas to authorized persons.
 - (3) The employer shall supply a respirator, selected in accordance with paragraph (h)(3) of this section; to each person who enters a regulated area and shall require each affected employee to use that respirator whenever MC exposures are likely to exceed the 8-hour TWA PEL or STEL.
- [Note to paragraph (e)(3):** An employer who has implemented all feasible engineering, work practice and administrative controls (as required in paragraph (f) of this section), and who has established a regulated area (as required by paragraph (e)(1) of this section) where MC exposure can be reliably predicted to exceed the 8-hour TWA PEL or the STEL only on certain days (for example, because of work or process schedule) would need to have affected employees use respirators in that regulated area only on those days.]
- (4) The employer shall ensure that, within a regulated area, employees do not engage in non-work activities that may increase dermal or oral MC exposure.
 - (5) The employer shall ensure that while employees are wearing respirators, they do not engage in activities (such as taking medication or chewing gum or tobacco) that interfere with respirator seal or performance.
 - (6) The employer shall demarcate regulated areas from the rest of the workplace in any manner that adequately establishes and alerts employees to the boundaries of the area and minimizes the number of authorized employees exposed to MC within the regulated area.
 - (7) An employer at a multi-employer worksite who establishes a regulated area shall communicate the access restrictions and locations of these areas to all other employers with work operations at that worksite.
- (f) Methods of compliance.
- (1) Engineering and work practice controls. The employer shall institute and maintain the effectiveness of engineering controls and work practices to reduce employee exposure to or below the PELs except to the extent that the employer can demonstrate that such controls are not feasible. Wherever the feasible engineering controls and work practices that can be instituted are not sufficient to reduce employee exposure to or below the 8-TWA PEL or STEL, the employer shall use them to reduce employee exposure to the lowest levels achievable by these controls and shall supplement them by the use of respiratory protection that complies with the requirements of paragraph (g) of this section.
 - (2) Prohibition of rotation. The employer shall not implement a schedule of employee rotation as a means of compliance with the PELs.
 - (3) Leak and spill detection.
 - (i) The employer shall implement procedures to detect leaks of MC in the workplace. In work areas where spills may occur, the employer shall make provisions to contain any spills and to safely dispose of any MC-contaminated waste materials.
 - (ii) The employer shall ensure that all incidental leaks are repaired and that incidental spills are cleaned promptly by employees who use the appropriate personal protective equipment and are trained in proper methods of cleanup. [Note to paragraph (f)(3)(ii): See Appendix A of this section for examples of procedures that satisfy this requirement. Employers covered by this standard may also be subject to the hazardous waste and emergency response provisions contained in 29 CFR 1910.120 (q).]
- (g) Respiratory protection.
- (1) General. For employees who use respirators required by this section, the employer must provide respirators that comply with the requirements of this paragraph. Respirators must be used during:

- (i) Periods when an employee's exposure to MC exceeds the 8-hour TWA PEL, or STEL (for example, when an employee is using MC in a regulated area).
 - (ii) Periods necessary to install or implement feasible engineering and work-practice controls.
 - (iii) A few work operations, such as some maintenance operations and repair activities, for that the employer demonstrates that engineering and work-practice controls are infeasible.
 - (iv) Work operations for that feasible engineering and work-practice controls are not sufficient to reduce employee exposures to or below the PELs.
 - (v) Emergencies.
- (2) Respirator program.
- (i) The employer must implement a respiratory protection program in accordance with 29 CFR 1910.134 (b) through (m) (except (d)(1)(iii) and (d)(3)(iii)(B)(1) and (2)).
 - (ii) Employers who provide employees with gas masks with organic-vapor canister for the purpose of emergency escape must replace the canisters after any emergency use and before the gas masks are returned to service.
- (3) Respirator selection. Employers must:
- (i) Select, and provide to employees, the appropriate atmosphere-supplying respirator specified in paragraph (d)(3)(i)(A) of 29 CFR 1910.134; however, employers must not select or use half masks of any type because MC may cause eye irritation or damage.
 - (ii) For emergency escape, provide employees with one of the following respirator options: A self-contained breathing apparatus operated in the continuous-flow or pressure-demand mode; or a gas mask with an organic vapor canister.
- (4) Medical evaluation. Before having an employee use a supplied-air respirator in the negative-pressure mode, or a gas mask with an organic-vapor canister for emergency escape, the employer must:
- (i) Have a physician or other licensed health-care professional (PLHCP) evaluate the employee's ability to use such respiratory protection.
 - (ii) Ensure that the PLHCP provides their findings in a written opinion to the employee and the employer.
- (h) Protective Work Clothing and Equipment.**
- (1) Where needed to prevent MC-induced skin or eye irritation, the employer shall provide clean protective clothing and equipment that is resistant to MC, at no cost to the employee, and shall ensure that each affected employee uses it. Eye and face protection shall meet the requirements of 29 CFR 1910.133 or 29 CFR 1915.153, as applicable.
 - (2) The employer shall clean, launder, repair and replace all protective clothing and equipment required by this paragraph as needed to maintain their effectiveness.
 - (3) The employer shall be responsible for the safe disposal of such clothing and equipment. [Note to paragraph (h)(4): See Appendix A for examples of disposal procedures that will satisfy this requirement.]
- (i) Hygiene facilities.**
- (1) If it is reasonably foreseeable that employees' skin may contact solutions containing 0.1 percent or greater MC (for example, through splashes, spills or improper work practices), the employer shall provide conveniently located washing facilities capable of removing the MC, and shall ensure that affected employees use these facilities as needed.
 - (2) If it is reasonably foreseeable that an employee's eyes may contact solutions containing 0.1 percent or greater MC (for example through splashes, spills or improper work practices), the employer shall provide appropriate eyewash facilities within the immediate work area for emergency use, and shall ensure that affected employees use those facilities when necessary.
- (j) Medical surveillance.**
- (1) Affected employees. The employer shall make medical surveillance available for employees who are or may be exposed to MC as follows:
 - (i) At or above the action level on 30 or more days per year, or above the 8-hour TWA PEL or the STEL on 10 or more days per year;
 - (ii) Above the 8-TWA PEL or STEL for any time period where an employee has been identified by a physician or other licensed health care professional as being at risk from cardiac disease or from some other serious MC-related health condition and such employee requests inclusion in the medical surveillance program;

- (iii) During an emergency.
- (2) Costs. The employer shall provide all required medical surveillance at no cost to affected employees, without loss of pay and at a reasonable time and place.
- (3) Medical personnel. The employer shall ensure that all medical surveillance procedures are performed by a physician or other licensed health care professional, as defined in paragraph (b) of this section.
- (4) Frequency of medical surveillance. The employer shall make medical surveillance available to each affected employee as follows:
 - (i) Initial surveillance. The employer shall provide initial medical surveillance under the schedule provided by paragraph (n)(2)(iii) of this section, or before the time of initial assignment of the employee, whichever is later. The employer need not provide the initial surveillance if medical records show that an affected employee has been provided with medical surveillance that complies with this section within 12 months before April 10, 1997.
 - (ii) Periodic medical surveillance. The employer shall update the medical and work history for each affected employee annually. The employer shall provide periodic physical examinations, including appropriate laboratory surveillance, as follows:
 - (A) For employees 45 years of age or older, within 12 months of the initial surveillance or any subsequent medical surveillance; and
 - (B) For employees younger than 45 years of age, within 36 months of the initial surveillance or any subsequent medical surveillance.
 - (iii) Termination of employment or reassignment. When an employee leaves the employer's workplace, or is reassigned to an area where exposure to MC is consistently at or below the action level and STEL, medical surveillance shall be made available if six months or more have elapsed since the last medical surveillance.
 - (iv) Additional surveillance. The employer shall provide additional medical surveillance at frequencies other than those listed above when recommended in the written medical opinion. (For example, the physician or other licensed health care professional may determine an examination is warranted in less than 36 months for employees younger than 45 years of age based upon evaluation of the results of the annual medical and work history.)
- (5) Content of medical surveillance.
 - (i) Medical and work history. The comprehensive medical and work history shall emphasize neurological symptoms, skin conditions, history of hematologic or liver disease, signs or symptoms suggestive of heart disease (angina, coronary artery disease), risk factors for cardiac disease, MC exposures, and work practices and personal protective equipment used during such exposures. [Note to paragraph (j)(5)(i): See Appendix B of this section for an example of a medical and work history format that would satisfy this requirement.]
 - (ii) Physical examination. Where physical examinations are provided as required above, the physician or other licensed health care professional shall accord particular attention to the lungs, cardiovascular system (including blood pressure and pulse), liver, nervous system, and skin. The physician or other licensed health care professional shall determine the extent and nature of the physical examination based on the health status of the employee and analysis of the medical and work history.
 - (iii) Laboratory surveillance. The physician or other licensed health care professional shall determine the extent of any required laboratory surveillance based on the employee's observed health status and the medical and work history. [Note to paragraph (j)(5)(iii): See Appendix B of this section for information regarding medical tests. Laboratory surveillance may include before-and after-shift carboxyhemoglobin determinations, resting ECG, hematocrit, liver function tests and cholesterol levels.]
 - (iv) Other information or reports. The medical surveillance shall also include any other information or reports the physician or other licensed health care professional determines are necessary to assess the employee's health in relation to MC exposure.
- (6) Content of emergency medical surveillance. The employer shall ensure that medical surveillance made available when an employee has been exposed to MC in emergency situations includes, at a minimum:
 - (i) Appropriate emergency treatment and decontamination of the exposed employee;
 - (ii) Comprehensive physical examination with special emphasis on the nervous system,

- cardiovascular system, lungs, liver and skin, including blood pressure and pulse;
- (iii) Updated medical and work history, as appropriate for the medical condition of the employee; and
- (iv) Laboratory surveillance, as indicated by the employee's health status. [Note to paragraph (j)(6)(iv): See Appendix B for examples of tests that may be appropriate.]
- (7) Additional examinations and referrals. Where the physician or other licensed health care professional determines it is necessary, the scope of the medical examination shall be expanded and the appropriate additional medical surveillance, such as referrals for consultation or examination, shall be provided.
- (8) Information provided to the physician or other licensed health care professional. The employer shall provide the following information to a physician or other licensed health care professional who is involved in the diagnosis of MC-induced health effects:
 - (i) A copy of this section including its applicable appendices;
 - (ii) A description of the affected employee's past, current and anticipated future duties as they relate to the employee's MC exposure;
 - (iii) The employee's former or current exposure levels or, for employees not yet occupationally exposed to MC, the employee's anticipated exposure levels and the frequency and exposure levels anticipated to be associated with emergencies;
 - (iv) A description of any personal protective equipment, such as respirators, used or to be used; and
 - (v) Information from previous employment-related medical surveillance of the affected employee that is not otherwise available to the physician or other licensed health care professional.
- (9) Written medical opinions.
 - (i) For each physical examination required by this section, the employer shall ensure that the physician or other licensed health care professional provides to the employer and to the affected employee a written opinion regarding the results of that examination within 15 days of completion of the evaluation of medical and laboratory findings, but not more than 30 days after the examination. The written medical opinion shall be limited to the following information:
 - (A) The physician's or other licensed health care professional's opinion concerning whether exposure to MC may contribute to or aggravate the employee's existing cardiac, hepatic, neurological (including stroke) or dermal disease or whether the employee has any other medical conditions(s) that would place the employee's health at increased risk of material impairment from exposure to MC.
 - (B) Any recommended limitations upon the employee's exposure to MC, including removal from MC exposure, or upon the employee's use of respirators, protective clothing, or other protective equipment.
 - (C) A statement that the employee has been informed by the physician or other licensed health care professional that MC is a potential occupational carcinogen, of risk factors for heart disease, and the potential for exacerbation of underlying heart disease by exposure to MC through its metabolism to carbon monoxide; and
 - (D) A statement that the employee has been informed by the physician or other licensed health care professional of the results of the medical examination and any medical conditions resulting from MC exposure that require further explanation or treatment.
 - (ii) The employer shall instruct the physician or other licensed health care professional not to reveal to the employer, orally or in the written opinion, any specific records, findings, and diagnoses that have no bearing on occupational exposure to MC. [Note to paragraph (j)(9)(ii): The written medical opinion may also include information and opinions generated to comply with other OSHA health standards.]
- (10) Medical Presumption. For purposes of this paragraph (j) of this section, the physician or other licensed health care professional shall presume, unless medical evidence indicates to the contrary, that a medical condition is unlikely to require medical removal from MC exposure if the employee is not exposed to MC above the 8-hour TWA PEL. If the physician or other licensed health care professional recommends removal for an employee exposed below the 8-hour TWA PEL, the physician or other licensed health care professional shall cite specific medical evidence, sufficient to rebut the presumption that exposure below the 8-hour,

- TWA PEL is unlikely to require removal, to support the recommendation. If such evidence is cited by the physician or other licensed health care professional, the employer must remove the employee. If such evidence is not cited by the physician or other licensed health care professional, the employer is not required to remove the employee.
- (11) Medical Removal Protection (MRP).
- (i) Temporary medical removal and return of an employee.
 - (A) Except as provided in paragraph (j)(1) of this section, when a medical determination recommends removal because the employee's exposure to MC may contribute to or aggravate the employee's existing cardiac, hepatic, neurological (including stroke), or skin disease, the employer must provide medical removal protection benefits to the employee and either:
 - (1) Transfer the employee to comparable work where methylene chloride exposure is below the action level; or
 - (2) Remove the employee from MC exposure.
 - (B) If comparable work is not available and the employer is able to demonstrate that removal and the costs of extending MRP benefits to an additional employee, considering feasibility in relation to the size of the employer's business and the other requirements of this standard, make further reliance on MRP an inappropriate remedy, the employer may retain the additional employee in the existing job until transfer or removal becomes appropriate, provided:
 - (1) The employer ensures that the employee receives additional medical surveillance, including a physical examination at least every 60 days until transfer or removal occurs; and
 - (2) The employer or PLHCP informs the employee of the risk to the employee's health from continued MC exposure.
 - (C) The employer shall maintain in effect any job-related protective measures or limitations, other than removal, for as long as a medical determination recommends them to be necessary.
 - (ii) End of MRP benefits and return of the employee to former job status.
 - (A) The employer may cease providing MRP benefits at the earliest of the following:
 - (1) Six months;
 - (2) Return of the employee to the employee's former job status following receipt of a medical determination concluding that the employee's exposure to MC no longer will aggravate any cardiac, hepatic, neurological (including stroke), or dermal disease;
 - (3) Receipt of a medical determination concluding that the employee can never return to MC exposure.
 - (B) For the purposes of this paragraph (j), the requirement that an employer return an employee to the employee's former job status is not intended to expand upon or restrict any rights an employee has or would have had, absent temporary medical removal, to a specific job classification or position under the terms of a collective bargaining agreement.
- (12) Medical Removal Protection Benefits.
- (i) For purposes of this paragraph (j), the term medical removal protection benefits means that, for each removal, an employer must maintain for up to six months the earnings, seniority, and other employment rights and benefits of the employee as though the employee had not been removed from MC exposure or transferred to a comparable job.
 - (ii) During the period of time that an employee is removed from exposure to MC, the employer may condition the provision of medical removal protection benefits upon the employee's participation in follow-up medical surveillance made available pursuant to this section.
 - (iii) If a removed employee files a workers' compensation claim for a MC-related disability, the employer shall continue the MRP benefits required by this paragraph until either the claim is resolved or the 6-month period for payment of MRP benefits has passed, whichever occurs first. To the extent the employee is entitled to indemnity payments for earnings lost during the period of removal, the employer's obligation to provide medical removal protection benefits to the employee shall be reduced by the amount of such indemnity payments.

- (iv) The employer's obligation to provide medical removal protection benefits to a removed employee shall be reduced to the extent that the employee receives compensation for earnings lost during the period of removal from either a publicly or an employer-funded compensation program, or receives income from employment with another employer made possible by virtue of the employee's removal.
- (13) Voluntary Removal or Restriction of an employee. Where an employer, although not required by this section to do so, removes an employee from exposure to MC or otherwise places any limitation on an employee due to the effects of MC exposure on the employee's medical condition, the employer shall provide medical removal protection benefits to the employee equal to those required by paragraph (j)(12) of this section.
- (14) Multiple Health Care Professional Review Mechanism.
 - (i) If the employer selects the initial physician or licensed health care professional (PLHCP) to conduct any medical examination or consultation provided to an employee under this paragraph (j)(11), the employer shall notify the employee of the right to seek a second medical opinion each time the employer provides the employee with a copy of the written opinion of that PLHCP.
 - (ii) If the employee does not agree with the opinion of the employer-selected PLHCP, notifies the employer of that fact, and takes steps to make an appointment with a second PLHCP within 15 days of receiving a copy of the written opinion of the initial PLHCP, the employer shall pay for the PLHCP chosen by the employee to perform at least the following:
 - (A) Review any findings, determinations or recommendations of the initial PLHCP; and
 - (B) Conduct such examinations, consultations, and laboratory tests as the PLHCP deems necessary to facilitate this review.
 - (iii) If the findings, determinations or recommendations of the second PLHCP differ from those of the initial PLHCP, then the employer and the employee shall instruct the two health care professionals to resolve the disagreement.
 - (iv) If the two health care professionals are unable to resolve the disagreement within 15 days, then those two health care professionals shall jointly, designate a PLHCP who is a specialist in the field at issue. The employer shall pay for the specialist to perform at least the following:
 - (A) Review the findings, determinations, and recommendation of the first two PLHCPs; and
 - (B) Conduct such examinations, consultations, laboratory tests and discussions with the prior PLHCPs as the specialist deems necessary to resolve the disagreements of the prior health care professionals.
 - (v) The written opinion of the specialist shall be the definitive medical determination. The employer shall act consistent with the definitive medical determination, unless the employer and employee agree that the written opinion of one of the other two PLHCPs shall be the definitive medical determination.
 - (vi) The employer and the employee or authorized employee representative may agree upon the use of any expeditious alternate health care professional determination mechanism in lieu of the multiple health care professional review mechanism provided by this paragraph so long as the alternate mechanism otherwise satisfies the requirements contained in this paragraph.
- (k) Hazard communication. The employer shall communicate the following hazards associated with MC on labels and in material safety data sheets in accordance with the requirements of the Hazard Communication Standard, 29 CFR 1910.1200, 29 CFR 1915.1200, or 29 CFR 1926.59, as appropriate: cancer, cardiac effects (including elevation of carboxyhemoglobin), central nervous system effects, liver effects, and skin and eye irritation.
- (l) Employee information and training.
 - (1) The employer shall provide information and training for each affected employee prior to or at the time of initial assignment to a job involving potential exposure to MC.
 - (2) The employer shall ensure that information and training is presented in a manner that is understandable to the employees.
 - (3) In addition to the information required under the Hazard Communication Standard at 29 CFR 1910.1200, 29 CFR 1915.1200, or 29 CFR 1926.59, as appropriate:
 - (i) The employer shall inform each affected employee of the requirements of this section

- and information available in its appendices, as well as how to access or obtain a copy of it in the workplace;
- (ii) Wherever an employee's exposure to airborne concentrations of MC exceeds or can reasonably be expected to exceed the action level, the employer shall inform each affected employee of the quantity, location, manner of use, release, and storage of MC and the specific operations in the workplace that could result in exposure to MC, particularly noting where exposures may be above the 8-hour TWA PEL or STEL;
- (4) The employer shall train each affected employee as required under the Hazard Communication standard at 29 CFR 1910.1200, 29 CFR 1915.1200, or 29 CFR 1926.59, as appropriate.
 - (5) The employer shall re-train each affected employee as necessary to ensure that each employee exposed above the action level or the STEL maintains the requisite understanding of the principles of safe use and handling of MC in the workplace.
 - (6) Whenever there are workplace changes, such as modifications of tasks or procedures or the institution of new tasks or procedures, that increase employee exposure, and where those exposures exceed or can reasonably be expected to exceed the action level, the employer shall update the training as necessary to ensure that each affected employee has the requisite proficiency.
 - (7) An employer whose employees are exposed to MC at a multi-employer worksite shall notify the other employers with work operations at that site in accordance with the requirements of the Hazard Communication Standard, 29 CFR 1910.1200, 29 CFR 1915.1200, or 29 CFR 1926.59, as appropriate.
 - (8) The employer shall provide to the Assistant Secretary or the Director, upon request, all available materials relating to employee information and training.
- (m) Record Keeping.**
- (1) Objective data.
 - (i) Where an employer seeks to demonstrate that initial monitoring is unnecessary through reasonable reliance on objective data showing that any materials in the workplace containing MC will not release MC at levels that exceed the action level or the STEL under foreseeable conditions of exposure, the employer shall establish and maintain an accurate record of the objective data relied upon in support of the exemption.
 - (ii) This record shall include at least the following information:
 - (A) The MC-containing material in question;
 - (B) The source of the objective data;
 - (C) The testing protocol, results of testing, and/or analysis of the material for the release of MC;
 - (D) A description of the operation exempted under paragraph (d)(2)(i) of this section and how the data support the exemption; and
 - (E) Other data relevant to the operations, materials, processing, or employee exposures covered by the exemption.
 - (iii) The employer shall maintain this record for the duration of the employer's reliance upon such objective data.
 - (2) Exposure measurements.
 - (i) The employer shall establish and keep an accurate record of all measurements taken to monitor employee exposure to MC as prescribed in paragraph (d) of this section.
 - (ii) Where the employer has 20 or more employees, this record shall include at least the following information:
 - (A) The date of measurement for each sample taken;
 - (B) The operation involving exposure to MC that is being monitored;
 - (C) Sampling and analytical methods used and evidence of their accuracy;
 - (D) Number, duration, and results of samples taken;
 - (E) Type of personal protective equipment, such as respiratory protective devices, worn, if any; and
 - (F) Name, social security number, job classification and exposure of all of the employees represented by monitoring, indicating that employees were actually monitored.
 - (iii) Where the employer has fewer than 20 employees, the record shall include at least the following information:
 - (A) The date of measurement for each sample taken;

- (B) Number, duration, and results of samples taken; and
- (C) Name, social security number, job classification and exposure of all of the employees represented by monitoring, indicating that employees were actually monitored.
- (iv) The employer shall maintain this record for at least thirty (30) years, in accordance with 29 CFR 1910.1020.
- (3) Medical surveillance.
 - (i) The employer shall establish and maintain an accurate record for each employee subject to medical surveillance under paragraph (j) of this section.
 - (ii) The record shall include at least the following information:
 - (A) The name, social security number and description of the duties of the employee;
 - (B) Written medical opinions; and
 - (C) Any employee medical conditions related to exposure to MC.
 - (iii) The employer shall ensure that this record is maintained for the duration of employment plus thirty (30) years, in accordance with 29 CFR 1910.1020.
- (4) Availability.
 - (i) The employer, upon written request, shall make all records required to be maintained by this section available to the Assistant Secretary and the Director for examination and copying in accordance with 29 CFR 1910.1020. [Note to paragraph (m)(4)(i): All records required to be maintained by this section may be kept in the most administratively convenient form (for example, electronic or computer records would satisfy this requirement).]
 - (ii) The employer, upon request, shall make any employee exposure and objective data records required by this section available for examination and copying by affected employees, former employees, and designated representatives in accordance with 29 CFR 1910.1020.
 - (iii) The employer, upon request, shall make employee medical records required to be kept by this section available for examination and copying by the subject employee and by anyone having the specific written consent of the subject employee in accordance with 29 CFR 1910.1020.
- (5) Transfer of records. The employer shall comply with the requirements concerning transfer of records set forth in 29 CFR 1910.1020(h).
- (n) [Reserved]
- (o) Appendices. The information contained in the appendices does not, by itself, create any additional obligations not otherwise imposed or detract from any existing obligation.

**Appendix A to Section 1910.1052:
Substance Safety Data Sheet and Technical Guidelines for Methylene Chloride**

I. Substance Identification

- A. Substance: Methylene chloride CH₂CL₂.
- B. Synonyms: MC, Dichloromethane (DCM); Methylene dichloride; Methylene bichloride; Methane dichloride; CAS: 75-09-2; NCI-C50102.
- C. Physical data:
 - 1. Molecular weight: 84.9.
 - 2. Boiling point (760 mm Hg): 39.8° C (104° F).
 - 3. Specific gravity (water=1): 1.3.
 - 4. Vapor density (air=1 at boiling point): 2.9.
 - 5. Vapor pressure at 20° C (68° F): 350 mm Hg.
 - 6. Solubility in water, g/100 g water at 20° C (68° F)=1.32.
 - 7. Appearance and odor: colorless liquid with a chloroform-like odor.
- D. Uses:

MC is used as a solvent, especially where high volatility is required. It is a good solvent for oils, fats, waxes, resins, bitumen, rubber and cellulose acetate and is a useful paint stripper and degreaser. It is used in paint removers, in propellant mixtures for aerosol containers, as a solvent for plastics, as a degreasing agent, as an extracting agent in the pharmaceutical industry and as a blowing agent in polyurethane foams. Its solvent property is sometimes

- increased by mixing with methanol, petroleum naphtha or tetrachloroethylene.
- E. Appearance and odor:
MC is a clear colorless liquid with a chloroform-like odor. It is slightly soluble in water and completely miscible with most organic solvents.
 - F. Permissible exposure:
Exposure may not exceed 25 parts MC per million parts of air (25 ppm) as an eight-hour time-weighted average (8-hour TWA PEL) or 125 parts of MC per million parts of air (125 ppm) averaged over a 15-minute period (STEL).

II. Health Hazard Data

- A. MC can affect the body if it is inhaled or if the liquid comes in contact with the eyes or skin. It can also affect the body if it is swallowed.
- B. Effects of overexposure:
 1. Short-term Exposure:
MC is an anesthetic. Inhaling the vapor may cause mental confusion, light-headedness, nausea, vomiting, and headache. Continued exposure may cause increased light-headedness, staggering, unconsciousness, and even death. High vapor concentrations may also cause irritation of the eyes and respiratory tract. Exposure to MC may make the symptoms of angina (chest pains) worse. Skin exposure to liquid MC may cause irritation. If liquid MC remains on the skin, it may cause skin burns. Splashes of the liquid into the eyes may cause irritation.
 2. Long-term (chronic) exposure:
The best evidence that MC causes cancer is from laboratory studies in which rats, mice and hamsters inhaled MC 6 hours per day, 5 days per week for 2 years. MC exposure produced lung and liver tumors in mice and mammary tumors in rats. No carcinogenic effects of MC were found in hamsters. There are also some human epidemiological studies that show an association between occupational exposure to MC and increases in biliary (bile duct) cancer and a type of brain cancer. Other epidemiological studies have not observed a relationship between MC exposure and cancer. OSHA interprets these results to mean that there is suggestive (but not absolute) evidence that MC is a human carcinogen.
- C. Reporting signs and symptoms:
You should inform your employer if you develop any signs or symptoms and suspect that they are caused by exposure to MC.
- D. Warning Properties:
 1. Odor Threshold:
Different authors have reported varying odor thresholds for MC. Kirk-Othmer and Sax both reported 25 to 50 ppm; Summer and May both reported 150 ppm; Spector reports 320 ppm. Patty, however, states that since one can become adapted to the odor, MC should not be considered to have adequate warning properties.
 2. Eye Irritation Level:
Kirk-Othmer reports that "MC vapor is seriously damaging to the eyes." Sax agrees with Kirk-Othmer's statement. The ACGIH Documentation of TLVs states that irritation of the eyes has been observed in workers exposed to concentrations up to 5000 ppm.
 3. Evaluation of Warning Properties:
Since a wide range of MC odor thresholds are reported (25-320 ppm), and human adaptation to the odor occurs, MC is considered to be a material with poor warning properties.

III. Emergency First Aid Procedures

In the event of emergency, institute first aid procedures and send for first aid or medical assistance.

- A. Eye and Skin Exposures:
If there is a potential for liquid MC to come in contact with eye or skin, face shields and skin protective equipment must be provided and used. If liquid MC comes in contact with the eye, get medical attention. Contact lenses should not be worn when working with this chemical.
- B. Breathing:
If a person breathes in large amounts of MC, move the exposed person to fresh air at once.

If breathing has stopped, perform cardiopulmonary resuscitation. Keep the affected person warm and at rest. Get medical attention as soon as possible.

C. Rescue:

Move the affected person from the hazardous exposure immediately. If the exposed person has been overcome, notify someone else and put into effect the established emergency rescue procedures. Understand the facility's emergency rescue procedures and know the locations of rescue equipment before the need arises. Do not become a casualty yourself.

IV. Respirators, Protective Clothing, and Eye Protection

A. Respirators:

Good industrial hygiene practices recommend that engineering controls be used to reduce environmental concentrations to the permissible exposure level. However, there are some exceptions where respirators may be used to control exposure. Respirators may be used when engineering and work practice controls are not feasible, when such controls are in the process of being installed, or when these controls fail and need to be supplemented. Respirators may also be used for operations that require entry into tanks or closed vessels, and in emergency situations.

If the use of respirators is necessary, the only respirators permitted are those that have been approved by the Mine Safety and Health Administration (MSHA) or the National Institute for Occupational Safety and Health (NIOSH). Supplied-air respirators are required because air-purifying respirators do not provide adequate respiratory protection against MC.

In addition to respirator selection, a complete written respiratory protection program should be instituted that includes regular training, maintenance, inspection, cleaning, and evaluation. If you can smell MC while wearing a respirator, proceed immediately to fresh air. If you experience difficulty in breathing while wearing a respirator, tell your employer.

B. Protective Clothing:

Employees must be provided with and required to use impervious clothing, gloves, face shields (eight-inch minimum), and other appropriate protective clothing necessary to prevent repeated or prolonged skin contact with liquid MC or contact with vessels containing liquid MC. Any clothing that becomes wet with liquid MC should be removed immediately and not reworn until the employer has ensured that the protective clothing is fit for reuse.

Contaminated protective clothing should be placed in a regulated area designated by the employer for removal of MC before the clothing is laundered or disposed of. Clothing and equipment should remain in the regulated area until all of the MC contamination has evaporated; clothing and equipment should then be laundered or disposed of as appropriate.

C. Eye Protection:

Employees should be provided with and required to use splash-proof safety goggles where liquid MC may contact the eyes.

V. Housekeeping and Hygiene Facilities

For purposes of complying with 29 CFR 1910.141, the following items should be emphasized:

- A. The workplace should be kept clean, orderly, and in a sanitary condition. The employer should institute a leak and spill detection program for operations involving liquid MC in order to detect sources of fugitive MC emissions.
- B. Emergency drench showers and eyewash facilities are recommended. These should be maintained in a sanitary condition. Suitable cleansing agents should also be provided to assure the effective removal of MC from the skin.
- C. Because of the hazardous nature of MC, contaminated protective clothing should be placed in a regulated area designated by the employer for removal of MC before the clothing is laundered or disposed of.

VI. Precautions for Safe Use, Handling, and Storage

A. Fire and Explosion Hazards:

MC has no flash point in a conventional closed tester, but it forms flammable vapor-air mixtures at approximately 100° C (212° F), or higher. It has a lower explosion limit of 12%, and an upper explosion limit of 19% in air. It has an autoignition temperature of 556.1° C

- (1033° F), and a boiling point of 39.8° C (104° F). It is heavier than water with a specific gravity of 1.3. It is slightly soluble in water.
- B. **Reactivity Hazards:**
 Conditions contributing to the instability of MC are heat and moisture.
 Contact with strong oxidizers, caustics, and chemically active metals such as aluminum or magnesium powder, sodium and potassium may cause fires and explosions.
 Special precautions: Liquid MC will attack some forms of plastics, rubber, and coatings.
- C. **Toxicity:**
 Liquid MC is painful and irritating if splashed in the eyes or if confined on the skin by gloves, clothing, or shoes. Vapors in high concentrations may cause narcosis and death. Prolonged exposure to vapors may cause cancer or exacerbate cardiac disease.
- D. **Storage:**
 Protect against physical damage. Because of its corrosive properties, and its high vapor pressure, MC should be stored in plain, galvanized or lead lined, mild steel containers in a cool, dry, well ventilated area away from direct sunlight, heat source and acute fire hazards.
- E. **Piping Material:**
 All piping and valves at the loading or unloading station should be of material that is resistant to MC and should be carefully inspected prior to connection to the transport vehicle and periodically during the operation.
- F. **Usual Shipping Containers:**
 Glass bottles, 5- and 55-gallon steel drums, tank cars, and tank trucks.
- Note:** This section addresses MC exposure in marine terminal and longshore employment only where leaking or broken packages allow MC exposure that is not addressed through compliance with 29 CFR parts 1917 and 1918, respectively.
- G. **Electrical Equipment:**
 Electrical installations in Class I hazardous locations as defined in Article 500 of the National Electrical Code, should be installed according to Article 501 of the code; and electrical equipment should be suitable for use in atmospheres containing MC vapors. See Flammable and Combustible Liquids Code (NFPA No. 325M), Chemical Safety Data Sheet SD-86 (Manufacturing Chemists' Association, Inc.).
- H. **Fire Fighting:**
 When involved in fire, MC emits highly toxic and irritating fumes such as phosgene, hydrogen chloride and carbon monoxide. Wear breathing apparatus and use water spray to keep fire-exposed containers cool. Water spray may be used to flush spills away from exposures. Extinguishing media are dry chemical, carbon dioxide, foam. For purposes of compliance with 29 CFR 1910.307, locations classified as hazardous due to the presence of MC shall be Class I.
- I. **Spills and Leaks:**
 Persons not wearing protective equipment and clothing should be restricted from areas of spills or leaks until cleanup has been completed. If MC has spilled or leaked, the following steps should be taken:
1. Remove all ignition sources.
 2. Ventilate area of spill or leak.
 3. Collect for reclamation or absorb in vermiculite, dry sand, earth, or a similar material.
- J. **Methods of Waste Disposal:**
 Small spills should be absorbed onto sand and taken to a safe area for atmospheric evaporation. Incineration is the preferred method for disposal of large quantities by mixing with a combustible solvent and spraying into an incinerator equipped with acid scrubbers to remove hydrogen chloride gases formed. Complete combustion will convert carbon monoxide to carbon dioxide. Care should be taken for the presence of phosgene.
- K. You should not keep food, beverage, or smoking materials, or eat or smoke in regulated areas where MC concentrations are above the permissible exposure limits.
- L. Portable heating units should not be used in confined areas where MC is used.
- M. Ask your supervisor where MC is used in your work area and for any additional plant safety and health rules.

VII. Medical Requirements

Your employer is required to offer you the opportunity to participate in a medical surveillance program if you are exposed to MC at concentrations at or above the action level (12.5 ppm 8-hour TWA) for more than 30 days a year or at concentrations exceeding the PELs (25 ppm 8-hour TWA or 125 ppm 15-minute STEL) for more than 10 days a year. If you are exposed to MC at concentrations over either of the PELs, your employer will also be required to have a physician or other licensed health care professional ensure that you are able to wear the respirator that you are assigned. Your employer must provide all medical examinations relating to your MC exposure at a reasonable time and place and at no cost to you.

VIII. Monitoring and Measurement Procedures

A. Exposure above the Permissible Exposure Limit:

1. Eight-hour exposure evaluation: Measurements taken for the purpose of determining employee exposure under this section are best taken with consecutive samples covering the full shift. Air samples must be taken in the employee's breathing zone.
2. Monitoring techniques: The sampling and analysis under this section may be performed by collection of the MC vapor on two charcoal adsorption tubes in series or other composition adsorption tubes, with subsequent chemical analysis. Sampling and analysis may also be performed by instruments such as real-time continuous monitoring systems, portable direct reading instruments, or passive dosimeters as long as measurements taken using these methods accurately evaluate the concentration of MC in employees' breathing zones.

OSHA method 80 is an example of a validated method of sampling and analysis of MC. Copies of this method are available from OSHA or can be downloaded from the Internet at <http://www.osha.gov>. The employer has the obligation of selecting a monitoring method that meets the accuracy and precision requirements of the standard under his or her unique field conditions. The standard requires that the method of monitoring must be accurate, to a 95 percent confidence level, to plus or minus 25 percent for concentrations of MC at or above 25 ppm, and to plus or minus 35 percent for concentrations at or below 25 ppm. In addition to OSHA method 80, there are numerous other methods available for monitoring for MC in the workplace.

- B. Since many of the duties relating to employee exposure are dependent on the results of measurement procedures, employers must assure that the evaluation of employee exposure is performed by a technically qualified person.

IX. Observation of Monitoring

Your employer is required to perform measurements that are representative of your exposure to MC and you or your designated representative are entitled to observe the monitoring procedure. You are entitled to observe the steps taken in the measurement procedure, and to record the results obtained. When the monitoring procedure is taking place in an area where respirators or personal protective clothing and equipment are required to be worn, you or your representative must also be provided with, and must wear, protective clothing and equipment.

X. Access To Information

- A. Your employer is required to inform you of the information contained in this Appendix. In addition, your employer must instruct you in the proper work practices for using MC, emergency procedures, and the correct use of protective equipment.
- B. Your employer is required to determine whether you are being exposed to MC. You or your representative has the right to observe employee measurements and to record the results obtained. Your employer is required to inform you of your exposure. If your employer determines that you are being over exposed, he or she is required to inform you of the actions that are being taken to reduce your exposure to within permissible exposure limits.
- C. Your employer is required to keep records of your exposures and medical examinations. These records must be kept by the employer for at least thirty (30) years.
- D. Your employer is required to release your exposure and medical records to you or your representative upon your request.

- E. Your employee is required to provide labels and material safety data sheets (MSDS) for all materials, mixtures or solutions composed of greater than 0.1 percent MC. An example of a label that would satisfy these requirements would be:

Danger Contains Methylene Chloride Potential Cancer Hazard

May worsen heart disease because methylene chloride is converted to carbon monoxide in the body. May cause dizziness, headache, irritation of the throat and lungs, loss of consciousness and death at high concentrations (for example, if used in a poorly ventilated room).

Avoid Skin Contact. Contact with liquid causes skin and eye irritation.

XI. Common Operations and Controls

The following list includes some common operations in that exposure to MC may occur and control methods that may be effective in each case:

Operations	Controls
Use as solvent in paint and varnish removers; manufacture of aerosols; cold cleaning and ultrasonic cleaning and as a solvent in furniture stripping.	General dilution ventilation; local exhaust ventilation; personal protective equipment; substitution.
Use as solvent in vapor degreasing.	Process enclosure; local exhaust ventilation; chilling coils; substitution.
Use as a secondary refrigerant in air conditioning and scientific testing.	General dilution ventilation; local exhaust ventilation; personal protective equipment.

**Appendix B to Section 1910.1052
Medical Surveillance for Methylene Chloride**

I. Primary Route of Entry

Inhalation.

II. Toxicology

Methylene Chloride (MC) is primarily an inhalation hazard. The principal acute hazardous effects are the depressant action on the central nervous system, possible cardiac toxicity and possible liver toxicity. The range of CNS effects are from decreased eye/hand coordination and decreased performance in vigilance tasks to narcosis and even death of individuals exposed at very high doses. Cardiac toxicity is due to the metabolism of MC to carbon monoxide, and the effects of carbon monoxide on heart tissue. Carbon monoxide displaces oxygen in the blood, decreases the oxygen available to heart tissue, increasing the risk of damage to the heart, that may result in heart attacks in susceptible individuals. Susceptible individuals include persons with heart disease and those with risk factors for heart disease.

Elevated liver enzymes and irritation to the respiratory passages and eyes have also been reported for both humans and experimental animals exposed to MC vapors.

MC is metabolized to carbon monoxide and carbon dioxide via two separate pathways. Through the first pathway, MC is metabolized to carbon monoxide as an end-product via the P-450 mixed function oxidase pathway located in the microsomal fraction of the cell. This biotransformation of MC to carbon monoxide occurs through the process of microsomal oxidative dechlorination that takes place primarily in the liver. The amount of conversion to carbon monoxide is significant as measured by the concentration of carboxyhemoglobin, up to 12% measured in the blood following occupational exposure of up to 610 ppm. Through the second pathway, MC is metabolized to carbon dioxide as an end product (with formaldehyde and formic acid as metabolic intermediates) via the glutathione dependent enzyme found in the cytosolic fraction of the liver cell.

Metabolites along this pathway are believed to be associated with the carcinogenic activity of MC.

MC has been tested for carcinogenicity in several laboratory rodents. These rodent studies indicate that there is clear evidence that MC is carcinogenic to male and female mice and female rats. Based on epidemiologic studies, OSHA has concluded that there is suggestive evidence of increased cancer risk in MC-related worker populations. The epidemiological evidence is consistent with the finding of excess cancer in the experimental animal studies. NIOSH regards MC as a potential occupational carcinogen and the International Agency for Research Cancer (IARC) classifies MC as an animal carcinogen. OSHA considers MC as a suspected human carcinogen.

III. Medical Signs and Symptoms of Acute Exposure

Skin exposure to liquid MC may cause irritation or skin burns. Liquid MC can also be irritating to the eyes. MC is also absorbed through the skin and may contribute to the MC exposure by inhalation. At high concentrations in air, MC may cause nausea, vomiting, light-headedness, numbness of the extremities, changes in blood enzyme levels, and breathing problems, leading to bronchitis and pulmonary edema, unconsciousness and even death.

At lower concentrations in air, MC may cause irritation to the skin, eye, and respiratory tract and occasionally headache and nausea. Perhaps the greatest problem from exposure to low concentrations of MC is the CNS effects on coordination and alertness that may cause unsafe operations of machinery and equipment, leading to self-injury or accidents.

Low levels and short duration exposures do not seem to produce permanent disability, but chronic exposures to MC have been demonstrated to produce liver toxicity in animals, and therefore, the evidence is suggestive for liver toxicity in humans after chronic exposure.

Chronic exposure to MC may also cause cancer.

IV. Surveillance and Preventive Considerations

As discussed above, MC is classified as a suspect or potential human carcinogen. It is a central nervous system (CNS) depressant and a skin, eye and respiratory tract irritant. At extremely high concentrations, MC has caused liver damage in animals.

MC principally affects the CNS, where it acts as a narcotic. The observation of the symptoms characteristic of CNS depression, along with a physical examination, provides the best detection of early neurological disorders. Since exposure to MC also increases the carboxyhemoglobin level in the blood, ambient carbon monoxide levels would have an additive effect on that carboxyhemoglobin level. Based on such information, a periodic post-shift carboxyhemoglobin test as an index of the presence of carbon monoxide in the blood is recommended, but not required, for medical surveillance.

Based on the animal evidence and three epidemiologic studies previously mentioned, OSHA concludes that MC is a suspect human carcinogen. The medical surveillance program is designed to observe exposed workers on a regular basis. While the medical surveillance program cannot detect MC-induced cancer at a preneoplastic stage, OSHA anticipates that, as in the past, early detection and treatments of cancers leading to enhanced survival rates will continue to evolve.

A. Medical and Occupational History:

The medical and occupational work history plays an important role in the initial evaluation of workers exposed to MC. It is therefore extremely important for the examining physician or other licensed health care professional to evaluate the MC-exposed worker carefully and completely and to focus the examination on MC's potentially associated health hazards. The medical evaluation must include an annual detailed work and medical history with special emphasis on cardiac history and neurological symptoms.

An important goal of the medical history is to elicit information from the worker regarding potential signs or symptoms associated with increased levels of carboxyhemoglobin due to the presence of carbon monoxide in the blood. Physicians or other licensed health care professionals should ensure that the smoking history of all MC exposed employees is known. Exposure to MC may cause a significant increase in carboxyhemoglobin level in all exposed persons. However, smokers as well as workers with anemia or heart disease and those concurrently exposed to carbon monoxide are at especially high risk of toxic effects because of an already reduced oxygen carrying capacity of the blood.

A comprehensive or interim medical and work history should also include occurrence of headache, dizziness, fatigue, chest pain, shortness of breath, pain in the limbs, and irritation of the skin and eyes.

In addition, it is important for the physician or other licensed health care professional to become familiar with the operating conditions in that exposure to MC is likely to occur. The physician or other licensed health care professional also must become familiar with the signs and symptoms that may indicate that a worker is receiving otherwise unrecognized and exceptionally high exposure levels of MC.

An example of a medical and work history that would satisfy the requirement for a comprehensive or interim work history is represented by the following:

The following is a list of recommended questions and issues for the self-administered questionnaire for methylene chloride exposure.

Questionnaire For Methylene Chloride Exposure

I. Demographic Information

1. Name
2. Social Security Number
3. Date
4. Date of Birth
5. Age
6. Present occupation
7. Sex
8. Race

II. Occupational History

1. Have you ever worked with methylene chloride, dichloromethane, methylene dichloride, or CH_2Cl_2 (all are different names for the same chemical)? Please list that on the occupational history form if you have not already.
2. If you have worked in any of the following industries and have not listed them on the occupational history form, please do so.
 - Furniture stripping
 - Polyurethane foam manufacturing
 - Chemical manufacturing or formulation
 - Pharmaceutical manufacturing
 - Any industry in that you used solvents to clean and degrease equipment or parts
 - Construction, especially painting and refinishing
 - Aerosol manufacturing
 - Any industry in that you used aerosol adhesives
3. If you have not listed hobbies or household projects on the occupational history form, especially furniture refinishing, spray painting, or paint stripping, please do so.

III. Medical History

A. General

1. Do you consider yourself to be in good health? If no, state reason(s).
2. Do you or have you ever had:
 - a. Persistent thirst
 - b. Frequent urination (three times or more at night)
 - c. Dermatitis or irritated skin
 - d. Non-healing wounds
3. What prescription or non-prescription medications do you take, and for what reasons?
4. Are you allergic to any medications, and what type of reaction do you have?

B. Respiratory

1. Do you have or have you ever had any chest illnesses or diseases? Explain.
2. Do you have or have you ever had any of the following:
 - a. Asthma
 - b. Wheezing
 - c. Shortness of breath
3. Have you ever had an abnormal chest X-ray? If so, when, where, and what were the findings?
4. Have you ever had difficulty using a respirator or breathing apparatus? Explain.
5. Do any chest or lung diseases run in your family? Explain.
6. Have you ever smoked cigarettes, cigars, or a pipe? Age started:
7. Do you now smoke?
8. If you have stopped smoking completely, how old were you when you stopped?
9. On the average of the entire time you smoked, how many packs of cigarettes, cigars, or bowls of tobacco did you smoke per day?

C. Cardiovascular

1. Have you ever been diagnosed with any of the following: That of the following apply to you now or did apply to you at some time in the past, even if the problem is controlled by medication? Please explain any yes answers (i.e., when problem was diagnosed, length of time on medication).
 - a. High cholesterol or triglyceride level
 - b. Hypertension (high blood pressure)
 - c. Diabetes
 - d. Family history of heart attack, stroke, or blocked arteries
2. Have you ever had chest pain? If so, answer the next five questions.
 - a. What was the quality of the pain (i.e., crushing, stabbing, squeezing)?
 - b. Did the pain go anywhere (i.e., into jaw, left arm)?
 - c. What brought the pain out?
 - d. How long did it last?
 - e. What made the pain go away?
3. Have you ever had heart disease, a heart attack, stroke, aneurysm, or blocked arteries anywhere in you body? Explain (when, treatment).
4. Have you ever had bypass surgery for blocked arteries in your heart or anywhere else? Explain.
5. Have you ever had any other procedures done to open up a blocked artery (balloon angioplasty, carotid endarterectomy, clot-dissolving drug)?
6. Do you have or have you ever had (explain each):
 - a. Heart murmur
 - b. Irregular heartbeat
 - c. Shortness of breath while lying flat
 - d. Congestive heart failure
 - e. Ankle swelling
 - f. Recurrent pain anywhere below the waist while walking
7. Have you ever had an electrocardiogram (EKG)? When?
8. Have you ever had an abnormal EKG? If so, when, where, and what were the findings?
9. Do any heart diseases, high blood pressure, diabetes, high cholesterol, or high triglycerides run in your family? Explain.

D. Hepatobiliary and Pancreas

1. Do you now or have you ever drunk alcoholic beverages?
Age started: _____ Age stopped: _____.
2. Average numbers per week:
 - a. Beers: _____, ounces in usual container:
 - b. Glasses of wine: _____, ounces per glass:
 - c. Drinks: _____, ounces in usual container:
3. Do you have or have you ever had (explain each):
 - a. Hepatitis (infectious, autoimmune, drug-induced, or chemical)

- b. Jaundice
- c. Elevated liver enzymes or elevated bilirubin
- d. Liver disease or cancer

E. Central Nervous System

1. Do you or have you ever had (explain each):
 - a. Headache
 - b. Dizziness
 - c. Fainting
 - d. Loss of consciousness
 - e. Garbled speech
 - f. Lack of balance
 - g. Mental/psychiatric illness
 - h. Forgetfulness

F. Hematologic

1. Do you have, or have you ever had (explain each):
 - a. Anemia
 - b. Sickle cell disease or trait
 - c. Glucose-6-phosphate dehydrogenase deficiency
 - d. Bleeding tendency disorder
2. If not already mentioned previously, have you ever had a reaction to sulfa drugs or to drugs used to prevent or treat malaria? What was the drug? Describe the reaction.

B. Physical Examination

The complete physical examination, when coupled with the medical and occupational history, assists the physician or other licensed health care professional in detecting pre-existing conditions that might place the employee at increased risk, and establishes a baseline for future health monitoring. These examinations should include:

1. Clinical impressions of the nervous system, cardiovascular function and pulmonary function, with additional tests conducted where indicated or determined by the examining physician or other licensed health care professional to be necessary.
2. An evaluation of the advisability of the worker using a respirator, because the use of certain respirators places an additional burden on the cardiopulmonary system. It is necessary for the attending physician or other licensed health care professional to evaluate the cardiopulmonary function of these workers, in order to inform the employer in a written medical opinion of the worker's ability or fitness to work in an area requiring the use of certain types of respiratory protective equipment. The presence of facial hair or scars that might interfere with the worker's ability to wear certain types of respirators should also be noted during the examination and in the written medical opinion.

Because of the importance of lung function to workers required to wear certain types of respirators to protect themselves from MC exposure, these workers must receive an assessment of pulmonary function before they begin to wear a negative pressure respirator and at least annually thereafter. The recommended pulmonary function tests include measurement of the employee's forced vital capacity (FVC), forced expiratory volume at one second (FEV(1)), as well as calculation of the ratios of FEV(1) to FVC, and the ratios of measured FVC and measured FEV(1) to expected respective values corrected for variation due to age, sex, race, and height. Pulmonary function evaluation must be conducted by a physician or other licensed health care professional experienced in pulmonary function tests.

The following is a summary of the elements of a physical exam that would fulfill the requirements under the MC standard:

Physical Exam

I. Skin and appendages

1. Irritated or broken skin
2. Jaundice
3. Clubbing cyanosis, edema
4. Capillary refill time
5. Pallor

II. Head

1. Facial deformities
2. Scars
3. Hair growth

III. Eyes

1. Scleral icterus
2. Corneal arcus
3. Pupillary size and response
4. Fundoscopic exam

IV. Chest

1. Standard exam

V. Heart

1. Standard exam
2. Jugular vein distension
3. Peripheral pulses

VI. Abdomen

1. Liver span

VII. Nervous System

1. Complete standard neurologic exam

VIII. Laboratory

1. Hemoglobin and hematocrit
2. Alanine aminotransferase (ALT, SGPT)
3. Post-shift carboxyhemoglobin

IX. Studies

1. Pulmonary function testing
2. Electrocardiogram

An evaluation of the oxygen carrying capacity of the blood of employees (for example by measured red blood cell volume) is considered useful, especially for workers acutely exposed to MC. It is also recommended, but not required, that end of shift carboxyhemoglobin levels be determined periodically, and any level above 3% for non-smokers and above 10% for smokers should prompt an investigation of the worker and his workplace. This test is recommended because MC is metabolized to CO, that combines strongly with hemoglobin, resulting in a reduced capacity of the blood to transport oxygen in the body. This is of particular concern for cigarette smokers because they already have a diminished hemoglobin capacity due to the presence of CO in cigarette smoke.

C. Additional Examinations and Referrals

1. Examination by a Specialist

When a worker examination reveals unexplained symptoms or signs (i.e. in the physical examination or in the laboratory tests), follow-up medical examinations are necessary to assure that MC exposure is not adversely affecting the worker's health. When the examining physician or other licensed health care professional finds it necessary, additional tests should be included to determine the nature of the medical problem and the underlying cause. Where relevant, the worker should be sent to a specialist for further testing and treatment as deemed necessary.

The final rule requires additional investigations to be covered and it also permits physicians or other licensed health care professionals to add appropriate or necessary tests to improve the diagnosis of disease should such tests become available in the future.

2. Emergencies

The examination of workers exposed to MC in an emergency should be directed at the organ systems most likely to be affected. If the worker has received a severe acute exposure, hospitalization may be required to assure proper medical intervention. It is not possible to precisely define "severe," but the physician or other licensed health care professional's judgement should not merely rest on hospitalization. If the worker has suffered significant conjunctival, oral, or nasal irritation, respiratory distress, or discomfort, the physician or other licensed health care professional should instigate appropriate follow-up procedures. These include attention to the eyes, lungs and the neurological system. The frequency of follow-up examinations should be determined by the attending physician or other licensed health care professional. This testing permits the early identification essential to proper medical management of such workers.

D. Employer Obligations

The employer is required to provide the responsible physician or other licensed health care professional and any specialists involved in a diagnosis with the following information: a copy of the MC standard including relevant appendices, a description of the affected employee's duties as they relate to his or her exposure to MC; an estimate of the employee's exposure including duration (e.g., 15hr/wk, three 8-hour shifts/wk, full time); a description of any personal protective equipment used by the employee, including respirators; and the results of any previous medical determinations for the affected employee related to MC exposure to the extent that this information is within the employer's control.

E. Physicians' or Other Licensed Health Care Professionals' Obligations

The standard requires the employer to ensure that the physician or other licensed health care professional provides a written statement to the employee and the employer. This statement should contain the physician's or licensed health care professional's opinion as to whether the employee has any medical condition placing him or her at increased risk of impaired health from exposure to MC or use of respirators, as appropriate. The physician or other licensed health care professional should also state his or her opinion regarding any restrictions that should be placed on the employee's exposure to MC or upon the use of protective clothing or equipment such as respirators. If the employee wears a respirator as a result of his or her exposure to MC, the physician or other licensed health care professional's opinion should also contain a statement regarding the suitability of the employee to wear the type of respirator assigned. Furthermore, the

employee should be informed by the physician or other licensed health care professional about the cancer risk of MC and about risk factors for heart disease, and the potential for exacerbation of underlying heart disease by exposure to MC through its metabolism to carbon monoxide. Finally, the physician or other licensed health care professional should inform the employer that the employee has been told the results of the medical examination and of any medical conditions that require further explanation or treatment. This written opinion must not contain any information on specific findings or diagnosis unrelated to employee's occupational exposures.

The purpose in requiring the examining physician or other licensed health care professional to supply the employer with a written opinion is to provide the employer with a medical basis to assist the employer in placing employees initially, in assuring that their health is not being impaired by exposure to MC, and to assess the employee's ability to use any required protective equipment.

Appendix C to Section 1910.1052:
Questions and Answers—Methylene Chloride Control in Furniture Stripping



—Questions and Answers—
Methylene Chloride Control in
Furniture Stripping



U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Centers for Disease Control and Prevention
National Institute for Occupational Safety and Health
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Q's & A's

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Introduction

This Pamphlet answers commonly asked questions about the hazards from exposure to methylene chloride. It also describes approaches to controlling methylene chloride exposure during the most common furniture stripping processes. Although these approaches were developed and field tested by NIOSH, each setting requires custom installation because of the different air flow interferences at each site.

What is the Stripping Solution Base?

The most common active ingredient in paint removers is a chemical called methylene chloride. Methylene chloride is present in the paint

remover to penetrate, blister, and finally lift the old finish. Other chemicals in paint removers work to accelerate the stripping process, to retard evaporation, and to act as thickening agents. These other ingredients may include: methanol, toluene, acetone, or paraffin.¹

Is Methylene Chloride Bad for Me?

Exposure to methylene chloride may cause short-term health effects or long-term health effects.

Short-Term (acute) Health Effects

Exposure to high levels of paint removers over short periods of time can cause irritation to the skin, eyes, mucous membranes, and respiratory tract. Other symptoms of high

exposure are dizziness, headache, and lack of coordination. The occurrence of any of these symptoms indicates that you are being exposed to high levels of the methylene chloride. At the onset of any of these symptoms, you should leave the work area, get some fresh air, and determine why the levels were high.

A portion of inhaled methylene chloride is converted by the body to carbon monoxide, which can lower the blood's ability to carry oxygen. When the solvent is used properly, however, the levels of carbon monoxide should not be hazardous. Individuals with cardiovascular or pulmonary health problems should check with their physician before using the paint stripper. Individuals experiencing severe symptoms such as shortness of breath or chest pains should obtain proper medical care immediately.²

Long-term (Chronic) Health Effects

Methylene chloride has been shown to cause cancer in certain laboratory animal tests. The available human studies do not provide the necessary information to determine whether methylene chloride causes cancer in humans. However, as a result of the animal studies, methylene chloride is

Q's & A's

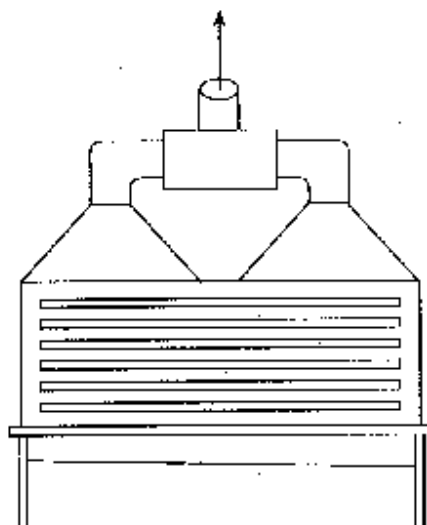
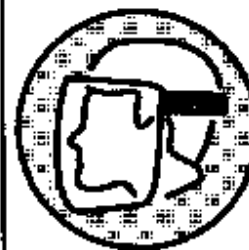
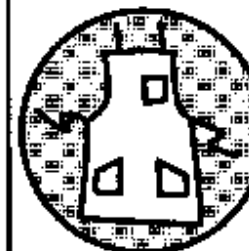


Figure 1 — Slot Hood



Q's & A's

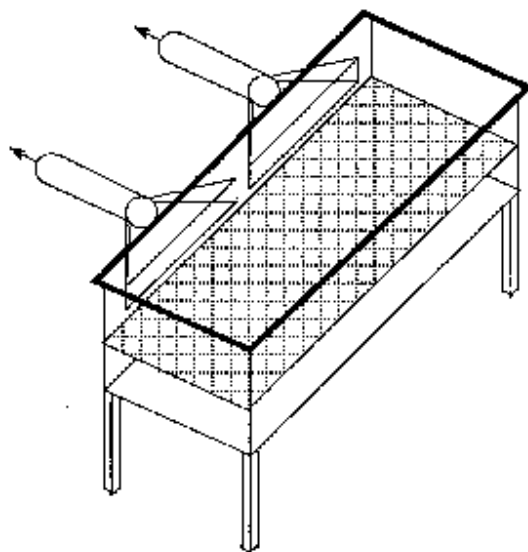


Figure 2 — Downdraft Hood

considered a potential occupational carcinogen. There is also considerable indirect evidence to suggest that workers exposed to methylene chloride may be at increased risk of developing ischemic heart disease. Therefore, it is prudent to minimize exposures to solvent vapors.¹

What Do Federal Agencies Say About Methylene Chloride?

In 1991, the Occupational Safety and Health Administration published a Notice of Proposed Rulemaking for methylene chloride. The proposed standard would establish an eight-hour time-weighted average exposure limit of 25 parts per million (ppm), as well

as a short-term exposure limit of 125 ppm determined from a 15 minute sampling period. That is a sharp reduction from the current limit of 500 ppm. The proposed standard would also set a 12.5 ppm action level (a level that would trigger periodic exposure monitoring and medical surveillance provisions).²

The National Institute for Occupational Safety and Health recommends that methylene chloride be regarded as a "potential occupational carcinogen." NIOSH further recommends that occupational exposure to methylene chloride be controlled to the lowest feasible limit. This recommendation was based on the observation of cancers and tumors in both rats and mice exposed to methylene chloride in air.³

How Can I Be Exposed to Methylene Chloride while Stripping Furniture?

Methylene chloride can be inhaled when vapors are in the air. Inhalation of the methylene chloride vapors is generally the most important source of exposure. Methylene chloride evaporates quicker than most chemicals. The odor threshold of methylene chloride is 300 ppm.⁴ Therefore, once you smell methylene chloride, you are being over-exposed. Pouring, moving, or stirring the chemical will increase the rate of evaporation.

Methylene chloride can be absorbed through the skin either by directly touching the chemical or through your gloves. Methylene chloride can be swallowed if it gets on your hands, clothes, or beard, or if food or drinks become contaminated.

How Can Breathing Exposures be Reduced?

Install a Local Exhaust Ventilation System

Local exhaust ventilation can be used in control exposures. Local exhaust ventilation systems

capture contaminated air from the source before it spreads into the workers' breathing zone.⁷ If engineering controls are not effective, only a self-contained breathing apparatus equipped with a full facemask and operated in a positive-pressure mode or a supplied-air respirator affords the necessary level of protection. Air-purifying respirators such as organic vapor cartridges can only be used for escape situations.⁸

A local exhaust system consists of the following: a hood, a fan, ductwork, and a replacement air system.^{9,10,11} Two processes are commonly used in furniture stripping: flow-over and dip tanks. For flow-over systems there are two common local exhaust controls for methylene chloride: a slot hood and a downdraft hood. A slot hood of different design is most often used for dip tanks. (See Figures 1, 2, and 3)

The hood is made of sheet metal and connected to the tank. All designs require a centrifugal fan to exhaust the fumes, ductwork connecting the hood and the fan, and a replacement air system to bring conditioned air into the building to replace the air exhausted.

In constructing or designing a slot or downdraft hood, use the following data:

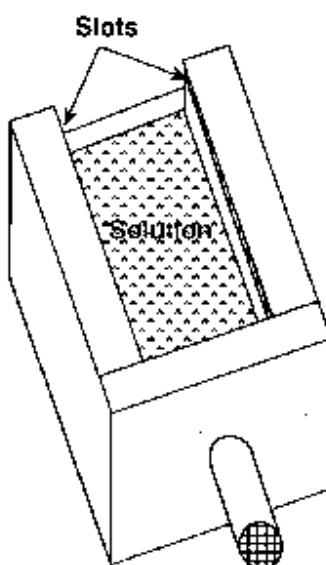


Figure 3 — Slot Hood for Dip Tank

Slot hood (Figure 1)

- At least 2200 cfm per 8' X 4' tank
- 1 - 2 inch slots
- Slot velocity - 1000 fpm
- 3 - 5 slots
- Plenum at least 1 foot deep

Downdraft hood (Figure 2)

- At least 1600 cfm per 8' X 4' tank
- Plenum at least 9" deep

Slot hood for Dip Tank (Figure 3)

- At least 2900 cfm per 8' X 4' tank
- 3/4" slot that runs the length of the front and back of the tank
- Slot velocity -- 3200 fpm
- Plenum on the sides of the tank should be 6" deep by 36" long
- 12" duct leads from the center of the front plenum to the fan

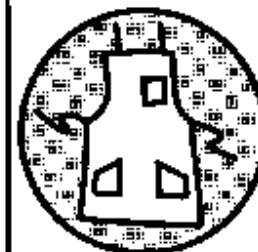
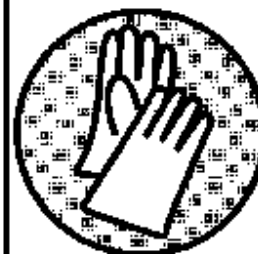
Safe work practices

Workers can lower exposures by decreasing their access to the methyl-

ene chloride.¹²

- 1) Turn on dip tank control system several minutes before entering the stripping area.
- 2) Avoid unnecessary transferring or moving of stripping solution.
- 3) Keep face out of the air stream between the solution covered furniture and the exhaust system.
- 4) Keep face out of vapor zone above the stripping solution and dip tank.
- 5) Retrieve dropped items with a long handled tool.
- 6) Keep the solution-recycling system off when not in use. Cover reservoir for recycling system.
- 7) Cover dip tank when not in use.
- 8) Provide adequate ventilation for rinse area.

Q's & A's



Q's & A's

How Can Skin Exposures be Reduced?

Skin exposures can be reduced by wearing gloves whenever you are in contact with the stripping solution.¹³

- 1) Two gloves should be worn. The inner glove should be made from polyethylene/ethylene vinyl alcohol (e.g. Silver Shield[®] or 4H[®]). This material, however, does not provide good physical resistance against tears, so an outer glove made from nitrile or neoprene should be worn.
- 2) Shoulder-length gloves will be more protective.
- 3) Change gloves before the break-through time occurs. Rotate several pairs of gloves throughout the day. Let the gloves dry in a warm well ventilated area at least over night before reuse.
- 4) Keep gloves clean by rinsing often. Keep gloves in good condition. Inspect the gloves before use for pin-holes, cracks, thin spots, and stiffer than normal or sticky surfaces.
- 5) Wear a face shield or goggles to protect face and eyes.

What Other Problems Occur?

Stripping Solution Temperature

Most manufacturers of stripping solution recom-

mend controlling the solution to a temperature of 70°F. This temperature is required for the wax in the solution to form a vapor barrier on top of the solution to keep the solution from evaporating too quickly. If the temperature is too high, the wax will not form the vapor barrier. If it is too cold, the wax will solidify and separate from the solvent causing increased evaporation. Use a belt heater to heat the solution to the correct temperature. Call your solution manufacturer for the correct temperature for your solution.¹⁴

Make-Up Air

Air will enter a building in an amount to equal the amount of air exhausted whether or not provision is made for this replacement. If a local exhaust system is added a make-up or replacement air system must be added to replace the air removed. Without a replacement air system, air will enter the building through cracks causing uncontrollable eddy currents. If the building perimeter is tightly sealed, it will prevent the air from entering and severely decrease the amount exhausted from the

ventilation system. This will cause the building to be under negative pressure and decrease the performance of the exhaust system.¹⁵

Dilution Ventilation

With general or dilution ventilation, unconditioned air is moved through the workroom by means of fans or open windows, which dilutes the pollutants in the air. Dilution ventilation does not provide effective protection to other workers and does not confine the methylene chloride vapors to one area.¹⁶

Phosgene Poisoning from Use of Kerosene Heaters

Do not use kerosene heaters or other open flame heaters while stripping furniture. Use of kerosene heaters in connection with methylene chloride can create lethal or dangerous concentrations of phosgene. Methylene chloride vapor is mixed with the air used for the combustion of kerosene in kerosene stoves. The vapor thus passes through the flames, coming into close contact with carbon monoxide at high temperatures. Any chlorine formed by decomposition may, under these conditions, react with carbon monoxide and form phosgene.¹⁷



REFERENCES

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- ¹⁴ Kwick Kleen Industrial Solvents, Inc. [1981]. Operations Manual, Kwick Kleen Industrial Solvents, Inc., Vincennes, IN.
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- ¹⁷ Geritsen, W.B. and C.H. Buschmann [1960]. Phosgene Poisoning Caused by the Use of Chemical Paint Removers containing Methylene Chloride in Ill-Ventilated Rooms Heated by Kerosene Stoves. *British Journal of Industrial Medicine* 17:187.

Q's & A's

Where Should I go for More Information?

The NIOSH 800- number is a toll-free technical information service that provides convenient public access to NIOSH and its information resources. Callers may request information about any aspect of occupational safety and health.

1-800-35-NIOSH
(1-800-356-4674)

(b) Definitions. As used in 29 CFR 1910.1052 and applied to this section:

- "29 CFR 1910.120" means chapter 12-99.1.
- "29 CFR 1910.133" means section 1910.133 in chapter 12-64.1.
- "29 CFR 1910.134" means section 1910.134 in chapter 12-64.1.
- "29 CFR 1910.307" means section 12-89.1-1.
- "29 CFR 1910.141" means chapter 12-67.
- "29 CFR 1910.1000" means section 12-202-4.02.
- "29 CFR 1910.1020" means section 1910.1020 in section 12-202-3.1.
- "29 CFR 1910.1200" means section 1910.1200 in chapter 12-203.1.
- "29 CFR 1926.59" means section 1910.1200 in chapter 12-203.1.
- "Assistant Secretary" means the director of the department of labor. [Eff 7/10/97; am 4/11/98; am 7/6/98; am 12/21/06; am 4/19/07] (Auth: HRS §396-4)

(Imp: HRS §396-4)

§12-202-42 Chromium (VI). Incorporation of federal standard. Title 29, Code of Federal Regulations, section 1910.1026, entitled "Chromium (VI)", published by the Office of the Federal Register, National Archives and Records Administration, on February 28, 2006; and October 30, 2006, are made part of this chapter. [Eff 12/21/06; am 4/19/07] (Auth: HRS §396-4) (Imp: HRS §396-4)

1910.1026 Chromium (VI)

(a) Scope.

- (1) This standard applies to occupational exposures to chromium (VI) in all forms and compounds in general industry, except:
- (2) Exposures that occur in the application of pesticides regulated by the Environmental Protection Agency or another Federal government agency (e.g., the treatment of wood with preservatives);
- (3) Exposures to portland cement; or
- (4) Where the employer has objective data demonstrating that a material containing chromium or a specific process, operation, or activity involving chromium cannot release dusts, fumes, or mists of chromium (VI) in concentrations at or above 0.5 µg/m³ as an 8-hour time-weighted average (TWA) under any expected conditions of use.

(b) Definitions. For the purposes of this section the following definitions apply:

Action level means a concentration of airborne chromium (VI) of 2.5 micrograms per cubic meter of air (2.5 µg/m³) calculated as an 8-hour time-weighted average (TWA).

Assistant Secretary means the Assistant Secretary of Labor for Occupational Safety and Health, U.S. Department of Labor, or designee.

Chromium (VI) [hexavalent chromium or Cr(VI)] means chromium with a valence of positive six, in any form and in any compound.

Director means the Director of the National Institute for Occupational Safety and Health (NIOSH), U.S. Department of Health and Human Services, or designee.

Emergency means any occurrence that results, or is likely to result, in an uncontrolled release of chromium (VI). If an incidental release of chromium (VI) can be controlled at the time of release by employees in the immediate release area, or by maintenance personnel, it is not an emergency.

Employee exposure means the exposure to airborne chromium (VI) that would occur if the employee were not using a respirator.

High-efficiency particulate air [HEPA] filter means a filter that is at least 99.97 percent efficient in removing mono-dispersed particles of 0.3 micrometers in diameter or larger.

Historical monitoring data means data from chromium (VI) monitoring conducted prior to May 30, 2006, obtained during work operations conducted under workplace conditions closely resembling the processes, types of material, control methods, work practices, and environmental conditions in the employer's current operations.

Objective data means information such as air monitoring data from industry-wide surveys or calculations based on the composition or chemical and physical properties of a substance demonstrating the employee exposure to chromium (VI) associated with a particular product or material or a specific process, operation, or activity. The data must reflect workplace conditions closely resembling the processes, types of material, control methods, work practices, and environmental conditions in the employer's current operations.

Physician or other licensed health care professional [PLHCP] is an individual whose legally permitted scope of practice (i.e., license, registration, or certification) allows him or her to independently provide or be delegated the responsibility to provide some or all of the particular health care services required by paragraph (k) of this section.

Regulated area means an area, demarcated by the employer, where an employee's exposure to airborne concentrations of chromium (VI) exceeds, or can reasonably be expected to exceed, the PEL.

This section means this § 1910.1026 chromium (VI) standard.

(c) Permissible exposure limit (PEL). The employer shall ensure that no employee is exposed to an airborne concentration of chromium (VI) in excess of 5 micrograms per cubic meter of air ($5 \mu\text{g}/\text{m}^3$), calculated as an 8-hour time-weighted average (TWA).

(d) Exposure determination.

- (1) General. Each employer who has a workplace or work operation covered by this section shall determine the 8-hour TWA exposure for each employee exposed to chromium (VI). This determination shall be made in accordance with either paragraph (d)(2) or paragraph (d)(3) of this section.
- (2) Scheduled monitoring option.
 - (i) The employer shall perform initial monitoring to determine the 8-hour TWA exposure for each employee on the basis of a sufficient number of personal breathing zone air samples to accurately characterize full shift exposure on each shift, for each job classification, in each work area. Where an employer does representative sampling instead of sampling all employees in order to meet this requirement, the employer shall sample the employee(s) expected to have the highest chromium (VI) exposures.
 - (ii) If initial monitoring indicates that employee exposures are below the action level, the employer may discontinue monitoring for those employees whose exposures are represented by such monitoring.
 - (iii) If monitoring reveals employee exposures to be at or above the action level, the employer shall perform periodic monitoring at least every six months.
 - (iv) If monitoring reveals employee exposures to be above the PEL, the employer shall perform periodic monitoring at least every three months.
 - (v) If periodic monitoring indicates that employee exposures are below the action level, and the result is confirmed by the result of another monitoring taken at least seven days later, the employer may discontinue the monitoring for those employees whose exposures are represented by such monitoring.
 - (vi) The employer shall perform additional monitoring when there has been any change in the production process, raw materials, equipment, personnel, work practices, or control methods that may result in new or additional exposures to chromium (VI), or when the employer has any reason to believe that new or additional exposures have occurred.
- (3) Performance-oriented option. The employer shall determine the 8-hour TWA exposure for each employee on the basis of any combination of air monitoring data, historical monitoring data, or objective data sufficient to accurately characterize employee exposure to chromium (VI).
- (4) Employee notification of determination results.
 - (i) Where the exposure determination indicates that employee exposure exceeds the PEL, within 15 working days the employer shall either post the results in an appropriate location that is accessible to all affected employees or shall notify each affected employee individually in writing of the results.
 - (ii) Whenever the exposure determination indicates that employee exposure is above the PEL, the employer shall describe in the written notification the corrective action being taken to reduce employee exposure to or below the PEL.
- (5) Accuracy of measurement. Where air monitoring is performed to comply with the requirements of this section, the employer shall use a method of monitoring and analysis that can measure chromium (VI) to within an accuracy of plus or minus 25 percent (+/- 25%) and can produce accurate measurements to within a statistical confidence level of 95 percent for airborne concentrations at or above the action level.
- (6) Observation of monitoring.
 - (i) Where air monitoring is performed to comply with the requirements of this section, the employer shall provide affected employees or their designated

- representatives an opportunity to observe any monitoring of employee exposure to chromium (VI).
- (ii) When observation of monitoring requires entry into an area where the use of protective clothing or equipment is required, the employer shall provide the observer with clothing and equipment and shall assure that the observer uses such clothing and equipment and complies with all other applicable safety and health procedures.
- (e) Regulated areas.**
- (1) Establishment. The employer shall establish a regulated area wherever an employee's exposure to airborne concentrations of chromium (VI) is, or can reasonably be expected to be, in excess of the PEL.
- (2) Demarcation. The employer shall ensure that regulated areas are demarcated from the rest of the workplace in a manner that adequately establishes and alerts employees of the boundaries of the regulated area.
- (3) Access. The employer shall limit access to regulated areas to:
- (i) Persons authorized by the employer and required by work duties to be present in the regulated area;
- (ii) Any person entering such an area as a designated representative of employees for the purpose of exercising the right to observe monitoring procedures under paragraph (d) of this section; or
- (iii) Any person authorized by the Occupational Safety and Health Act or regulations issued under it to be in a regulated area.
- (f) Methods of compliance.**
- (1) Engineering and work practice controls.
- (i) Except as permitted in paragraph (f)(1)(ii) and paragraph (f)(1)(iii) of this section, the employer shall use engineering and work practice controls to reduce and maintain employee exposure to chromium (VI) to or below the PEL unless the employer can demonstrate that such controls are not feasible. Wherever feasible engineering and work practice controls are not sufficient to reduce employee exposure to or below the PEL, the employer shall use them to reduce employee exposure to the lowest levels achievable, and shall supplement them by the use of respiratory protection that complies with the requirements of paragraph (g) of this section.
- (ii) Where painting of aircraft or large aircraft parts is performed in the aerospace industry, the employer shall use engineering and work practice controls to reduce and maintain employee exposure to chromium (VI) to or below 25 $\mu\text{g}/\text{m}^3$ unless the employer can demonstrate that such controls are not feasible. The employer shall supplement such engineering and work practice controls with the use of respiratory protection that complies with the requirements of paragraph (g) of this section to achieve the PEL.
- (iii) Where the employer can demonstrate that a process or task does not result in any employee exposure to chromium (VI) above the PEL for 30 or more days per year (12 consecutive months), the requirement to implement engineering and work practice controls to achieve the PEL does not apply to that process or task.
- (2) Prohibition of rotation. The employer shall not rotate employees to different jobs to achieve compliance with the PEL.
- (g) Respiratory protection.**
- (1) General. The employer shall provide respiratory protection for employees during:
- (i) Periods necessary to install or implement feasible engineering and work practice controls;
- (ii) Work operations, such as maintenance and repair activities, for which engineering and work practice controls are not feasible;
- (iii) Work operations for which an employer has implemented all feasible engineering and work practice controls and such controls are not sufficient to reduce exposures to or below the PEL;
- (iv) Work operations where employees are exposed above the PEL for fewer than 30 days per year, and the employer has elected not to implement engineering and work practice controls to achieve the PEL; or
- (v) Emergencies.

- (2) Respiratory protection program. Where respirator use is required by this section, the employer shall institute a respiratory protection program in accordance with 29 CFR 1910.134.
- (h) Protective work clothing and equipment.**
- (1) Provision and use. Where a hazard is present or is likely to be present from skin or eye contact with chromium (VI), the employer shall provide appropriate personal protective clothing and equipment at no cost to employees, and shall ensure that employees use such clothing and equipment.
- (2) Removal and storage.
- (i) The employer shall ensure that employees remove all protective clothing and equipment contaminated with chromium (VI) at the end of the work shift or at the completion of their tasks involving chromium (VI) exposure, whichever comes first.
- (ii) The employer shall ensure that no employee removes chromium (VI)-contaminated protective clothing or equipment from the workplace, except for those employees whose job it is to launder, clean, maintain, or dispose of such clothing or equipment.
- (iii) When contaminated protective clothing or equipment is removed for laundering, cleaning, maintenance, or disposal, the employer shall ensure that it is stored and transported in sealed, impermeable bags or other closed, impermeable containers.
- (iv) Bags or containers of contaminated protective clothing or equipment that are removed from change rooms for laundering, cleaning, maintenance, or disposal shall be labeled in accordance with the requirements of the Hazard Communication Standard, 29 CFR 1910.1200.
- (3) Cleaning and replacement.
- (i) The employer shall clean, launder, repair and replace all protective clothing and equipment required by this section as needed to maintain its effectiveness.
- (ii) The employer shall prohibit the removal of chromium (VI) from protective clothing and equipment by blowing, shaking, or any other means that disperses chromium (VI) into the air or onto an employee's body.
- (iii) The employer shall inform any person who launders or cleans protective clothing or equipment contaminated with chromium (VI) of the potentially harmful effects of exposure to chromium (VI) and that the clothing and equipment should be laundered or cleaned in a manner that minimizes skin or eye contact with chromium (VI) and effectively prevents the release of airborne chromium (VI) in excess of the PEL.
- (i) Hygiene areas and practices.**
- (1) General. Where protective clothing and equipment is required, the employer shall provide change rooms in conformance with 29 CFR 1910.141. Where skin contact with chromium (VI) occurs, the employer shall provide washing facilities in conformance with 29 CFR 1910.141. Eating and drinking areas provided by the employer shall also be in conformance with § 1910.141.
- (2) Change rooms. The employer shall assure that change rooms are equipped with separate storage facilities for protective clothing and equipment and for street clothes, and that these facilities prevent cross-contamination.
- (3) Washing facilities.
- (i) The employer shall provide readily accessible washing facilities capable of removing chromium (VI) from the skin, and shall ensure that affected employees use these facilities when necessary.
- (ii) The employer shall ensure that employees who have skin contact with chromium (VI) wash their hands and faces at the end of the work shift and prior to eating, drinking, smoking, chewing tobacco or gum, applying cosmetics, or using the toilet.
- (4) Eating and drinking areas.
- (i) Whenever the employer allows employees to consume food or beverages at a worksite where chromium (VI) is present, the employer shall ensure that eating and drinking areas and surfaces are maintained as free as practicable of chromium (VI).

- (ii) The employer shall ensure that employees do not enter eating and drinking areas with protective work clothing or equipment unless surface chromium (VI) has been removed from the clothing and equipment by methods that do not disperse chromium (VI) into the air or onto an employee's body.
- (5) Prohibited activities. The employer shall ensure that employees do not eat, drink, smoke, chew tobacco or gum, or apply cosmetics in regulated areas, or in areas where skin or eye contact with chromium (VI) occurs; or carry the products associated with these activities, or store such products in these areas.
- (j) Housekeeping.**
 - (1) General. The employer shall ensure that:
 - (i) All surfaces are maintained as free as practicable of accumulations of chromium (VI).
 - (ii) All spills and releases of chromium (VI) containing material are cleaned up promptly.
 - (2) Cleaning methods.
 - (i) The employer shall ensure that surfaces contaminated with chromium (VI) are cleaned by HEPA-filter vacuuming or other methods that minimize the likelihood of exposure to chromium (VI).
 - (ii) Dry shoveling, dry sweeping, and dry brushing may be used only where HEPA-filtered vacuuming or other methods that minimize the likelihood of exposure to chromium (VI) have been tried and found not to be effective.
 - (iii) The employer shall not allow compressed air to be used to remove chromium (VI) from any surface unless:
 - (iii)
 - (A) The compressed air is used in conjunction with a ventilation system designed to capture the dust cloud created by the compressed air; or
 - (B) No alternative method is feasible.
 - (iv) The employer shall ensure that cleaning equipment is handled in a manner that minimizes the reentry of chromium (VI) into the workplace.
 - (3) Disposal.** The employer shall ensure that:
 - (i) Waste, scrap, debris, and any other materials contaminated with chromium (VI) and consigned for disposal are collected and disposed of in sealed, impermeable bags or other closed, impermeable containers.
 - (ii) Bags or containers of waste, scrap, debris, and any other materials contaminated with chromium (VI) that are consigned for disposal are labeled in accordance with the requirements of the Hazard Communication Standard, 29 CFR 1910.1200.
- (k) Medical surveillance.**
 - (1) General.
 - (i) The employer shall make medical surveillance available at no cost to the employee, and at a reasonable time and place, for all employees:
 - (A) Who are or may be occupationally exposed to chromium (VI) at or above the action level for 30 or more days a year;
 - (B) Experiencing signs or symptoms of the adverse health effects associated with chromium (VI) exposure; or
 - (C) Exposed in an emergency.
 - (ii) The employer shall assure that all medical examinations and procedures required by this section are performed by or under the supervision of a PLHCP.
 - (2) Frequency. The employer shall provide a medical examination:
 - (i) Within 30 days after initial assignment, unless the employee has received a chromium (VI) related medical examination that meets the requirements of this paragraph within the last twelve months;
 - (ii) Annually;
 - (iii) Within 30 days after a PLHCP's written medical opinion recommends an additional examination;
 - (iv) Whenever an employee shows signs or symptoms of the adverse health effects associated with chromium (VI) exposure;
 - (v) Within 30 days after exposure during an emergency which results in an uncontrolled release of chromium (VI); or

- (vi) At the termination of employment, unless the last examination that satisfied the requirements of paragraph (k) of this section was less than six months prior to the date of termination.
- (3) Contents of examination. A medical examination consists of:
 - (i) A medical and work history, with emphasis on: Past, present, and anticipated future exposure to chromium (VI); any history of respiratory system dysfunction; any history of asthma, dermatitis, skin ulceration, or nasal septum perforation; and smoking status and history;
 - (ii) A physical examination of the skin and respiratory tract; and
 - (iii) Any additional tests deemed appropriate by the examining PLHCP.
- (4) Information provided to the PLHCP. The employer shall ensure that the examining PLHCP has a copy of this standard, and shall provide the following information:
 - (i) A description of the affected employee's former, current, and anticipated duties as they relate to the employee's occupational exposure to chromium (VI);
 - (ii) The employee's former, current, and anticipated levels of occupational exposure to chromium (VI);
 - (iii) A description of any personal protective equipment used or to be used by the employee, including when and for how long the employee has used that equipment; and
 - (iv) Information from records of employment-related medical examinations previously provided to the affected employee, currently within the control of the employer.
- (5) PLHCP's written medical opinion.
 - (i) The employer shall obtain a written medical opinion from the PLHCP, within 30 days for each medical examination performed on each employee, which contains:
 - (A) The PLHCP's opinion as to whether the employee has any detected medical condition(s) that would place the employee at increased risk of material impairment to health from further exposure to chromium (VI);
 - (B) Any recommended limitations upon the employee's exposure to chromium (VI) or upon the use of personal protective equipment such as respirators;
 - (C) A statement that the PLHCP has explained to the employee the results of the medical examination, including any medical conditions related to chromium (VI) exposure that require further evaluation or treatment, and any special provisions for use of protective clothing or equipment.
 - (ii) The PLHCP shall not reveal to the employer specific findings or diagnoses unrelated to occupational exposure to chromium (VI).
 - (iii) The employer shall provide a copy of the PLHCP's written medical opinion to the examined employee within two weeks after receiving it.
- (I) Communication of chromium (VI) hazards to employees.
 - (1) General. In addition to the requirements of the Hazard Communication Standard, 29 CFR 1910.1200, employers shall comply with the following requirements.
 - (2) Employee information and training.
 - (i) The employer shall ensure that each employee can demonstrate knowledge of at least the following:
 - (A) The contents of this section; and
 - (B) The purpose and a description of the medical surveillance program required by paragraph (k) of this section.
 - (ii) The employer shall make a copy of this section readily available without cost to all affected employees.
- (m) Recordkeeping.
 - (1) Air monitoring data.
 - (i) The employer shall maintain an accurate record of all air monitoring conducted to comply with the requirements of this section.
 - (ii) This record shall include at least the following information:
 - (A) The date of measurement for each sample taken;
 - (B) The operation involving exposure to chromium (VI) that is being monitored;
 - (C) Sampling and analytical methods used and evidence of their accuracy;

- (D) Number, duration, and the results of samples taken;
 - (E) Type of personal protective equipment, such as respirators worn; and
 - (F) Name, social security number, and job classification of all employees represented by the monitoring, indicating which employees were actually monitored.
- (iii) The employer shall ensure that exposure records are maintained and made available in accordance with 29 CFR 1910.1020.
- (2) Historical monitoring data.
 - (i) Where the employer has relied on historical monitoring data to determine exposure to chromium (VI), the employer shall establish and maintain an accurate record of the historical monitoring data relied upon.
 - (ii) The record shall include information that reflects the following conditions:
 - (A) The data were collected using methods that meet the accuracy requirements of paragraph (d)(5) of this section;
 - (B) The processes and work practices that were in use when the historical monitoring data were obtained are essentially the same as those to be used during the job for which exposure is being determined;
 - (C) The characteristics of the chromium (VI) containing material being handled when the historical monitoring data were obtained are the same as those on the job for which exposure is being determined;
 - (D) Environmental conditions prevailing when the historical monitoring data were obtained are the same as those on the job for which exposure is being determined; and
 - (E) Other data relevant to the operations, materials, processing, or employee exposures covered by the exception.
 - (iii) The employer shall ensure that historical exposure records are maintained and made available in accordance with 29 CFR 1910.1020.
 - (3) Objective data.
 - (i) The employer shall maintain an accurate record of all objective data relied upon to comply with the requirements of this section.
 - (ii) This record shall include at least the following information:
 - (A) The chromium containing material in question;
 - (B) The source of the objective data;
 - (C) The testing protocol and results of testing, or analysis of the material for the release of chromium (VI);
 - (D) A description of the process, operation, or activity and how the data support the determination; and
 - (E) Other data relevant to the process, operation, activity, material, or employee exposures.
 - (iii) The employer shall ensure that objective data are maintained and made available in accordance with 29 CFR 1910.1020.
 - (4) Medical surveillance.
 - (i) The employer shall establish and maintain an accurate record for each employee covered by medical surveillance under paragraph (k) of this section.
 - (ii) The record shall include the following information about the employee:
 - (A) Name and social security number;
 - (B) A copy of the PLHCP's written opinions;
 - (C) A copy of the information provided to the PLHCP as required by paragraph (k)(4) of this section.
 - (iii) The employer shall ensure that medical records are maintained and made available in accordance with 29 CFR 1910.1020.
- (n) Dates.**
- (1) For employers with 20 or more employees, all obligations of this section, except engineering controls required by paragraph (f) of this section, commence November 27, 2006.
 - (2) For employers with 19 or fewer employees, all obligations of this section, except engineering controls required by paragraph (f) of this section, commence May 30, 2007.
 - (3) Except as provided in (n)(4), for all employers, engineering controls required by paragraph (f) of this section shall be implemented no later than May 31, 2010.

- (4) In facilities that become parties to the settlement agreement included in Appendix A, engineering controls required by paragraph (f) of this section shall be implemented no later than December 31, 2008.

Appendix A to Sec. 1910.1026

In the United States Court of Appeals for the Third Circuit

Surface Finishing Industry Council et al., Petitioners, v. U.S. Occupational Safety and Health Administration, Respondent.

[Docket No. 06-2272 and consolidated cases]

Public Citizen Health Research Group et al., Petitioners, v. Occupational Safety and Health Administration, United States Department of Labor, Respondent.

[Docket No. 06-1818]

Settlement Agreement

The parties to this Settlement Agreement ("Agreement") are the Occupational Safety and Health Administration, United States Department of Labor ("OSHA"), the Surface Finishing Industry Council or its successors ("SFIC"), surface-finishing and metal-finishing facilities which have opted into this Agreement pursuant to paragraph 7 ("Company" or "Companies"), Public Citizen Health Research Group ("HRG"), and the United Steel, Paper and Forestry, Rubber, Manufacturing, Energy, Allied Industrial and Service Workers International Union ("Steelworkers").

Whereas, On February 28, 2006, OSHA promulgated a revised hexavalent chromium standard for general industry ("the Standard") that includes a permissible exposure limit ("PEL") for hexavalent chromium of 5 micrograms per cubic meter (" $5 \mu\text{g}/\text{m}^3$ ") measured as an 8-hour time-weighted average ("TWA"), and a deadline of May 31, 2010, for employers to come into compliance with this PEL through the implementation of engineering controls. The deadline for compliance with the remaining provisions of the Standard, including those requiring the use of respiratory protection to comply with the PEL, is November 27, 2006, for employers with twenty (20) or more employees, and May 30, 2007, for employers with nineteen (19) or fewer employees. 29 CFR 1910.1026, 71 FR 10100 (Feb. 28, 2006);

Whereas, SFIC filed a Petition for Review of the Standard in the Eleventh Circuit that was consolidated with other Petitions in the Third Circuit (Case No. 06-2272);

Whereas, SFIC filed a Motion for Leave to Intervene in the matter of HRG's Petition for Review in the Third Circuit (Case No. 06-1818), which has been granted;

Now, therefore, the parties to this Agreement do hereby agree to the following terms:

1. Term of this Agreement. This Agreement will be effective upon execution and will expire on May 31, 2010.
2. Accelerated implementation of engineering controls. The Companies agree that in accordance with 29 CFR 1910.1026(f)(1) they will implement those feasible engineering controls necessary to reduce hexavalent chromium levels at their facilities by December 31, 2008, to or below the 5 $\mu\text{g}/\text{m}^3$ PEL. In fulfilling this obligation, the Companies may select from the engineering and work practice controls listed in Exhibit A to this Agreement or adopt any other controls.
3. Compliance plan and monitoring. In accordance with 29 CFR 1910.1026(d)(4)(ii), each Company will prepare, and update as required, a written plan setting forth the specific control steps being taken to reduce employee exposure to or below the PEL by December 31, 2008. In addition, Companies will make an initial exposure determination as required by 29 CFR 1910.1026(d)(1) using either the procedures for personal breathing zone air samples described in 29 CFR 1910.1026(d)(2) or the performance-oriented option described at 29 CFR 1910.1026(d)(3). Thereafter, Companies will conduct periodic monitoring in accordance with the "Scheduled Monitoring Option" provisions at 29 CFR 1910.1026(d)(2) and related provisions at 29 CFR 1910.1026(d)(4)-(6). The Companies agree that upon request compliance plans prepared in accordance with this paragraph, as well as all monitoring results obtained in compliance with this

- paragraph, will be provided to OSHA, affected employees and employee representatives.
4. Respirator use. The respiratory protection provisions at 29 CFR 1910.1026(f) and (g) will apply to the Companies in accordance with the terms and dates set forth in the Standard, except that prior to December 31, 2008, for Companies that are in compliance with this Agreement, OSHA will enforce those respiratory protection provisions only with respect to employees who fall into one of the following six (6) categories: (1) Employees who are exposed to hexavalent chromium in excess of the PEL while performing tasks described in Exhibit B to this Agreement; (2) through November 30, 2007, employees whose exposures to hexavalent chromium exceed a "respirator threshold" of 20 [μ g/m³] (measured as an 8-hour TWA); (3) beginning December 1, 2007, employees whose exposures to hexavalent chromium exceed a "respirator threshold" of 12.5 [μ g/m³] (measured as an 8-hour TWA); (4) employees who are exposed to hexavalent chromium and request a respirator; (5) any other employees who are required by the Companies to wear a respirator; and (6) employees with exposures for which respirators were required under the previous hexavalent chromium standard (1910.1000) and any other employees covered by respirator programs in effect on May 30, 2006.
 5. Employee information and training. Company employees will be trained pursuant to the provisions of 29 CFR 1910.1026(l)(2). In addition, the Companies agree to train employees in the provisions of this Agreement within sixty (60) days of the Opt-In Date (defined in paragraph 7 of this Agreement). The training regarding this Agreement shall be provided in language the employees can understand.
 6. Enforcement. Within thirty (30) days of the execution of this Agreement, OSHA will publish a notice in the Federal Register amending 29 CFR 1910.1026 as follows:
 - (1) A copy of this Agreement will be attached to the Standard as Appendix A;
 - (2) a new paragraph, 1910.1026(n)(4), will be added to the Standard, and will read: "In facilities that become parties to the settlement agreement included in Appendix A, engineering controls required by paragraph (f) of this section shall be implemented no later than December 31, 2008"; and
 - (3) existing paragraph 1910.1026(n)(3) will be amended to read: "Except as provided in (n)(4), for all employers, engineering controls required by paragraph (f) of this section shall be implemented no later than May 31, 2010."
 7. Opt-In Date for Companies to become parties to this Agreement. The Federal Register notice described in paragraph 6 of this Agreement will provide notice of the provisions of this Agreement, and of the revisions to the Standard described in paragraph 6, and will provide until November 30, 2006, for eligible facilities to become parties to this Agreement, and be subject to all of the duties, obligations, and rights herein. The last date for signing by facilities shall be referred to as the Opt-In Date. The opt in option will be available on a facility by facility basis and only to SFIC members and other surface-finishing and metal-finishing job shop facilities within the jurisdiction of Federal OSHA. (For purposes of this Agreement, a "job shop" is defined as a facility that sells plating or anodizing services to other companies.) Moreover, the terms of this Agreement apply only with respect to the performance of surface-finishing and metal-finishing operations in those facilities. Although this Agreement applies only to facilities within the jurisdiction of Federal OSHA, OSHA will encourage States with OSHA-approved State occupational safety and health plans to either honor and implement the terms of this Agreement, including the amendments to the standard described in paragraph 6, or to take an alternative position, which may include entering into separate arrangements with surface- and metal-finishing job shop facilities (or their representatives) in their jurisdiction.
 8. Effect on third parties. Nothing in this Agreement constitutes an admission by SFIC or the Companies that a significant risk of material health impairment exists for hexavalent chromium justifying a reduction of the PEL to 5 [μ g/m³]. Nor does anything in this Agreement constitute any other admission by SFIC or the Companies for purposes of this litigation or future litigation or standards-setting. This Agreement is not intended to give any rights to any third party except as expressly provided herein.
 9. OSHA inspections. OSHA may do monitoring inspections to assess compliance with and progress under this Agreement and the Standard, and nothing in this Agreement limits OSHA's right to conduct inspections at Companies' facilities in accordance with the Occupational Safety and Health Act.

10. Scope of Agreement. The terms of this Agreement apply only in the circumstances and to the Companies specified herein. In entering into this Agreement, OSHA is not making any representations regarding its enforcement policy with respect to either (1) The hexavalent chromium standard as applied to employers who are not parties to this Agreement or (2) any other occupational safety or health standards.
11. Effect of invalidation of the Standard. If the Standard is invalidated, nothing in this Agreement shall prevent the application to SFIC or the Companies of any PEL that is promulgated by OSHA on remand. This Agreement would not foreclose SFIC or the Companies from participating in rulemaking proceedings or otherwise challenging any new PEL promulgated by OSHA on remand.
12. Withdrawal of Petitions and Interventions. SFIC agrees to move to withdraw its Petition for Review in the above-captioned case, Case No. 06-2272, within five (5) working days of the execution of this Agreement. SFIC further will move to dismiss its motion to intervene in Case No. 06-1818 and all other challenges simultaneously with its motion to withdraw in Case No. 06-2272 as Petitioner.
13. Attorneys' fees. Each party agrees to bear its own attorneys' fees, costs, and other expenses that have been incurred in connection with SFIC's Petition for Review, SFIC's intervention in HRG's Petition for Review, and the negotiation of this Agreement up to and including filing of the motions to dismiss.
14. Support of Agreement. In the event that all or any portion of this Agreement is challenged in any forum, the signatories below agree to move to intervene in support of this Agreement.

Agreed to this 25th day of October, 2006.

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Exhibit A

Available Engineering and Work Practice Controls

The Companies agree that work towards the implementation of these available engineering and work practice controls should not be delayed to accommodate their completion by December 31, 2008. The Companies are encouraged to implement from among these controls as soon as practicable.

1. Parts Transfer Practices

Minimize droplet formation. Instruments akin to garden hoses are used to rinse off parts coming out of chemical baths. This causes many small droplets to form, which are easily atomized or vaporized and contribute to airborne chromium concentration. The industry is currently developing ways to minimize the formation of small droplets, dripping, or splashing, possibly by reducing hose pressure.

Minimize air current flow. Strong air currents across these droplets may contribute to their vaporization, and therefore minimizing air current flow across the droplets may reduce airborne hexavalent chromium levels.

Slow part speeds as feasible. The speed at which parts are pulled out of a chemical tank causes splashing, which adds to chromium vaporization. By slowing the speed at which parts are taken out of tanks, splashing and vaporization can be minimized. The feasibility of this control must be evaluated in light of the negative effect on productivity.

2. Plating Bath Surface Tension Management and Fume Suppression

Lower surface tension. Lower surface tension in chemical baths leads to fewer drops forming. Chromium baths currently have a surface tension of 35 dynes per centimeter. As a comparison, water has a surface tension of 72 dynes per centimeter. Lowering surface tension further would lead to reduced airborne hexavalent chromium levels.

Fume suppressants. Fume suppressants create a physical barrier between the chemical bath and the air, which prevents vaporization. Some suppressants, however, may cause pitting or other metal damage, and therefore their use is not always possible.

3. Facility Air Disturbance Monitoring

Improvement of local exhaust ventilation (LEV) capture efficiency. The majority of electroplating facilities are not air-conditioned. As a result, doors are kept open to let in cool air, but this causes air currents that prevent the LEVs from performing efficiently. The use of fans has a similar effect. Industry is researching how to minimize these air currents so that LEVs can perform as designed. Such methods may include the use of partitions to degrade air current flow, or checklists that may include location and positioning of cross drafts, fans, doors, windows, partitions and process equipment that Companies can use to audit their workplaces in order to improve their capture efficiency.

4. Technology Enhancements In Lieu of LEV Retrofitting

Eductors. Many chemical baths are currently mixed via air agitation: Air pipes bubble air into the tank to keep the chemicals mixed and to prevent them from settling. An adverse effect of this agitation is that air bubbles escape at the surface of the tank, resulting in some chromium vaporization. By using eductors (horn-shaped nozzles) in tanks, the chemicals flow from a pump to create solution movement below the surface without the use of air bubbles, and the amount of chromium vaporization can be significantly reduced.

5. Different Means of Chromium Additions

Liquid Chromium. Dry hexavalent chromium flakes are occasionally added to tanks, which can generate airborne particulates of hexavalent chromium. Adding liquid chromium at or near the surface of a tank would lower airborne chromium levels and reduce splashing from tanks.

Hydration of flakes before addition. To add liquid chromium to tanks, the dry flakes must be hydrated. Whether this process is performed by chemical suppliers that provide plating solutions to metal finishing companies or by metal finishing companies that have the necessary experience and equipment, appropriate work practices such as mixing techniques must be implemented to minimize the potential airborne levels of hexavalent chromium.

6. Dust Control

Better housekeeping. Chrome dust that comes off products that are polished or grinded is actually elemental chromium, not hexavalent chromium, so polishing and grinding contribute little to airborne hexavalent chromium levels. However, Companies should use good housekeeping practices, including wet mopping, and wet wipedowns, to reduce the amount of dust present.

7. Improvement and Maintenance of Existing LEVs

Improvement and maintenance of existing LEVs. Companies may repair and maintain their current LEVs. Because the final rule indicates that at least 75 percent of the industry is in compliance with the PEL with LEVs working at 40% of capacity, increasing LEV function can materially affect compliance.

8. Other Controls

Other methods. Companies are constantly determining best work practices and technological controls through laboratory research and practical experience. Companies will implement other engineering and work practice controls as necessary and as practicable to reduce potential hexavalent chromium workplace exposures.

Exhibit B

Workplace Tasks Requiring Respirators Where PEL Is Exceeded

Some well-known and relatively few, discrete tasks related to metal finishing activities result in potentially higher workplace exposures of hexavalent chromium. Where the applicable PEL for hexavalent chromium is exceeded, respirators shall be worn to conduct the following activities:

- (1) Hexavalent chromium chemical additions. In order to have the metal deposited onto the part, hexavalent chromium must be added to the plating tank periodically. This is a discrete activity that involves the addition of either a dry flake of hexavalent chromium chemicals or a liquid solution of hexavalent chromium into the plating tank. Respirators shall be worn during the period it takes to add the hexavalent chromium chemical to the tank.
- (2) Hexavalent chromium preparation and mixing. Different mixtures of hexavalent chromium chemicals are needed for different types of chromium plating processes. For example, hard chromium plating can require higher concentrations of hexavalent chromium because a thicker coating and longer plating process may be needed for the critical product quality and performance. Similarly, different types of decorative chromium plating processes may need different levels of hexavalent chromium and other chemicals such as catalysts. These mixtures can be in the form of dry flakes or liquid solutions. All of these different hexavalent chromium chemical mixtures are generally prepared by metal finishing suppliers and distributors. Some metal finishing companies may also prepare hexavalent chromium solutions from the dry flakes prior to addition to the plating tanks. Respirators shall be worn during the period it takes to prepare these hexavalent chromium mixtures and solutions whether the activity is conducted at a chemical supplier or a metal finishing company.
- (3) Hexavalent chromium tank cleaning. Occasionally, the tanks used for chromium plating may need to be emptied and cleaned. This process would involve the draining of the solution and then the removal of any residues in the tank. Workers cleaning out these tanks may have to enter the tank or reach into it to remove the residues. Respirators (as well as other appropriate PPE) shall be worn during the period it takes to clean the tanks and prepare them for use again.
- (4) Hexavalent chromium painting operations. Some metal finishing operations apply paints with higher concentrations of hexavalent chromium to a line of parts, particularly for aerospace applications when a high degree of corrosion protection is needed for critical product performance. Paints are generally applied in such operations with some type of spray mechanism or similar dispersion practice. In some instances, it may be difficult to keep workplace exposures below the PEL for such paint spraying activities. Respirators shall be worn during such spray painting operations.