DEPARTMENT OF LABOR AND HUMAN RESOURCES
Office of the Secretary
Hato Rey, Puerto Rico

No. 4976
Date: October 7 1993 3:30 P.M.
Approved: Baltasar Corrada del Río
Secretary of State

By: [signature]
Assistant Secretary of State

R E S O L U T I O N

I, César Juan Almodóvar Marchany, Puerto Rico Secretary of Labor and Human Resources, pursuant to the authority conferred by Section 8 of Puerto Rico Occupational Safety and Health Act, Number 16 of August 5, 1975 as amended (29 LPRA) 361 et seq.,) hereby amend the Puerto Rico Occupational Safety and Health Regulation, Number Twelve (Part 1915,1916,1917 and 1918) approved on February 1st, 1978 and amended on March 23,September 30, 1983, March 16,1987, April 8, September 28, 1988, February 13, 1990 and March 10, 1993 by adopting the following amendment:

Occupational Exposure to Cadmium; Corrections Vol. 58, No. 77 of April 23, 1993 (21778-21850).

The adoption of this amendment shall be effective immediately after its approval.

Given on this 30 day of September 1993.

[signature]
CESAR JUAN ALMODOVAR MARCHANY

DEPARTMENT OF LABOR

Occupational Safety and Health Administration

29 CFR Parts 1910, 1915 and 1928

[Docket No. H-057a]

Occupational Exposure to Cadmium; Correction

AGENCY: Occupational Safety and Health Administration (OSHA), Department of Labor.

ACTION: Final rule; correction and amendment.

SUMMARY: The Occupational Safety and Health Administration is correcting errors in the entire Occupational Exposure to Cadmium Final Rule which appeared in the Federal Register on September 14, 1992 (57 FR 42101) and adding new provisions on Occupational Health to cover the agriculture industry. Regulations covering the agriculture industry were inadvertently omitted from the September 14 rule.

EFFECTIVE DATE: December 14, 1992.

FOR FURTHER INFORMATION CONTACT: Mr. James Foster, Occupational Safety and Health Administration, Office of Information and Public Affairs, room N-3647, U.S. Department of Labor, 200 Constitution Avenue NW., Washington, DC 20210. Telephone: 202-219-8151.

SUPPLEMENTARY INFORMATION:

Background

OSHA has promulgated a standard to reduce occupational exposure to all forms of cadmium in the general, agriculture and maritime industries. A separate standard for the construction industry was also published. Both standards establish a time-weighted-average permissible exposure limit (TWA PEL) of 5 micrograms per cubic meter of air (5 $\mu g/m^3$) and an action level (AL) of 2.5 $\mu g/m^3$.

Need for Correction

During the proofreading process of these regulations, technical and typographical errors were discovered. This notice is being published to correct these errors. With the exception of the explanation and related correction below these corrections are essentially self-explanatory.

The amendments in this document rectify the technical failure to print the standard for the agricultural industries (29 CFR Part 1928), and reflect OSHA's consistent intention to cover the general, agricultural and maritime industries (57 FR 42333; 55 FR 4121; February 6, 1990).

OSHA deleted the saccharin solution aerosol qualitative fit test protocol from the Cadmium final rule based upon a misreading of a comment submitted by the Maryland Occupational Safety and Health Administration (MOSH). The comment suggested the deletion of a reference to disposable dust respirators from the saccharin solution protocol in page 4131 Appendix C of the proposed Cadmium standard, 55 FR 4052 (February 6, 1990), since the standard prohibited the use of such respirators unless equipped with high efficiency filters. MOSH deemed the deletion to be necessary to avoid confusion. OSHA mistakenly deleted the entire protocol instead of only eliminating the reference to disposable dust respirators from the saccharin solution protocol. OSHA is correcting the preamble to the final rule and Appendix C by reinstating the deleted protocol and eliminating the reference to disposable dust respirators from the saccharin solution protocol to accurately reflect MOSH's comment.

OSHA also corrected the final rule by deleting the word "within" from a very narrow and specific portion of the medical surveillance program concerning the timing of follow-up biological monitoring examinations of veteran employees. Such examinations must be conducted "approximately one year" after the employees' initial biological monitoring results are determined (57 FR 42352). This correction was made in order to reflect the intent of the preamble and to prevent possible misinterpretation.

Correction of Publication

The following corrections are made in the final rule for Occupational Exposure to Cadmium published in the Federal Register on September 14, 1992 (57 FR 42101).

1. On page 42102, the CFR heading for the document is corrected to read, "29 CFR Parts 1910, 1915, 1926, and 1928".

2. On page 42102, first column, third paragraph, lines 11 through 15 are corrected to read, "has also established separate engineering control air limits (SECAL) of either 15 $\mu g/m^3$ or 50 $\mu g/m^3$ as the lowest feasible levels above the PEL that can be achieved by engineering and work practice controls."

3. On page 42102, second column, second paragraph after the heading, "A. General", lines 5 and 6, is corrected to read, "at 29 CFR 1910.1027 for general industry, § 1915.1027 for maritime, § 1928.1027 for agriculture and § 1926.63 for the construction industry.".

4. On page 42103, third column, first full paragraph after the heading, "C. Regulation", line 2, is corrected to read, "standard is also found in section 8(c)".

5. On page 42109, second column, second full paragraph, line 13, is corrected to read, "lethal concentration of cadmium was".

6. On page 42109, third column, line 2, is corrected to read "this exposure level, there is".

7. On page 42110, third column, first full paragraph, line 28, is corrected to read, "proteinuria (Exs. 8-86-B, p. 63; 4-54). In"

8. On page 42113, third column below table V-2, paragraph "Iv. Jarup et al.", line 15, the word "had" is corrected to read "have".

9. On page 42114, second column, table V-3., left most column, the sixth entry is corrected to read, ">15,000".

10. On page 42115, third column, line 1, is corrected to read, "Cr the proportion of cases of β_2-M".

11. On page 42115, third column, first full paragraph, lines 12, 13 and 14 are corrected to read "using the model: log (B_2-M) =[a×age]+[b×cumulative dose]+[c]. Elinder".

12. On page 42115, third column, third full paragraph, lines 13 and 14 are corrected to read, "working lifetime (1 mg/m^3×45 years=22.2 $\mu g/m^3$.) If exposures are".

13. On page 42115, table V-6., far left column, line 5, under the heading, "Cum exposure (mg/m^3-yrs)", is corrected to read, "25".

14. On page 42115, table V-6., middle column, under the heading "Slight proteinuria[1] No. (percent)[2]", fourth entry, the symbol "<" is deleted.

15. On page 42116, table V-8., is corrected to read,

"TABLE V-8.—PREVALENCE OF KIDNEY DYSFUNCTION BY CUMULATIVE CADMIUM EXPOSURE

Cumulative exposure[1]	Number normal[2]	Number abnormal[3]	Percent abnormal
≤500	96	5	4.9
>500-≤1000	14	0	0.0
>1000-≤1500	3	5	62.5
>1500	4	20	83.3

[1] Cumulative Exposure measured in ug/m^3-year

[2] Normal measured by Retinol Binding Protein (RPB): < 40 µg RPB/mmol Cr

[3] Abnormal measured by Retinol Binding Protein (RBP): > 40 µg RPB/mmol Cr".

16. On page 42117, table V-10., right most column, third entry, under the heading "P Value", is corrected to read, "<0.0001".

17. On page 42118, first column, second paragraph, line 9 is corrected to

read, "In persons with cumulative exposure ≥".

18. On page 42119, first column, third full paragraph, line 11, is corrected to read, "μg/liter and total protein ≤135 mg/l. For".

19. On page 42129, the heading for Table V–19 is corrected to read, "Levels of Cadmium in Blood and Urine Among Workers in Pigment Production: Average Levels of Cadmium in Blood (μg/liter whole blood) and Cadmium in Urine (μg/gram creatinine)".

20. On page 42131, third column, third paragraph, line 11, is corrected to read, "The unexposed group whose".

21. On page 42132, third column, second full paragraph under the heading, "Ix. Summary", line 10, is corrected to read, "were 10.3 μg/lwb and 8.78 μg/g Cr.".

22. On page 42134, first column, first paragraph, line 3, is corrected to read, "and may cause damage; there is medical".

23. On page 42149, third column, first full paragraph, lines 10 through 12 are corrected to read, "CdO-exposed rats. Neither Dr. Heinrich nor Dr. Oberdörster, however, could give an estimate of the carcinogenic".

24. On page 42168, table VI–2., column headed, "Weibull model[a]", delete the superscript "a".

25. On page 42170, second column, table VI–5, the entries in the column marked "Cumulative dose (μg/m³-yrs)" is corrected to read:

45
225
450
900
1800
2250
4500

26. On page 42171, second column, third full paragraph, lines 4 and 5, are corrected to read, "(Exs. 38; 19–43; L–140–23; 144–8a; 144–8b; 114–8c; 114–17). The Globe plant".

27. On page 42174, third column, line 16, is corrected to read "et al., Ex. 4–34; Levy et al., Ex. 8–117).".

28. On page 42177, Table VI–7., the "Combined" "Exp" column, the entries marked "7" on lines 2 and 10 are deleted.

29. On page 42178, first column, fourth paragraph, line 4, change the "≤" symbol to a "≥" symbol.

30. On page 42178, second column, third paragraph, the equation under "Linear:" is corrected to read, "$h=\alpha+E_j(\Theta_jW_j)+\Gamma\chi+\delta Y+\beta X$".

31. On page 42178, third column, line 10, is corrected to read, "$[E_j; (\Theta_jW_j)=\Theta_j$, where j' is the particular".

32. On page 42178, third column, line 13, is corrected to read, "χ represents Hispanic ethnicity (χ=1 if".

33. On page 42179, second column below table VI–8., move the word "Where:" to below the formula and preceding the definition "RR_i is the risk ratio for lung cancer predicted by the model based on the exposure scenario assumed.".

34. On page 42179, second column, line 4 following the formula is corrected to read, "$q_1(i)$ is the background age-specific lung".

35. On page 42180, second column, table VI–9., the heading, "Relative Rate Model" should only be above the columns labeled, "Poisson regression[a]" and "Cox regression[b]".

36. On page 42180, second column, table VI–9., footnotes "a" and "b" are corrected to read,

"a is β=0.00061 (μg-years/m³)$^{-1}$
b is β=0.00028 (μg-years/m³)$^{-1}$".

37. On page 42181, first column, third paragraph, line 2, is corrected to read, "restriction a_{NH}=0 (corresponding to".

38. 38. On page 42181, third column, table VI–10., is corrected to read:

TABLE VI–10.—RESULTS OF APPLYING OSHA'S MODIFIED RELATIVE RISK MODEL TO THE 1984 FOLLOWUP OF THE THUN COHORT

	Case I[a] (a_{NH} = 0)	Case II[a] (a_{NH} estimated)
a_H (s.e.)	−1.4 (0.60)	−1.8 (0.91)
a_{NH}	0	−0.48 (0.77)
β[b]	0.00027 (0.000098)	0.00054 (0.00057)
Deviance	10.29	9.88

[a]Case I assumes lung cancer mortality rates for U.S. white males are appropriate background rates for non-Hispanic white males in this cohort. Case II permits background rates for non-Hispanic white males to differ from rates for U.S. white males by the multiplicative constant, exp (a_{NH}).
[b]Units are (μg-years/m³)$^{-1}$.

39. On page 42181, table VI–11, is corrected to read:

TABLE VI–11.—OBSERVED AND PREDICTED LUNG CANCER DEATHS FROM THE RELATIVE RISK MODEL APPLIED TO THE 1984 UPDATE TO THE THUN COHORT

Exposure (μg-years/m³)	Number of lung cancers observed	Number of lung cancers predicted	
		Case I[a] (a_{NH}=0)	Case II[a] (a_{NH} estimated)
Non-Hispanics			
795	1	4.1	3.0
2466	7	4.4	3.8
5699	6	4.0	3.9
10836	7	9.5	10.3

TABLE VI–11.—OBSERVED AND PREDICTED LUNG CANCER DEATHS FROM THE RELATIVE RISK MODEL APPLIED TO THE 1984 UPDATE TO THE THUN COHORT—Continued

Exposure (µg-years/m³)	Number of lung cancers observed	Number of lung cancers predicted	
		Case I[a] (a_{NH}=0)	Case II[a] (a_{NH} estimated)
Hispanics			
795	1	0.71	0.50
2466	0	0.67	0.63
5699	0	0.75	0.80
10636	2	0.87	1.0
		X^2=8.5 (NS) 6 df	X^2=8.8 (NS) 5 df

NS=nonsignificant lack of fit
df=degrees of freedom
[a]Case I assumes lung cancer mortality rates for U.S. white males are appropriate background rates for non-Hispanic white males in this cohort. Case II permits background rates for non-Hispanic white males to differ from rates for U.S. white males by the multiplicative constant, exp (a_{NH}).

40. On page 42181, second column below table VI–11., line 1, the "=" symbol is corrected to read, "≡".

41. On page 42182, third column, second paragraph following the heading, "Potential for Confounding by Arsenic Exposure in Thun Cohort", line 15, is corrected to read, "That said, we can interpret the post-1940 data with".

42. On page 42187, second column, first full paragraph, line 4, is corrected to read, "exposure group (<584 mg-days/m³) of the".

43. On page 42187, second column, first full paragraph, line 20 is corrected to read, "cohort by Steyner et al. (Ex I–140–20)".

44. On page 42190, table VI–15., column under the heading "Falck (Ex. 4–28)", line 2, the word "hazing" is corrected to read "brazing".

45. On page 42191, first column, footnote number 5, line 2, the word, "thed" is corrected to read, "the".

46. On page 42191, first column, footnote number 5, line 5, the word, "multiples" is corrected to read, "multiplies".

47. On page 42192, third column, first full paragraph, line 18, is corrected to read, "test. As indicated by table VI–18, the".

48. On page 42193, table VI–18, first column, the sixth entry under the heading, "Jarup 2[c] (Ex. 8–661):", is corrected to read, ">15,000".

49. On page 42193, table VI–19, footnote c, is corrected to read, "[c] Restriction imposed of τ=1 (linear dose response)."

50. On page 42194, second column, third full paragraph, line 17, is corrected to read, "$X \geq X_0$".

51. On page 42195, third column, third paragraph, line 2, is corrected to read, "biological arguments that indicate a".

52. Beginning on page 42348, third column, second full paragraph, is corrected to read,

"MOSH also recommended that the saccharin solution aerosol protocol be corrected by deleting the reference to disposable dust respirators to reflect the fact that disposable dust respirators not equipped with high efficiency filters are not permitted by the proposed cadmium standard.".

53. On page 42351, second column, third new paragraph, line 13, is corrected to read, "guide employers and laboratories in".

54. On page 42381, first column, lines 12 and 13, are corrected to read, "cadmium: electrical grounding with cadmium welding, or electrical work using".

55. On page 42383, second column, the last line is corrected to read, "Electrical grounding with cadmium welding;".

56. On page 42385, third column, third paragraph, line 9, is corrected to read, "Electrical grounding with cadmium welding;".

57. On page 42388, second column, paragraph numbered "1.", line 8, is corrected to read, "1965, 41 U.S.C. 351 et seq.; sec. 107 Contract".

58. On page 42388, second column, paragraph numbered "1.", line 11, is corrected to read, "41, Longshoremen's and Harbor Workers' ".

59. On page 42388, second column, paragraph numbered "1.", line 12, is corrected to read, "Compensation Act, 33 U.S.C. 941; National".

PART 1910—[AMENDED]

PART 1915—[AMENDED]

60. On page 42388, second column, paragraph numbered "2.", is corrected to read,

"2. The authority citation for subpart Z of part 1910 is revised to read as follows:

Authority: Sections 4, 6, and 8, Occupational Safety and Health Act, 29 U.S.C. 653, 655, and 657; Secretary of Labor's Orders Nos. 12–71 (36 FR 8754), 8–76 (41 FR 25059), 9–83 (48 FR 35736) or 1–90 (55 FR 9033), as applicable; and 29 CFR part 1911.

All of subpart Z, issued under section 6(b) of the Occupational Safety and Health Act, 29 U.S.C. 655(b) except those substances listed in the Final Rule Limits columns of Table Z–1–A, which have identical limits listed in the Transitional Limits columns of Table Z–1–A, Table Z–2, or Table Z–3. The latter were issued under section 6(a) (29 U.S.C. 655(a)).

Section 1910.1000, the Transitional Limits columns of Table Z–1–A, Table Z–2, and Table Z–3 also issued under 5 U.S.C. 533. Section 1910.1000, the Transitional Limits columns of Table Z–1–A, Table Z–2, and Table Z–3 not issued under 29 CFR part 1911 except for the arsenic, benzene, cotton dust, and formaldehyde listings.

Section 1910.1001 also issued under sec. 107 of Contract Work Hours and Safety Standards Act, 40 U.S.C. 333.

Section 1910.1002 not issued under 29 U.S.C. 655 or 29 CFR part 1911; also issued under 5 U.S.C. 553.

Section 1910.1025 also issued under 5 U.S.C. 553.

Section 1910.1043 also issued under 5 U.S.C. 551 et seq.

Sections 1910.1200, 1910.1499 and 1910.1500 also issued under 5 U.S.C. 553.".

61. Beginning on page 42388, third column, paragraph "6.", is corrected to read.

"6. In § 1910.1000, Table Z–2, footnotes "1" and "2" are renamed "a" and "b", respectively, and a footnote superscript "c" is added after the entries "Cadmium fume (Z37.5–1970)" and "Cadmium dust (Z37.5–1970)" and footnote "c" is added after footnote "b" to read "c. This standard applies to any operations or sectors for which § 1910.1027 is stayed or otherwise not in effect.".

62. On page 42389, first column, amendatory instruction 7. is corrected by revising the phrase "a new subpart Z" to read "subparts m through y are added and reserved and a new subpart Z—Toxic and Hazardous Substances".

63. On page 42389, first column, paragraph (b), seventh definition, lines 1 and 2, are corrected to read, "High-efficiency particulate air (HEPA) filter means a filter capable".

64. On page 42391, first column, paragraph (f)(4) is deleted.

65. On page 42391, Table 2.—Respiratory Protection for Cadmium, column under the heading "Required respirator type [b]", line 11, the phrase "unknown concentrations" is deleted.

66. On page 42391, Table 2.—Respiratory Protection for Cadmium, footnote c, is corrected to read, "HEPA means High-efficiency Particulate Air.".

67. On page 42392, second column, paragraph (i)(2)(iv), line 6, is corrected to read "paragraph (m)(3) of this section.".

68. On page 42393, third column, paragraph (l)(3)(i)(B), line 3, is corrected to read, "CdB one year after the initial".

69. On page 42395, first column, paragraph (l)(4)(iv), lines 7 through 10, are corrected to read, "specified in paragraphs (l)(3) (ii) or (iii); or, beginning on January 1, 1999, in excess of the levels specified in paragraphs (l)(3) (ii) or (iv) of this section, the".

70. On page 42395, first column, paragraph (l)(4)(v)(A), line 8, is corrected to read, "(l)(3)(i)(B) of this section one year".

71. On page 42395, second column, paragraph (l)(4)(v)(B), line 9, the word, "within" is deleted.

72. On page 42395, second column, paragraph (l)(4)(v)(B), line 12, is corrected to read, "monitoring, specified in".

73. On page 42396, first column, paragraph (l)(6)(iv), line 3, is corrected to read, "(l)(6)(i), (ii), or (iii) of this section are".

74. On page 42396, third column, paragraph (l)(11)(iv), line 5, is corrected to read, "medical removal trigger".

75. On page 42397, third column, paragraph (l)(16), lines 5 through 7, are corrected to read, "condition or disorder caused by occupational exposure to cadmium associated with employment as".

76. On page 42398, first column, paragraph (m)(4)(iii)(A), lines 4 and 5, are corrected to read, "incorporated in appendix A to this section:".

77. On page 42398, second column, paragraph (m)(4)(iii)(H), is corrected to read, "(H) The employee's rights of access to records under § 1910.20 (e) and (g).".

78. On page 42400, second column, paragraph "C. Employee Requirements", line 10, is corrected to read, "source of unnecessary cadmium exposure.".

79. On page 42402, third column, paragraph "b.", line 5, is corrected to read, "telephone: 202–219–7894.".

80. On page 42407, second column, a new paragraph "4." is to be inserted immediately preceding paragraph "C. Quantitative Fit Test (QNFT) Protocol" to read as follows.

"4. Saccharin Solution Aerosol Protocol

The entire screening and testing procedure shall be explained to the test subject prior to the conduct of the screening test.

(a) Taste threshold screening. The saccharin taste threshold screening, performed without wearing a respirator, is intended to determine whether the individual being tested can detect the taste of saccharin.

(1) Threshold screening as well as fit testing subjects shall wear an enclosure about the head and shoulders that is approximately 12 inches in diameter by 14 inches tall with at least the front portion clear and that allows free movements of the head when a respirator is worn. An enclosure substantially similar to the 3M hood assembly, parts # FT 14 and # FT 15 combined, is adequate.

(2) The test enclosure shall have a 3/4-inch hole in front of the test subject's nose and mouth area to accommodate the nebulizer nozzle.

(3) The test subject shall don the test enclosure. Throughout the threshold screening test, the test subject shall breathe through his/her wide open mouth with tongue extended.

(4) Using a DeVilbiss Model 40 Inhalation Medication Nebulizer the test conductor shall spray the threshold check solution into the enclosure. This nebulizer shall be clearly marked to distinguish it from the fit test solution nebulizer.

(5) The threshold check solution consists of 0.83 grams of sodium saccharin USP in 1 cc of warm water. It can be prepared by putting 1 cc of the fit test solution (see(b)(5) below) in 100 cc of distilled water.

(6) To produce the aerosol, the nebulizer bulb is firmly squeezed so that it collapses completely, then released and allowed to fully expand.

(7) Ten squeezes are repeated rapidly and then the test subject is asked whether the saccharin can be tasted.

(8) If the first response is negative, ten more squeezes are repeated rapidly and the test subject is again asked whether the saccharin is tasted.

(9) If the second response is negative, ten more squeezes are repeated rapidly and the test subject is again asked whether the saccharin is tasted.

(10) The test conductor will take note of the number of squeezes required to solicit a taste response.

(11) If the saccharin is not tasted after 30 squeezes (step 10), the test subject may not perform the saccharin fit test.

(12) If a taste response is elicited, the test subject shall be asked to take note of the taste for reference in the fit test.

(13) Correct use of the nebulizer means that approximately 1 cc of liquid is used at a time in the nebulizer body.

(14) The nebulizer shall be thoroughly rinsed in water, shaken dry, and refilled at least each morning and afternoon or at least every four hours.

(b) Saccharin solution aerosol fit test procedure.

(1) The test subject may not eat, drink (except plain water), or chew gum for 15 minutes before the test.

(2) The fit test uses the same enclosure described in (a) above.

(3) The test subject shall don the enclosure while wearing the respirator selected in section (a) above. The respirator shall be properly adjusted and equipped with a particulate filter(s).

(4) A second DeVilbiss Model 40 Inhalation Medication Nebulizer is used to spray the fit test solution into the enclosure. This nebulizer shall be clearly marked to distinguish it from the screening test solution nebulizer.

(5) The fit test solution is prepared by adding 83 grams of sodium saccharin to 100 cc of warm water.

(6) As before, the test subject shall breathe through the open mouth with tongue extended.

(7) The nebulizer is inserted into the hole in the front of the enclosure and the fit test solution is sprayed into the enclosure using the same number of squeezes required to elicit a taste response in the screening test.

(8) After generating the aerosol the test subject shall be instructed to perform the exercises in section I.A. 14 above.

(9) Every 30 seconds the aerosol concentration shall be replenished using one half the number of squeezes as initially.

(10) The test subject shall indicate to the test conductor if at any time during the fit test the taste of saccharin is detected.

(11) If the taste of saccharin is detected, the fit is deemed unsatisfactory and a different respirator shall be tried".

81. On page 42412, first column, Appendix E, paragraph 3.5.5., is corrected to read, "Magnesium nitrate, $Mg(NO_3)_2 \cdot 6H_2O$".

82. On page 42412, second column, paragraph 3.5.8., line 3, is corrected to read, "$Mg(NO_3)_2 \cdot 6H_2O$ in approximately 200 mL deionized".

83. On page 42412, table at the top of the third column, the fifth entry in the column marked "Aliquot" is corrected to read "5".

84. On page 42412, third column, paragraph 3.10.1, line 17, is corrected to read, "method are given in Attachment 1.".

85. On page 42413, second column, line 14, is corrected to read, "Attachment 2."

86. On page 42414, first column, paragraph 4.2.1., line 12, is corrected to read, "parameters are listed in Attachment 1.".

87. On page 42414, second column, line 6, is corrected to read, "are listed in Attachment 2.".

88. On page 42414, second column, paragraph 4.3.2., line 2, is corrected to read, "$NH_4H_2PO_4$ and magnesium nitrate, $Mg(NO_3)_2$ $6H_2O$,".

89. On page 42419, first column, first full paragraph, line 10, is corrected to read, "decisions made by the" by deleting the word "discretionary".

90. On page 42419, third column, fourth full paragraph labeled, "Target Value:", lines 5 through 10 is corrected to read,

"rule. For CDB, the target values are 5, 10, and 15 µg/l. For CDU, the target values are 3, 7, and 15 µg/g CRTU. For β_2MU, the target values are 300, 750 and 1500 µg/g CRTU. (Note that target values may vary as a function of time.)".

91. On page 42420, second column, first paragraph, lines 6 through 12 are deleted.

92. On page 42420, second column, first paragraph, line 13, is corrected to read, "In determining which laboratories to employ for".

93. On page 42421, third column, sixth full paragraph, lines 13 and 14 are corrected to read "than for CTQ proficiency testing should be accompanied".

94. On page 42422, first column, line 3, delete the parenthetical notation, "(i.e., compliance samples),".

95. On page 42422, second column, fourth paragraph under paragraph 3.3.1.1., line 3, the symbol "+" is deleted.

96. On page 42422, third column, second paragraph, lines 6 and 7 are corrected to read, "compliance samples or at least one set of QC samples per analysis of compliance samples, whichever is greater. If only 2 samples".

97. On page 42422, third column, sixth paragraph, line 5, place a "^" above the "σ".

98. On page 42422, third column, sixth paragraph, line 7, is corrected to read, "(e.g., ± 1 µg or 15% of the mean, whichever is".

99. On page 42423, first column under Table 2, second paragraph, line 11, should be corrected to read, "the period; and, use of $\hat{X} \pm 2\hat{\sigma}$(as defined".

100. On page 42423, first column under table 2, third paragraph, line 7, is corrected to read, "values, $\hat{X}$, (with N being the total number of samples analyzed):".

101. On page 42423, second column under table 2, first line below the first formula, place a "^" above the "σ".

102. On page 42423, second column under table 2, third line below the first formula, place a "^" above the "σ".

103. On page 42423, second column below table 2, second formula, place a "^" above the "σ" on the left side of the equation and correct the lower case "n" in the denominator to read an upper case "N".

104. On page 42423, second column below table 2, first full paragraph under the second formula, line 2, is corrected to read, "Attachment 1) indicates that QC samples".

105. On page 42424, first column, first full paragraph, lines 2 and 3, place "^" above the "σ"s.

106. On page 42426, first column, fourth paragraph, line 16, the word "inperindividual" is corrected to read, "interindividual".

107. On page 42429, first column, first paragraph, line 6, the term, "cadmium-13" is corrected to read, "cadmium-113".

108. On page 42430, third column, first paragraph, line 4, is corrected to read, "± 10% of the true value at CDB".

109. On page 42430, in table 4, eighth column, delete the "±" so the heading is corrected to read, "Geometric mean (GSD)[e]".

110. On page 42430, in table 4, the text of footnotes a through g were omitted. The text of the footnotes should be as follows:

[a] Concentrations reported in µg Cd/l blood unless otherwise stated.

[b] NS—never smoked; S—current cigarette smoker.

[c] S.D.—Arithmetic Standard Deviation.

[d] C.I.—Confidence interval.

[e] GSD—Geometric Standard Deviation.

[f] Based on an assumed lognormal distribution.

[g] Based on an assumed normal distribution.

111. On page 42431 and page 42432, in table 5, column heading "Geometric mean (±GSD)[e]" is corrected to read "Geometric mean (GSD)[e]".

112. On page 42431 and page 42432, in Table 5, column heading,

"Lower 95th percentile of range[c] ( )[f]

should be corrected to read,

"Lower 95th percentile of range[c] ( )[f]

113. On page 42431 and page 42432, in Table 5, column heading,

"Upper 95th percentile of range[c] ( )[f]"

should be corrected to read,

"Upper 95th percentile of range[c] ( )[f]

114. On page 42431, in table 5, column headed "Mean concentration of cadmium in air (µg/m³)", first entry, is corrected to read, "≤90".

115. On page 42431, in table 5, column headed "Employment in years (mean)", tenth entry, is corrected to read "(4.2)[g]".

116. On page 42431 and page 42432, in table 5, the text of footnotes a through g was omitted. The text of the footnotes should be as follows:

[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.

117. On page 42432, third column, paragraph 5.1.7.3., line 12, is corrected to read, "presented in Attachment 1 is based on the".

118. On page 42434, second column, first full paragraph, lines 6 and 7, are corrected to read, "(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".

119. On page 42435 and page 42356, table 8, in the heading, the word "CONCENTRATION'S" is corrected to read, "CONCENTRATIONS".

120. On page 42435 and page 42356, table 8, column heading "Geometric mean (±GSD)[e]" is corrected to read "Geometric mean (GSD)[e]".

121. On page 42435, table 8, in the second column headed, "Work Environment", delete the space between entry 16, "(Smokers)", and entry 17, "(Nonsmokers)", so that the data in the

columns to the right correspond correctly.

122. On page 42435 and 42436, in table 8, the text of footnotes a through h was omitted. The text of the footnotes should be as follows:

[a] Concentrations are reported in µg/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.

123. On page 42436, second column, line 12, is corrected to read, "lower than levels of other studies reported in Table 8.".

124. On page 42437, first column, first full paragraph, line 6, is corrected to read, "µg/l, a target precision of 40% is acceptable, while".

125. On page 42438, first column, line 22, is corrected to read, "listed in Table 9 (Section 5.3.7), the average".

126. On page 42438, third column, paragraph "5.3.7.1", line 17, is corrected to read, "dysfunction (including cadmium-exposed workers with none of".

127. On page 42438, in table 9, the text of footnotes a through f, h through k, and n and p was omitted. The text of the footnotes should be as follows:

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

128. On page 42440, first column, paragraph 5.3.8.3, line 5, the word, "Delphiad" is corrected to read, "Delphia".

129. On page 42440, second column, second paragraph under paragraph 5.4.3., line 4, the word, "chromofore", is corrected to read, "chromophore".

130. On page 42442, third column, first paragraph under the heading "Attachment 1—Nonmandatory Protocol for an Internal Quality Assurance/Quality Control Program" line 4, is corrected to read "satisfy OSHA requirements under".

131. On page 42442, third column, second paragraph under the heading "Attachment 1—Nonmandatory Protocol for an Internal Quality Assurance/Quality Control Program" line 2, is corrected to read "protocol, the QA/QC program for".

132. On page 42443, first column, first full paragraph is corrected to read, "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 ± 15%."

133. On page 42443, first column, first full paragraph under the heading "Initial Characterization Runs and Establishing Control" lines 3 and 4, are corrected to read, "of the analytes for which determinations will be made. The concentrations of quality".

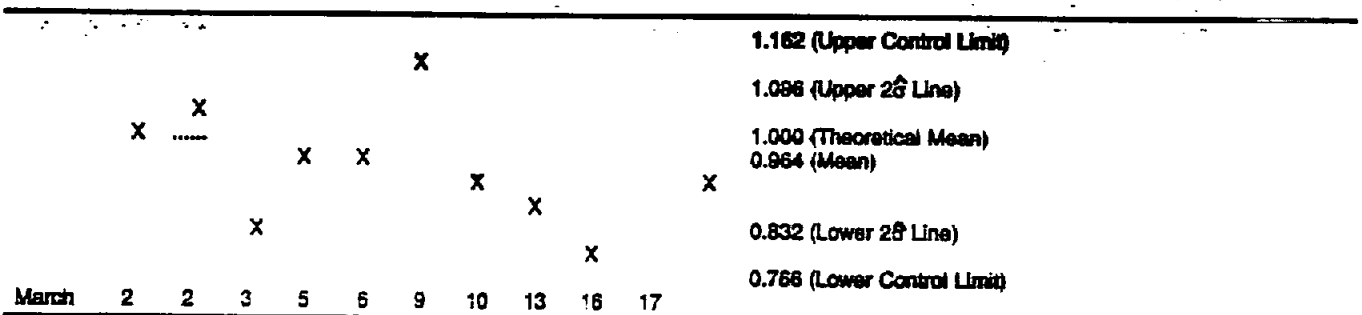
134. On page 42443, first column, last two lines above Figure 1, are corrected to read, "pool of each analyte for which determinations will be made and control charts".

135. On page 42443, second column, first paragraph following the second formula, lines 2 and 3 are corrected to read, "then given by the mean plus or minus 2 standard deviations ($\bar{X} \pm 2\hat{\sigma}$). The control".

136. On page 42443, third column, third paragraph, line 10, insert "^" above the "σ".

137. On page 42443, Figure 1, is corrected to read,

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



138. On page 42444, first column, first paragraph, lines 9 through 11, are corrected to read, "updated every 2 months.".

139. On page 42444, first column, in the fifth paragraph (numbered "2."), the statistical terms "2δ" are corrected to read "2$\hat{\sigma}$".

140. On page 42444, second column, first paragraph under the heading "Corrective Actions", lines 14 and 15, are corrected to read, "(CAR) must be completed. CARs should be kept on file by the laboratory.".

141. On page 42444, second and third column, the second paragraph under the heading "Corrective Actions" is deleted.

142. Beginning on page 42444 and continuing through page 42446, "Attachment 2" is corrected to read,

Attachment 2

Creatinine in Urine (Jaffe 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 noncreatinine, 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.

$$\text{Creatinine} + \text{Picrate} \xrightarrow{\text{NaOH}} \text{Red chromophore (absorbs at 510 nm)}$$

Reagents:

Compartment[a]	Form	Ingredient—Quantity[b]
No. 2, 3, & 4	Liquid Picrate ..	0.11 mmol.
No. 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 2–8°C. Do not freeze. Do not expose to temperatures above 35° C 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 Substances:[3]

• 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 endrogenous 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 5.0
Cephalexin	0.6–2.0	0.2–0.6	25 7.2
Cephamandole	1.3–2.5	0.3–0.5	25 4.9
Cephapirin	2.0	0.4	25 5.6
Cephradine	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 that 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 (percent)
Cephalothin	1–6	0.2–1.5	10025.2↓20–25
Cephoxitin	2.0	0.5	5.01.2↑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.

Procedure:

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

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	710642901	710642901	713697901
or			
Micro Sample System Kit	702694901	710356901	NA
and			
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	710654901	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: 200 µL
- 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[f] or 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 umol/L]
- Calibration Scheme: 3 levels, 3 packs per level
- Frequency: Each new pack lot. Every 3 months for any one pack lot.

PRESET CREATININE (CREA) TEST CONDITIONS

Item	ACA®II analyzer	ACA® III, IV, SX, V analyzer
Count by	One(1) (Five (5)).	NA
Decimal Point.	0.0 mg/dL	000.0 mg/dL
Location	[000. µmol/L]	[000 µmol/L]
Assigned Starting.	999.8	−1.000 E1
Point or Offset Cn.	[9823.]	[−8.840 E2]
Scale Factor or.	0.2000	2.004 E−1[h]
Assigned	mg/dL/count[h].	
Linear Term C1.	[0.3536 µmol/L/count].	[1.772E1]

PRESET CREATININE (CREA) TEST CONDITIONS—Continued

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 ACAR® 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:[i,j]

Males	0.8–1.3 mg/dL	[71–115 µmol/L]
Females	0.6–1.0 mg/dL	[53–88 µmol/L]

Urine:[i,j]

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:

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 Du Pont Representative.

g. If the Du Pont Chemistry Controls are being used, prepare them according to the instructions on the product insert sheets.

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.

REPRODUCIBILITY[k]

Material	Mean	Standard deviation (percent 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[m]	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:

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

Assay Range: 0.6–26.6 mg/dl (0–1768 µmol)

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

Analytical Specificity: See KNOWN INTERFERING SUBSTANCES section for details.

Bibliography:

[1] Larsen, K, Clin Chem Acta 41, 209 (1972).

[2] Tietz, NW, Fundamentals of Clinical Chemistry, W. B. Saunders Co., Philadelphia, PA, 1976, pp 47–52, 1211.

[3] Supplementary information pertaining to the effects of various drugs and patient conditions on in vivo or in vitro diagnostic levels can be found in "Drug Interferences with Clinical Laboratory Tests." Clin. Chem 21 (5) (1975), and "Effects of Disease on Clinical Laboratory Tests." Clin Chem, 26 (4) 1D–476D (1980).

[4] Watkins, R. Fieldkamp, SC, Thibert, RJ, and Zak, B, Clin Chem, 21, 1002 (1975).

[5] Kawas, ER, Richards, AH, and Bigger, R, An Evaluation of a Kinetic Creatinine Test for the DuPont ACA, Du Pont Company, Wilmington, DE (February 1973). (Reprints available from Du Pont Company, Diagnostic Systems)

[6] Westgard, JO, Effects of Hemolysis and Lipemia on ACA Creatinine Method 0.200 µL, Sample Size, DuPont Company, Wilmington, DE (October 1972).

[7] Physicians' Desk Reference, Medical Economics Company, 33 Edition, 1979.

[8] Henry, JB, Clinical Diagnosis and Management by Laboratory Methods, W.B. Saunders Co., Philadelphia, PA 1979, Vol. III.

[9] Knapp, MA, Tierney, LM Jr., Jawetz, E, Roe, RI, Camargo, CA, Physicians Handbook, Lange Medical Publications, Los Altos, CA, 1982 pp 635–636.

[10] Saran, AJ, Koch, TR, Drusano, GL, Columns Falsely Elevates Creatinine Levels, JAMA 247, 205–206 (1982).

[11] Gadsden, RH, and Phelps, CA, A Normal Range Study of Amylase in Urine and Serum on the Du Pont ACA, DuPont Company, Wilmington, DE (March 1978). (Reprints available from DuPont Company, Diagnostic Systems).

[12] Dicht, JJ, Reference Intervals for Serum Amylase and Urinary Creatinine on the Du Pont ACA® Discrete Clinical Analyzer, DuPont Company, Wilmington, DE (November 1984).

143. On page 42446, third column, the heading "Attachment 3" is corrected to read, "Attachment 3 Analysis of Creatinine for the Normalization of Cadmium and Beta-2-Microglobulin Concentrations in Urine (OSLTC Procedure)".

144. On page 42446, third column, lines 1, 2 and 3 under the heading "Attachment 3" are deleted.

145. On page 42447, first column, line 34, is corrected to read, "methylhydantoin-2-imide".

146. On page 42447 and page 42448, the Storage Data Table, is corrected to read,

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

147. On page 42448, first column, paragraph 2.7.2, line 6, is corrected to read, "(CDC) (Ref. 5.8.) and OSHA's Bloodborne Pathogens standard (29 CFR 1910.1039).".

148. On page 42448, second column, first paragraph under paragraph 3.3., line 1, is corrected to read, "3.3.1 Stock standards are prepared by".

149. On page 42452, first column, first formula, the result on the far right side of the equation reading "mg/L" is corrected by lowering it and made parallel to the middle column reading, "μg/mL".

150. On page 42452, first column, the far right side of the equation following paragraph "3.7.4.", is corrected to read, "μg A/g creatinine".

151. On page 42452, first column, heading "XI. Final Standard (Construction)" is corrected to read, "XII. Final Standard (Construction)".

PART 1926—[AMENDED]

152. On page 42452, second column, paragraph numbered, "10", line 6, is corrected to read, "C, D, E, and F of § 1910.1027 of subpart Z".

153. On page 42452, second column, paragraph (a)(6) is corrected to read, "(6) Electrical grounding with cadmium welding, or electrical work using cadmium-coated conduit;".

154. On page 42453, first column, second full paragraph, lines 1 and 2, are corrected to read, "High-efficiency Particulate Air (HEPA) filter means a filter capable".

155. On page 42454, second column, paragraph (f)(5)(i), lines 1 through 8, are corrected to read,

(5) *Compliance program.* Where employee exposure to cadmium exceeds the PEL and the employer is required under paragraph (f)(1) of this section to implement controls to comply with the PEL, prior to the commencement of the job the employer shall establish and implement a written compliance program to reduce employee exposure to or below the PEL. To the extent that.

156. On page 42455, table 1.—Respiratory Protection for Cadmium, right column, line 2 under the heading, "Required respirator type b", is corrected by inserting a closed parenthesis after the abbreviation. "("PAPR" ".

157. On page 42455, table 1.—Respiratory Protection for Cadmium, right column, line 11 under heading "Required respirator type b", is corrected to read, "A self-contained breathing apparatus with a full facepiece operated in the pressure".

158. On page 42455, table 1.—Respiratory Protection for Cadmium, footnote c, is corrected to read, "HEPA means High-efficiency Particulate Air.".

159. On page 42456, third column, paragraph (l)(1)(i)(A), line 9, is corrected to read, "grounding with cadmium welding; cutting,".

160. On page 42456, third column, paragraph (l)(1)(i)(A), line 17, the word "reinforcing" is corrected to read, "reinforced".

161. On page 42457, third column, paragraph (l)(3)(i)(B), line 1, is corrected to read "one year after the initial".

162. On page 42458, third column, paragraph (l)(4)(iv), lines 7 through 13 are corrected to read,

"specified in paragraphs (l)(3)(ii) or (iii) of this section; or beginning on January 1, 1999, in excess of the levels specified in paragraphs (l)(3)(ii) or (iv), the employer shall take the appropriate actions specified in paragraphs (l)(3)(ii)–(iv) of this section, respectively.".

163. On page 42458, third column, paragraph (l)(4)(v)(A), line 8, is corrected to read, "(l)(3)(i)(B) of this section one year".

164. On page 42459, first column, paragraph (l)(4)(v)(B), line 10, the word "within" is deleted.

165. On page 42459, first column, paragraph (l)(4)(v)(B), line 13, is corrected to read, "monitoring specified in".

166. On page 42459, second column, paragraph (l)(6)(iv), lines 1 through 5 are corrected to read,

"(iv) Where the results of the examination required under paragraphs (l)(6)(i), (ii) or (iii) of this section are abnormal, medical limitation or prohibition of respirator use shall be".

167. On page 42459, third column, paragraph (l)(8)(ii), line 3, is corrected to read, "surveillance under paragraph (l)(4)(v) of".

168. On page 42462, first column, paragraph (m)(4)(iii)(H), line 2, is corrected to read, "records under § 1910.20(e) and (g)."

In addition to the corrections above, Part 1928 is being amended as set forth below:

PART 1928—[AMENDED]

1. The authority citation for 29 CFR part 1928, Subpart M is revised to read as follows:

Authority: Secs. 4, 6, and 8, Occupational Safety and Health Act of 1970 (29 U.S.C. 653, 655, 657); Secretary of Labor's Orders Nos. 12–71 (36 FR 8754), 8–76 (41 FR 25059), 9–83 (48 FR 35736) or 1–90 (55 FR 9033), as applicable; and 29 CFR part 1911.

Section 1928.21 also issued under 5 U.S.C. 553.

2. Part 1928 is amended by adding and reserving subparts J through L and adding a new subpart M—Occupational Health, consisting of a new section 1928.1027, as set forth below.

Subpart M—Occupational Health

§ 1928.1027 Cadmium

(a) Scope. This standard applies to all occupational exposures to cadmium and cadmium compounds, in all forms, and in all industries covered by the Occupational Safety and Health Act, except the construction-related industries, which are covered under 29 CFR 1926.63.

(b) Definitions. *Action level* (AL) is defined as an airborne concentration of cadmium of 2.5 micrograms per cubic meter of air (2.5 $\mu g/m^3$), 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.

Authorized person means any person authorized by the employer and required by work duties to be present in regulated areas or any person authorized by the OSH Act or regulations issued under it to be in regulated areas.

Director means the Director of the National Institute for Occupational Safety and Health (NIOSH), U.S. Department of Health and Human Services, or designee.

Employee exposure and similar language referring to the air cadmium level to which an employee is exposed means the exposure to airborne cadmium that would occur if the employee were not using respiratory protective equipment.

Final medical determination is the written medical opinion of the employee's health status by the examining physician under paragraphs (l)(3)–(12) or, if multiple physician review under paragraph (l)(13) or the alternative physician determination under paragraph (l)(14) is invoked, it is the final, written medical finding, recommendation or determination that emerges from that process.

High-efficiency particulate air (HEPA) filter means a filter capable of trapping and retaining at least 99.97 percent of mono-dispersed particles of 0.3 micrometers in diameter.

Regulated area means an area demarcated by the employer where an employee's exposure to airborne concentrations of cadmium exceeds, or can reasonably be expected to exceed the permissible exposure limit (PEL).

This section means this cadmium standard.

(c) Permissible Exposure Limit (PEL). The employer shall assure that no employee is exposed to an airborne concentration of cadmium in excess of

TABLE I.—SEPARATE ENGINEERING CONTROL AIRBORNE LIMITS (SECALS) FOR PROCESSES IN SELECTED INDUSTRIES—Continued

Industry	Process	SECAL (µg/m³)
Zinc/Cadmium Refining [1]	All other processes	15
Pigment Manufacture	Cadmium refining, casting, melting, oxide production, sinter plant	50
	Calcine, crushing, milling, blending	50
	All other processes	15
Stabilizers [1]	Cadmium oxide charging, crushing, drying, blending	50
Lead Smelting [1]	Sinter plant, blast furnace, baghouse, yard area	50
Plating [1]	Mechanical plating	15

[1] Processes in these industries that are not specified in this table must achieve the PEL using engineering controls and work practices as required in f(1)(i).

(iii) The requirement to implement engineering and work practice controls to achieve the PEL or, where applicable, the SECAL does not apply where the employer demonstrates the following:

(A) The employee is only intermittently exposed; and

(B) The employee is not exposed above the PEL on 30 or more days per year (12 consecutive months).

(iv) Wherever engineering and work practice controls are required and are not sufficient to reduce employee exposure to or below the PEL or, where applicable, the SECAL, the employer nonetheless shall implement such controls to reduce exposures to the lowest levels achievable. The employer shall supplement such controls with respiratory protection that complies with the requirements of paragraph (g) of this section and the PEL.

(v) The employer shall not use employee rotation as a method of compliance.

(2) *Compliance program.*

(i) Where the PEL is exceeded, the employer shall establish and implement a written compliance program to reduce employee exposure to or below the PEL by means of engineering and work practice controls, as required by paragraph (f)(1) of this section. To the extent that engineering and work practice controls cannot reduce exposures to or below the PEL, the employer shall include in the written compliance program the use of appropriate respiratory protection to achieve compliance with the PEL.

(ii) Written compliance programs shall include at least the following:

(A) A description of each operation in which cadmium is emitted; e.g., machinery used, material processed, controls in place, crew size, employee job responsibilities, operating procedures, and maintenance practices;

(B) A description of the specific means that will be employed to achieve compliance, including engineering plans and studies used to determine methods selected for controlling exposure to cadmium, as well as, where necessary, the use of appropriate respiratory protection to achieve the PEL;

(C) A report of the technology considered in meeting the PEL;

(D) Air monitoring data that document the sources of cadmium emissions;

(E) A detailed schedule for implementation of the program, including documentation such as copies of purchase orders for equipment, construction contracts, etc.;

(F) A work practice program that includes items required under paragraphs (h),(i), and (j) of this section;

(G) A written plan for emergency situations, as specified in paragraph (h) of this section; and

(H) Other relevant information.

(iii) The written compliance programs shall be reviewed and updated at least annually, or more often if necessary, to reflect significant changes in the employer's compliance status.

(iv) Written compliance programs shall be provided upon request for examination and copying to affected employees, designated employee representatives as well as to the Assistant Secretary, and the Director.

(3) *Mechanical ventilation.*

(i) When ventilation is used to control exposure, measurements that demonstrate the effectiveness of the system in controlling exposure, such as capture velocity, duct velocity, or static pressure shall be made as necessary to maintain its effectiveness.

(ii) Measurements of the system's effectiveness in controlling exposure shall be made as necessary within five working days of any change in production, process, or control that might result in a significant increase in employee exposure to cadmium.

(iii) *Recirculation of air.* If air from exhaust ventilation is recirculated into the workplace, the system shall have a high efficiency filter and be monitored to assure effectiveness.

(iv) Procedures shall be developed and implemented to minimize employee exposure to cadmium when maintenance of ventilation systems and changing of filters is being conducted.

(g) Respirator protection.

(1) *General.*

Where respirators are required by this section, the employer shall provide them at no cost to the employee and shall assure that they are used in compliance with the requirements of this section. Respirators shall be used in the following circumstances:

(i) Where exposure levels exceed the PEL, during the time period necessary to install or implement feasible engineering and work practice controls;

(ii) In those maintenance and repair activities and during those brief or intermittent operations where exposures exceed the PEL and engineering and work practice controls are not feasible or are not required;

(iii) In regulated areas, as prescribed in paragraph (e) of this section;

(iv) Where the employer has implemented all feasible engineering and work practice controls and such controls are not sufficient to reduce exposures to or below the PEL;

(v) In emergencies;

(vi) Wherever an employee who is exposed to cadmium at or above the action level requests a respirator;

(vii) Wherever an employee is exposed above the PEL in an industry to which a SECAL is applicable; and

(viii) Wherever an employee is exposed to cadmium above the PEL and engineering controls are not required under paragraph (f)(1)(iii) of this section.

(2) *Respirator selection.*

(i) Where respirators are required under this section, the employer shall select and provide the appropriate respirator as specified in Table 2. The employer shall select respirators from among those jointly approved as acceptable protection against cadmium dust, fume, and mist by the Mine Safety and Health Administration (MSHA) and by the National Institute for Occupational Safety and Health (NIOSH) under the provisions of 30 CFR part 11.

five micrograms per cubic meter of air (5 $\mu g/m^3$), calculated as an eight-hour time-weighted average exposure (TWA).

(d) Exposure monitoring.

(1) *General.*

(i) Each employer who has a workplace or work operation covered by this section shall determine if any employee may be exposed to cadmium at or above the action level.

(ii) Determinations of employee exposure shall be made from breathing zone air samples that reflect the monitored employee's regular, daily 8-hour TWA exposure to cadmium.

(iii) Eight-hour TWA exposures shall be determined for each employee on the basis of one or more personal breathing zone air samples reflecting full shift exposure on each shift, for each job classification, in each work area. Where several employees perform the same job tasks, in the same job classification, on the same shift, in the same work area, and the length, duration, and level of cadmium exposures are similar, an employer may sample a representative fraction of the employees instead of all employees in order to meet this requirement. In representative sampling, the employer shall sample the employee(s) expected to have the highest cadmium exposures.

(2) *Specific.*

(i) *Initial monitoring.* Except as provided for in paragraphs (d)(2)(ii) and (d)(2)(iii) of this section, the employer shall monitor employee exposures and shall base initial determinations on the monitoring results.

(ii) Where the employer has monitored after September 14, 1991, under conditions that in all important aspects closely resemble those currently prevailing and where that monitoring satisfies all other requirements of this section, including the accuracy and confidence levels of paragraph (d)(6), the employer may rely on such earlier monitoring results to satisfy the requirements of paragraph (d)(2)(i) of this section.

(iii) Where the employer has objective data, as defined in paragraph (n)(2) of this section, demonstrating that employee exposure to cadmium will not exceed the action level under the expected conditions of processing, use, or handling, the employer may rely upon such data instead of implementing initial monitoring.

(3) *Monitoring frequency (periodic monitoring).*

(i) If the initial monitoring or periodic monitoring reveals employee exposures to be at or above the action level, the employer shall monitor at a frequency and pattern needed to represent the levels of exposure of employees and where exposures are above the PEL to assure the adequacy of respiratory selection and the effectiveness of engineering and work practice controls. However, such exposure monitoring shall be performed at least every six months. The employer, at a minimum, shall continue these semi-annual measurements unless and until the conditions set out in paragraph (d)(3)(ii) are met.

(ii) If the initial monitoring or the periodic monitoring indicates that employee exposures are below the action level and that result is confirmed by the results 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.

(4) *Additional monitoring.* The employer also shall institute the exposure monitoring required under paragraphs (d)(2)(i) and (d)(3) of this section whenever there has been a change in the raw materials, equipment, personnel, work practices, or finished products that may result in additional employees being exposed to cadmium at or above the action level or in employees already exposed to cadmium at or above the action level being exposed above the PEL, or whenever the employer has any reason to suspect that any other change might result in such further exposure.

(5) *Employee notification of monitoring results.*

(i) Within 15 working days after the receipt of the results of any monitoring performed under this section, the employer shall notify each affected employee individually in writing of the results. In addition, within the same time period the employer shall post the results of the exposure monitoring in an appropriate location that is accessible to all affected employees.

(ii) Wherever monitoring results indicate that employee exposure exceeds the PEL, the employer shall include in the written notice a statement that the PEL has been exceeded and a description of the corrective action being taken by the employer to reduce employee exposure to or below the PEL.

(6) *Accuracy of measurement.* The employer shall use a method of monitoring and analysis that has an accuracy of not less than plus or minus 25 percent (±25%), with a confidence level of 95 percent, for airborne concentrations of cadmium at or above the action level, the permissible exposure limit (PEL), and the separate engineering control air limit (SECAL).

(e) Regulated areas.

(1) *Establishment.* The employer shall establish a regulated area wherever an employee's exposure to airborne concentrations of cadmium is, or can reasonably be expected to be in excess of the permissible exposure limit (PEL).

(2) *Demarcation.* Regulated areas shall be demarcated from the rest of the workplace in any manner that adequately establishes and alerts employees of the boundaries of the regulated area.

(3) *Access.* Access to regulated areas shall be limited to authorized persons.

(4) *Provision of respirators.* Each person entering a regulated area shall be supplied with and required to use a respirator, selected in accordance with paragraph (g)(2) of this section.

(5) *Prohibited activities.* The employer shall assure that employees do not eat, drink, smoke, chew tobacco or gum, or apply cosmetics in regulated areas, carry the products associated with these activities into regulated areas, or store such products in these areas.

(f) Methods of compliance.

(1) *Compliance hierarchy.*

(i) Except as specified in paragraphs (f)(1) (ii), (iii) and (iv) of this section the employer shall implement engineering and work practice controls to reduce and maintain employee exposure to cadmium at or below the PEL, except to the extent that the employer can demonstrate that such controls are not feasible.

(ii) Except as specified in paragraphs (f)(1) (iii) and (iv) of this section, in industries where a separate engineering control air limit (SECAL) has been specified for particular processes (See Table 1), the employer shall implement engineering and work practice controls to reduce and maintain employee exposure at or below the SECAL, except to the extent that the employer can demonstrate that such controls are not feasible.

TABLE 1.—SEPARATE ENGINEERING CONTROL AIRBORNE LIMITS (SECALS) FOR PROCESSES IN SELECTED INDUSTRIES

Industry	Process	SECAL ($\mu g/m^3$)
Nickel Cadmium Battery	Plate making, plate preparation	50

TABLE 2.—RESPIRATORY PROTECTION FOR CADMIUM

Airborne concentration or condition of use[a]	Required respirator type[b]
10 x or less	A half mask, air-purifying respirator equipped with a HEPA[c] filter[d].
25 x or less	A powered air-purifying respirator ("PAPR") with a loose-fitting hood or helmet equipped with a HEPA filter, or a supplied-air respirator with a loose-fitting hood or helmet facepiece operated in the continuous flow mode.
50 x or less	A full facepiece air-purifying respirator equipped with a HEPA filter, or a powered air-purifying respirator with a tight-fitting half mask equipped with a HEPA filter, or a supplied air respirator with a tight-fitting half mask operated in the continuous flow mode.
250 x or less	A powered air-purifying respirator with a tight-fitting full facepiece equipped with a HEPA filter, or a supplied-air respirator with a tight-fitting full facepiece operated in the continuous flow mode.
1000 x or less	A supplied-air respirator with half mask or full facepiece operated in the pressure demand or other positive pressure mode.
>1000 x or unknown concentrations	A self-contained breathing apparatus with a full facepiece operated in the pressure demand or other positive pressure mode, or a supplied-air respirator with a full facepiece operated in the pressure demand or other positive pressure mode and equipped with an auxiliary escape type self contained breathing apparatus operated in the pressure demand mode.
Fire fighting	A self-contained breathing apparatus with full facepiece operated in the pressure demand or other positive pressure mode.

[a] Concentrations expressed as multiple of the PEL.
[b] Respirators assigned for higher environmental concentrations may be used at lower exposure levels. Quantitative fit testing is required for all tight-fitting air purifying respirators where airborne concentration of cadmium exceeds 10 times the TWA PEL ($10 \times 5\ \mu g/m^3 = 50\ \mu g/m^3$). A full facepiece respirator is required when eye irritation is experienced.
[c] HEPA means High Efficiency Particulate Air.
[d] Fit testing, qualitative or quantitative, is required.
Source: *Respiratory Decision Logic*, NIOSH, 1987.

(ii) The employer shall provide a powered, air-purifying respirator (PAPR) in lieu of a negative pressure respirator wherever:

(A) An employee entitled to a respirator chooses to use this type of respirator; and

(B) This respirator will provide adequate protection to the employee.

(3) *Respirator program.*

(i) Where respiratory protection is required, the employer shall institute a respirator protection program in accordance with 29 CFR 1910.134.

(ii) The employer shall permit each employee who is required to use an air purifying respirator to leave the regulated area to change the filter elements or replace the respirator whenever an increase in breathing resistance is detected and shall maintain an adequate supply of filter elements for this purpose.

(iii) The employer shall also permit each employee who is required to wear a respirator to leave the regulated area to wash his or her face and the respirator facepiece whenever necessary to prevent skin irritation associated with respirator use.

(iv) If an employee exhibits difficulty in breathing while wearing a respirator during a fit test or during use, the employer shall make available to the employee a medical examination in accordance with paragraph (l)(6)(ii) of this section to determine if the employee can wear a respirator while performing the required duties.

(v) No employee shall be assigned a task requiring the use of a respirator if, based upon his or her most recent examination, an examining physician determines that the employee will be unable to continue to function normally while wearing a respirator. If the physician determines the employee must be limited in, or removed from his or her current job because of the employee's inability to wear a respirator, the limitation or removal shall be in accordance with paragraphs (l)(11) and (12) of this section.

(4) *Respirator fit testing.*

(i) The employer shall assure that the respirator issued to the employee is fitted properly and exhibits the least possible facepiece leakage.

(ii) For each employee wearing a tight-fitting, air purifying respirator (either negative or positive pressure) who is exposed to airborne concentrations of cadmium that do not exceed 10 times the PEL ($10 \times 5\ \mu g/m^3 = 50\ \mu g/m^3$), the employer shall perform either quantitative or qualitative fit testing at the time of initial fitting and at least annually thereafter. If quantitative fit testing is used for a negative pressure respirator, a fit factor that is at least 10 times the protection factor for that class of respirators (Table 2) shall be achieved at testing.

(iii) For each employee wearing a tight-fitting air purifying respirator (either negative or positive pressure) who is exposed to airborne concentrations of cadmium that exceed 10 times the PEL ($10 \times 5\ \mu g/m^3 = 50\ \mu g/m^3$), the employer shall perform quantitative fit testing at the time of initial fitting and at least annually thereafter. For negative-pressure respirators, a fit factor that is at least 10 times the protection factor for that class of respirators (Table 2) shall be achieved during quantitative fit testing.

(iv) For each employee wearing a tight-fitting, supplied-air respirator or self-contained breathing apparatus, the employer shall perform quantitative fit testing at the time of initial fitting and at least annually thereafter. This shall be accomplished by fit testing an air purifying respirator of identical type facepiece, make, model, and size as the supplied air respirator or self-contained breathing apparatus that is equipped with HEPA filters and tested as a surrogate (substitute) in the negative pressure mode. A fit factor that is at least 10 times the protection factor for that class of respirators (Table 2) shall be achieved during quantitative fit testing. A supplied-air respirator or self-contained breathing apparatus with the same type facepiece, make, model, and size as the air purifying respirator with which the employee passed the quantitative fit test may then be used by that employee up to the protection factor listed in Table 2 for that class of respirators.

(v) Fit testing shall be conducted in accordance with Appendix C of this section.

(h) Emergency situations.

The employer shall develop and implement a written plan for dealing with emergency situations involving substantial releases of airborne cadmium. The plan shall include provisions for the use of appropriate respirators and personal protective equipment. In addition, employees not essential to correcting the emergency situation shall be restricted from the area and normal operations halted in that area until the emergency is abated.

(i) Protective work clothing and equipment.

(1) *Provision and use.*

If an employee is exposed to airborne cadmium above the PEL or where skin or eye irritation is associated with cadmium exposure at any level, the employer shall provide at no cost to the employee, and assure that the employee uses, appropriate protective work clothing and equipment that prevents contamination of the employee and the employee's garments. Protective work clothing and equipment includes, but is not limited to:

(i) Coveralls or similar full-body work clothing;

(ii) Gloves, head coverings, and boots or foot coverings; and

(iii) Face shields, vented goggles, or other appropriate protective equipment that complies with 29 CFR 1910.133.

(2) *Removal and storage.*

(i) The employer shall assure that employees remove all protective clothing and equipment contaminated with cadmium at the completion of the work shift and do so only in change rooms provided in accordance with paragraph (j)(1) of this section.

(ii) The employer shall assure that no employee takes cadmium-contaminated protective clothing or equipment from the workplace, except for employees authorized to do so for purposes of laundering, cleaning, maintaining, or disposing of cadmium contaminated protective clothing and equipment at an appropriate location or facility away from the workplace.

(iii) The employer shall assure that contaminated protective clothing and equipment, when removed for laundering, cleaning, maintenance, or disposal, is placed and stored in sealed, impermeable bags or other closed, impermeable containers that are designed to prevent dispersion of cadmium dust.

(iv) The employer shall assure that bags or containers of contaminated protective clothing and equipment that are to be taken out of the change rooms or the workplace for laundering, cleaning, maintenance or disposal shall bear labels in accordance with paragraph (m)(3) of this section.

(3) *Cleaning, replacement, and disposal.*

(i) The employer shall provide the protective clothing and equipment required by paragraph (i)(1) of this section in a clean and dry condition as often as necessary to maintain its effectiveness, but in any event at least weekly. The employer is responsible for cleaning and laundering the protective clothing and equipment required by this paragraph to maintain its effectiveness and is also responsible for disposing of such clothing and equipment.

(ii) The employer also is responsible for repairing or replacing required protective clothing and equipment as needed to maintain its effectiveness. When rips or tears are detected while an employee is working they shall be immediately mended, or the worksuit shall be immediately replaced.

(iii) The employer shall prohibit the removal of cadmium from protective clothing and equipment by blowing, shaking, or any other means that disperses cadmium into the air.

(iv) The employer shall assure that any laundering of contaminated clothing or cleaning of contaminated equipment in the workplace is done in a manner that prevents the release of airborne cadmium in excess of the permissible exposure limit prescribed in paragraph (c) of this section.

(v) The employer shall inform any person who launders or cleans protective clothing or equipment contaminated with cadmium of the potentially harmful effects of exposure to cadmium and that the clothing and equipment should be laundered or cleaned in a manner to effectively prevent the release of airborne cadmium in excess of the PEL.

(j) Hygiene areas and practices.

(1) *General.*

For employees whose airborne exposure to cadmium is above the PEL, the employer shall provide clean change rooms, handwashing facilities, showers, and lunchroom facilities that comply with 29 CFR 1910.141.

(2) *Change rooms.*

The employer shall assure that change rooms are equipped with separate storage facilities for street clothes and for protective clothing and equipment, which are designed to prevent dispersion of cadmium and contamination of the employee's street clothes.

(3) *Showers and handwashing facilities.*

(i) The employer shall assure that employees who are exposed to cadmium above the PEL shower during the end of the work shift.

(ii) The employer shall assure that employees whose airborne exposure to cadmium is above the PEL wash their hands and faces prior to eating, drinking, smoking, chewing tobacco or gum, or applying cosmetics.

(4) *Lunchroom facilities.*

(i) The employer shall assure that the lunchroom facilities are readily accessible to employees, that tables for eating are maintained free of cadmium, and that no employee in a lunchroom facility is exposed at any time to cadmium at or above a concentration of 2.5 $\mu g/m^3$.

(ii) The employer shall assure that employees do not enter lunchroom facilities with protective work clothing or equipment unless surface cadmium has been removed from the clothing and equipment by HEPA vacuuming or some other method that removes cadmium dust without dispersing it.

(k) Housekeeping.

(1) All surfaces shall be maintained as free as practicable of accumulations of cadmium.

(2) All spills and sudden releases of material containing cadmium shall be cleaned up as soon as possible.

(3) Surfaces contaminated with cadmium shall, wherever possible, be cleaned by vacuuming or other methods that minimize the likelihood of cadmium becoming airborne.

(4) HEPA-filtered vacuuming equipment or equally effective filtration methods shall be used for vacuuming. The equipment shall be used and emptied in a manner that minimizes the reentry of cadmium into the workplace.

(5) Shoveling, dry or wet sweeping, and brushing may be used only where vacuuming or other methods that minimize the likelihood of cadmium becoming airborne have been tried and found not to be effective.

(6) Compressed air shall not be used to remove cadmium from any surface unless the compressed air is used in conjunction with a ventilation system designed to capture the dust cloud created by the compressed air.

(7) Waste, scrap, debris, bags, containers, personal protective equipment, and clothing contaminated with cadmium and consigned for disposal shall be collected and disposed of in sealed impermeable bags or other closed, impermeable containers. These bags and containers shall be labeled in accordance with paragraph (m)(2) of this section.

(l) Medical surveillance.

(1) *General.*

(i) *Scope.*

(A) Currently exposed—The employer shall institute a medical surveillance program for all employees who are or

may be exposed to cadmium at or above the action level unless the employer demonstrates that the employee is not, and will not be, exposed at or above the action level on 30 or more days per year (twelve consecutive months); and.

(B) Previously exposed—The employer shall also institute a medical surveillance program for all employees who prior to the effective date of this section might previously have been exposed to cadmium at or above the action level by the employer, unless the employer demonstrates that the employee did not prior to the effective date of this section work for the employer in jobs with exposure to cadmium for an aggregated total of more than 60 months.

(ii) To determine an employee's fitness for using a respirator, the employer shall provide the limited medical examination specified in paragraph (l)(6) of this section.

(iii) The employer shall assure that all medical examinations and procedures required by this standard are performed by or under the supervision of a licensed physician, who has read and is familiar with the health effects section of Appendix A, the regulatory text of this section, the protocol for sample handling and laboratory selection in Appendix F, and the questionnaire of Appendix D. These examinations and procedures shall be provided without cost to the employee and at a time and place that is reasonable and convenient to employees.

(iv) The employer shall assure that the collecting and handling of biological samples of cadmium in urine (CdU), cadmium in blood (CdB), and beta-2 microglobulin in urine (β_2-M) taken from employees under this section is done in a manner that assures their reliability and that analysis of biological samples of cadmium in urine (CdU), cadmium in blood (CdB), and beta-2 microglobulin in urine (β_2-M) taken from employees under this section is performed in laboratories with demonstrated proficiency for that particular analyte. (See Appendix F.)

(2) *Initial examination.*

(i) The employer shall provide an initial (preplacement) examination to all employees covered by the medical surveillance program required in paragraph (l)(1)(i) of this section. The examination shall be provided to those employees within 30 days after initial assignment to a job with exposure to cadmium or no later than 90 days after the effective date of this section, whichever date is later.

(ii) The initial (preplacement) medical examination shall include:

(A) A detailed medical and work history, with emphasis on: past, present, and anticipated future exposure to cadmium; any history of renal, cardiovascular, respiratory, hematopoietic, reproductive, and/or musculo-skeletal system dysfunction; current usage of medication with potential nephrotoxic side-effects; and smoking history and current status; and

(B) Biological monitoring that includes the following tests:

(*1*) Cadmium in urine (CdU), standardized to grams of creatinine (g/Cr);

(*2*) Beta-2 microglobulin in urine (β_2-M), standardized to grams of creatinine (g/Cr), with pH specified, as described in Appendix F; and

(*3*) Cadmium in blood (CdB), standardized to liters of whole blood (lwb).

(iii) *Recent examination:* An initial examination is not required to be provided if adequate records show that the employee has been examined in accordance with the requirements of paragraph (l)(2)(ii) of this section within the past 12 months. In that case, such records shall be maintained as part of the employee's medical record and the prior exam shall be treated as if it were an initial examination for the purposes of paragraphs (l) (3) and (4) of this section.

(3) *Actions triggered by initial biological monitoring:*

(i) If the results of the initial biological monitoring tests show the employee's CdU level to be at or below 3 µg/g Cr, β_2-M level to be at or below 300 µg/g Cr and CdB level to be at or below 5 µg/lwb, then:

(A) For currently exposed employees, who are subject to medical surveillance under paragraph (l)(1)(i)(A) of this section, the employer shall provide the minimum level of periodic medical surveillance in accordance with the requirements in paragraph (l)(4)(i) of this section; and

(B) For previously exposed employees, who are subject to medical surveillance under paragraph (l)(1)(i)(B) of this section, the employer shall provide biological monitoring for CdU, β_2-M, and CdB one year after the initial biological monitoring and then the employer shall comply with the requirements of paragraph (l)(4)(v).

(ii) For all employees who are subject to medical surveillance under paragraph (l)(1)(i), if the results of the initial biological monitoring tests show the level of CdU to exceed 3 µg/g Cr, the level of β_2-M to exceed 300 µg/g Cr, or the level of CdB to exceed 5 µg/lwb, the employer shall:

(A) Within two weeks after receipt of biological monitoring results, reassess the employee's occupational exposure to cadmium as follows:

(*1*) reassess the employee's work practices and personal hygiene;

(*2*) reevaluate the employee's respirator use, if any, and the respirator program;

(*3*) review the hygiene facilities;

(*4*) reevaluate the maintenance and effectiveness of the relevant engineering controls;

(*5*) assess the employee's smoking history and status;

(B) Within 30 days after the exposure reassessment, specified in (i)(3)(ii)(A), take reasonable steps to correct any deficiencies found in the reassessment that may be responsible for the employee's excess exposure to cadmium; and,

(C) Within 90 days after receipt of biological monitoring results, provide a full medical examination to the employee in accordance with the requirements of paragraph (l)(4)(ii) of this section. After completing the medical examination, the examining physician shall determine in a written medical opinion whether to medically remove the employee. If the physician determines that medical removal is not necessary, then until the employee's CdU level falls to or below 3 µg/g Cr, β_2-M level falls to or below 300 µg/g Cr and CdB level falls to or below 5 µg/lwb, the employer shall:

(*1*) Provide biological monitoring in accordance with paragraph (l)(2)(ii)(B) of this section on a semiannual basis; and

(*2*) Provide annual medical examinations in accordance with paragraph (l)(4)(ii) of this section.

(iii) For all employees who are subject to medical surveillance under paragraph (l)(1)(i), if the results of the initial biological monitoring tests show the level of CdU to be in excess of 15 µg/g Cr, or the level of CdB to be in excess of 15 µg/lwb, or the level of β_2-M to be in excess of 1,500 µg/g Cr, the employer shall comply with the requirements of paragraphs (l)(3)(ii)(A)–(B) of this section. Within 90 days after receipt of biological monitoring results, the employer shall provide a full medical examination to the employee in accordance with the requirements of paragraph (l)(4)(ii) of this section. After completing the medical examination, the examining physician shall determine in a written medical opinion whether to medically remove the employee. However, if the initial biological monitoring results and the biological monitoring results obtained during the medical examination both

show that: CdU exceeds 15 µg/g Cr; or CdB exceeds 15 µg/lwb; or β_2-M exceeds 1500 µg/g Cr, and in addition CdU exceeds 3 µg/g Cr or CdB exceeds 5 µg/liter of whole blood, then the physician shall medically remove the employee from exposure to cadmium at or above the action level. If the second set of biological monitoring results obtained during the medical examination does not show that a mandatory removal trigger level has been exceeded, then the employee is not required to be removed by the mandatory provisions of this paragraph. If the employee is not required to be removed by the mandatory provisions of this paragraph or by the physician's determination, then until the employee's CdU level falls to or below 3 µg/g Cr, β_2-M level falls to or below 300 µg/g Cr and CdB level falls to or below 5 µg/lwb, the employer shall:

(A) Periodically reassess the employee's occupational exposure to cadmium;

(B) Provide biological monitoring in accordance with paragraph (l)(2)(ii)(B) of this section on a quarterly basis; and

(C) Provide semiannual medical examinations in accordance with paragraph (l)(4)(ii) of this section.

(iv) For all employees to whom medical surveillance is provided, beginning on January 1, 1999, and in lieu of paragraphs (l)(3)(i)–(iii):

(A) If the results of the initial biological monitoring tests show the employee's CdU level to be at or below 3 µg/g Cr, β_2-M level to be at or below 300 µg/g Cr and CdB level to be at or below 5 µg/lwb, then for currently exposed employees, the employer shall comply with the requirements of paragraph (l)(3)(i)(A), and for previously exposed employees, the employer shall comply with the requirements of paragraph (l)(3)(i)(B);

(B) If the results of the initial biological monitoring tests show the level of CdU to exceed 3 µg/g Cr, the level of β_2-M to exceed 300 µg/g Cr, or the level of CdB to exceed 5 µg/lwb, the employer shall comply with the requirements of paragraphs (l)(3)(ii)(A)–(C); and,

(C) If the results of the initial biological monitoring tests show the level of CdU to be in excess of 7 µg/g Cr, or the level of CdB to be in excess of 10 µg/lwb, or the level of β_2-M to be in excess of 750 µg/g Cr, the employer shall: comply with the requirements of paragraphs (l)(3)(ii)(A)–(B); and, within 90 days after receipt of biological monitoring results, provide a full medical examination to the employee in accordance with the requirements of paragraph (l)(4)(ii) of this section. After completing the medical examination, the examining physician shall determine in a written medical opinion whether to medically remove the employee. However, if the initial biological monitoring results and the biological monitoring results obtained during the medical examination both show that: CdU exceeds 7 µg/g Cr; or CdB exceeds 10 µg/lwb; or β_2-M exceeds 750 µg/g Cr, and in addition CdU exceeds 3 µg/g Cr or CdB exceeds 5 µg/liter of whole blood, then the physician shall medically remove the employee from exposure to cadmium at or above the action level. If the second set of biological monitoring results obtained during the medical examination does not show that a mandatory removal trigger level has been exceeded, then the employee is not required to be removed by the mandatory provisions of this paragraph. If the employee is not required to be removed by the mandatory provisions of this paragraph or by the physician's determination, then until the employee's CdU level falls to or below 3 µg/g Cr, β_2-M level falls to or below 300 µg/g Cr and CdB level falls to or below 5 µg/lwb, the employer shall: periodically reassess the employee's occupational exposure to cadmium; provide biological monitoring in accordance with paragraph (l)(2)(ii)(B) of this section on a quarterly basis; and provide semiannual medical examinations in accordance with paragraph (l)(4)(ii) of this section.

(4) ***Periodic medical surveillance.***

(i) For each employee who is covered under paragraph (l)(1)(i)(A), the employer shall provide at least the minimum level of periodic medical surveillance, which consists of periodic medical examinations and periodic biological monitoring. A periodic medical examination shall be provided within one year after the initial examination required by paragraph (l)(2) and thereafter at least biennially. Biological sampling shall be provided at least annually, either as part of a periodic medical examination or separately as periodic biological monitoring.

(ii) The periodic medical examination shall include:

(A) A detailed medical and work history, or update thereof, with emphasis on: past, present and anticipated future exposure to cadmium; smoking history and current status; reproductive history; current use of medications with potential nephrotoxic side-effects; any history of renal, cardiovascular, respiratory, hematopoietic, and/or musculo-skeletal system dysfunction; and as part of the medical and work history, for employees who wear respirators, questions 3–11 and 25–32 in Appendix D;

(B) A complete physical examination with emphasis on: blood pressure, the respiratory system, and the urinary system;

(C) A 14 inch by 17 inch, or a reasonably standard sized posterior-anterior chest X-ray (after the initial X-ray, the frequency of chest X-rays is to be determined by the examining physician);

(D) Pulmonary function tests, including forced vital capacity (FVC) and forced expiratory volume at 1 second (FEV1);

(E) Biological monitoring, as required in paragraph (l)(2)(ii)(B);

(F) Blood analysis, in addition to the analysis required under paragraph (l)(2)(ii)(B), including blood urea nitrogen, complete blood count, and serum creatinine;

(G) Urinalysis, in addition to the analysis required under paragraph (l)(2)(ii)(B), including the determination of albumin, glucose, and total and low molecular weight proteins;

(H) For males over 40 years old, prostate palpation, or other at least as effective diagnostic test(s); and

(I) Any additional tests deemed appropriate by the examining physician.

(iii) Periodic biological monitoring shall be provided in accordance with paragraph (l)(2)(ii)(B).

(iv) If the results of periodic biological monitoring or the results of biological monitoring performed as part of the periodic medical examination show the level of the employee's CdU, β_2-M, or CdB to be in excess of the levels specified in paragraphs (l)(3) (ii) or (iii); or, beginning on January 1, 1999, in excess of the levels specified in paragraphs (l)(3) (ii) or (iv) of this section, the employer shall take the appropriate actions specified in paragraphs (l)(3)(ii)–(iv) of this section.

(v) For previously exposed employees under paragraph (l)(1)(i)(B):

(A) If the employee's levels of CdU did not exceed 3 µg/g Cr, CdB did not exceed 5 µg/lwb, and β_2-M did not exceed 300 µg/g Cr in the initial biological monitoring tests, and if the results of the followup biological monitoring required by paragraph (l)(3)(i)(B) one year after the initial examination confirm the previous results, the employer may discontinue all periodic medical surveillance for that employee.

(B) If the initial biological monitoring results for CdU, CdB, or β_2-M were in excess of the levels specified in (l)(3)(i), but subsequent biological monitoring results required by (l)(3)(ii)–(iv) show

that the employee's CdU levels no longer exceed 3 μg/g Cr, CdB levels no longer exceed 5 μg/lwb, and β_2-M levels no longer exceed 300 μg/g Cr, the employer shall provide biological monitoring for CdU, CdB, and β_2-M one year after these most recent biological monitoring results. If the results of the followup biological monitoring, specified in this paragraph, confirm the previous results, the employer may discontinue all periodic medical surveillance for that employee.

(C) However, if the results of the follow-up tests specified in (l)(4)(v) (A) or (B) indicate that the level of the employee's CdU, β_2-M, or CdB exceeds these same levels, the employer is required to provide annual medical examinations in accordance with the provisions of paragraph (l)(4)(ii) until the results of biological monitoring are consistently below these levels or the examining physician determines in a written medical opinion that further medical surveillance is not required to protect the employee's health.

(vi) A routine, biennial medical examination is not required to be provided in accordance with paragraphs (l)(3)(i) and (l)(4) if adequate medical records show that the employee has been examined in accordance with the requirements of paragraph (l)(4)(ii) within the past 12 months. In that case, such records shall be maintained by the employer as part of the employee's medical record, and the next routine, periodic medical examination shall be made available to the employee within two years of the previous examination.

(5) *Actions triggered by medical examinations:*

(i) If the results of a medical examination carried out in accordance with this section indicate any laboratory or clinical finding consistent with cadmium toxicity that does not require employer action under paragraphs (1)(2), (3) or (4) of this section, the employer, within 30 days, shall reassess the employee's occupational exposure to cadmium and take the following corrective action until the physician determines they are no longer necessary:

(A) Periodically reassess: The employee's work practices and personal hygiene; the employee's respirator use, if any; the employee's smoking history and status; the respiratory protection program; the hygiene facilities; and the maintenance and effectiveness of the relevant engineering controls;

(B) Within 30 days after the reassessment, take all reasonable steps to correct the deficiencies found in the reassessment that may be responsible for the employee's excess exposure to cadmium;

(C) Provide semiannual medical reexaminations to evaluate the abnormal clinical sign(s) of cadmium toxicity until the results are normal or the employee is medically removed; and

(D) Where the results of tests for total proteins in urine are abnormal, provide a more detailed medical evaluation of the toxic effects of cadmium on the employee's renal system.

(6) *Examination for respirator use:*

(i) To determine an employee's fitness for respirator use, the employer shall provide a medical examination that includes the elements specified in (l)(6)(A)-(D). This examination shall be provided prior to the employee's being assigned to a job that requires the use of a respirator or no later than 90 days after this section goes into effect, whichever date is later, to any employee without a medical examination within the preceding 12 months that satisfies the requirements of this paragraph.

(A) A detailed medical and work history, or update thereof, with emphasis on: past exposure to cadmium; smoking history and current status; any history of renal, cardiovascular, respiratory, hematopoietic, and/or musculo-skeletal system dysfunction; a description of the job for which the respirator is required; and questions 3–11 and 25–32 in Appendix D;

(B) A blood pressure test;

(C) Biological monitoring of the employee's levels of CdU, CdB and β_2-M in accordance with the requirements of paragraph (l)(2)(ii)(B), unless such results already have been obtained within the previous 12 months; and

(D) Any other test or procedure that the examining physician deems appropriate.

(ii) After reviewing all the information obtained from the medical examination required in paragraph (l)(6)(i) of this section, the physician shall determine whether the employee is fit to wear a respirator.

(iii) Whenever an employee has exhibited difficulty in breathing during a respirator fit test or during use of a respirator, the employer, as soon as possible, shall provide the employee with a periodic medical examination in accordance with paragraph (l)(4)(ii) to determine the employee's fitness to wear a respirator.

(iv) Where the results of the examination required under paragraph (l)(6)(i), (ii) or (iii) of this section are abnormal, medical limitation or prohibition of respirator use shall be considered. If the employee is allowed to wear a respirator, the employee's ability to continue to do so shall be periodically evaluated by a physician.

(7) *Emergency examinations:*

(i) In addition to the medical surveillance required in paragraphs (l)(2)–(6) of this section, the employer shall provide a medical examination as soon as possible to any employee who may have been acutely exposed to cadmium because of an emergency.

(ii) The examination shall include the requirements of paragraph (l)(4)(ii), with emphasis on the respiratory system, other organ systems considered appropriate by the examining physician, and symptoms of acute overexposure, as identified in Appendix A of this section in paragraphs II(B)(1)-(2) and IV.

(8) *Termination of employment examination:*

(i) At termination of employment, the employer shall provide a medical examination in accordance with paragraph (l)(4)(ii) of this section, including a chest X-ray, to any employee to whom at any prior time the employer was required to provide medical surveillance under paragraphs (l)(1)(i) or (l)(7) of this section. However, if the last examination satisfied the requirements of paragraph (l)(4)(ii) of this standard and was less than six months prior to the date of termination, no further examination is required unless otherwise specified in paragraphs (l)(3) or (l)(5);

(ii) However, for employees covered by paragraph (l)(1)(i)(B), if the employer has discontinued all periodic medical surveillance under (l)(4)(v), no termination of employment medical examination is required.

(9) *Information provided to the physician:*

The employer shall provide the following information to the examining physician:

(i) A copy of this standard and appendices;

(ii) A description of the affected employee's former, current, and anticipated duties as they relate to the employee's occupational exposure to cadmium;

(iii) The employee's former, current, and anticipated future levels of occupational exposure to cadmium;

(iv) A description of any personal protective equipment, including respirators, used or to be used by the employee, including when and for how long the employee has used that equipment; and

(v) Relevant results of previous biological monitoring and medical examinations.

(10) *Physician's written medical opinion:*

(i) The employer shall promptly obtain a written, signed medical opinion from the examining physician for each

medical examination performed on each employee. This written opinion shall contain:

(A) The physician's diagnosis for the employee;

(B) The physician'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 cadmium, including any indications of potential cadmium toxicity;

(C) The results of any biological or other testing or related evaluations that directly assess the employee's absorption of cadmium;

(D) Any recommended removal from, or limitation on the activities or duties of the employee or on the employee's use of personal protective equipment, such as respirators;

(E) A statement that the physician has clearly and carefully explained to the employee the results of the medical examination, including all biological monitoring results and any medical conditions related to cadmium exposure that require further evaluation or treatment, and any limitation on the employee's diet or use of medications.

(ii) The employer promptly shall obtain a copy of the results of any biological monitoring provided by an employer to an employee independently of a medical examination under paragraphs (l)(2) and (l)(4), and, in lieu of a written medical opinion, an explanation sheet explaining those results.

(iii) The employer shall instruct the physician not to reveal orally or in the written medical opinion given to the employer specific findings or diagnoses unrelated to occupational exposure to cadmium.

(11) *Medical Removal Protection (MRP):*

(i) *General.*

(A) The employer shall temporarily remove an employee from work where there is excess exposure to cadmium on each occasion that medical removal is required under paragraphs (l)(3), (l)(4), or (l)(6) of this section and on each occasion that a physician determines in a written medical opinion that the employee should be removed from such exposure. The physician's determination may be based on biological monitoring results, inability to wear a respirator, evidence of illness, other signs or symptoms of cadmium-related dysfunction or disease, or any other reason deemed medically sufficient by the physician.

(B) The employer shall medically remove an employee in accordance with paragraph (l)(11) of this section regardless of whether at the time of removal a job is available into which the removed employee may be transferred.

(C) Whenever an employee is medically removed under paragraph (l)(11) of this section, the employer shall transfer the removed employee to a job where the exposure to cadmium is within the permissible levels specified in that paragraph as soon as one becomes available.

(D) For any employee who is medically removed under the provisions of paragraph (l)(11)(i) of this section, the employer shall provide follow-up biological monitoring in accordance with (l)(2)(ii)(B) at least every three months and follow-up medical examinations semi-annually at least every six months until in a written medical opinion the examining physician determines that either the employee may be returned to his/her former job status as specified under (l)(11)(iv)–(v) or the employee must be permanently removed from excess cadmium exposure.

(E) The employer may not return an employee who has been medically removed for any reason to his/her former job status until a physician determines in a written medical opinion that continued medical removal is no longer necessary to protect the employee's health.

(ii) Where an employee is found unfit to wear a respirator under paragraph (l)(6)(ii), the employer shall remove the employee from work where exposure to cadmium is above the PEL.

(iii) Where removal is based on any reason other than the employee's inability to wear a respirator, the employer shall remove the employee from work where exposure to cadmium is at or above the action level.

(iv) Except as specified in paragraph (l)(11)(v), no employee who was removed because his/her level of CdU, CdB and/or β_2-M exceeded the medical removal trigger levels in paragraph (l)(3) or (l)(4) may be returned to work with exposure to cadmium at or above the action level until the employee's levels of CdU fall to or below 3 μg/g Cr, CdB falls to or below 5 μg/lwb, and β_2-M falls to or below 300 μg/g Cr.

(v) However, when in the examining physician's opinion continued exposure to cadmium will not pose an increased risk to the employee's health and there are special circumstances that make continued medical removal an inappropriate remedy, the physician shall fully discuss these matters with the employee, and then in a written determination may return a worker to his/her former job status despite what would otherwise be unacceptably high biological monitoring results. Thereafter, the returned employee shall continue to be provided with medical surveillance as if he/she were still on medical removal until the employee's levels of CdU fall to or below 3 μg/g Cr, CdB falls to or below 5 μg/lwb, and β_2-M falls to or below 300 μg/g Cr.

(vi) Where an employer, although not required by (l)(11)(i)–(iii) of this section to do so, removes an employee from exposure to cadmium or otherwise places limitations on an employee due to the effects of cadmium exposure on the employee's medical condition, the employer shall provide the same medical removal protection benefits to that employee under paragraph (l)(12) as would have been provided had the removal been required under paragraph (l)(11)(i)–(iii) of this section.

(12) *Medical Removal Protection Benefits (MRPB).*

(i) The employer shall provide MRPB for up to a maximum of 18 months to an employee each time and while the employee is temporarily medically removed under paragraph (l)(11) of this section.

(ii) For purposes of this section, the requirement that the employer provide MRPB means that the employer shall maintain the total normal earnings, seniority, and all other employee rights and benefits of the removed employee, including the employee's right to his/her former job status, as if the employee had not been removed from the employee's job or otherwise medically limited.

(iii) Where, after 18 months on medical removal because of elevated biological monitoring results, the employee's monitoring results have not declined to a low enough level to permit the employee to be returned to his/her former job status:

(A) The employer shall make available to the employee a medical examination pursuant to this section in order to obtain a final medical determination as to whether the employee may be returned to his/her former job status or must be permanently removed from excess cadmium exposure; and

(B) The employer shall assure that the final medical determination indicates whether the employee may be returned to his/her former job status and what steps, if any, should be taken to protect the employee's health.

(iv) The employer may condition the provision of MRPB upon the employee's participation in medical surveillance provided in accordance with this section.

(13) *Multiple physician review.*

(i) If the employer selects the initial physician to conduct any medical examination or consultation provided to an employee under this section, the employee may designate a second physician to:

(A) Review any findings, determinations, or recommendations of the initial physician; and

(B) Conduct such examinations, consultations, and laboratory tests as the second physician deems necessary to facilitate this review.

(ii) The employer shall promptly notify an employee of the right to seek a second medical opinion after each occasion that an initial physician provided by the employer conducts a medical examination or consultation pursuant to this section. The employer may condition its participation in, and payment for, multiple physician review upon the employee doing the following within fifteen (15) days after receipt of this notice, or receipt of the initial physician's written opinion, whichever is later:

(A) Informing the employer that he or she intends to seek a medical opinion; and

(B) Initiating steps to make an appointment with a second physician.

(iii) If the findings, determinations, or recommendations of the second physician differ from those of the initial physician, then the employer and the employee shall assure that efforts are made for the two physicians to resolve any disagreement.

(iv) If the two physicians have been unable to quickly resolve their disagreement, then the employer and the employee, through their respective physicians, shall designate a third physician to:

(A) Review any findings, determinations, or recommendations of the other two physicians; and

(B) Conduct such examinations, consultations, laboratory tests, and discussions with the other two physicians as the third physician deems necessary to resolve the disagreement among them.

(v) The employer shall act consistently with the findings, determinations, and recommendations of the third physician, unless the employer and the employee reach an agreement that is consistent with the recommendations of at least one of the other two physicians.

(14) *Alternate physician determination.*

The employer and an employee or designated employee representative may agree upon the use of any alternate form of physician determination in lieu of the multiple physician review provided by paragraph (l)(13) of this section, so long as the alternative is expeditious and at least as protective of the employee.

(15) *Information the employer must provide the employee.*

(i) The employer shall provide a copy of the physician's written medical opinion to the examined employee within two weeks after receipt thereof.

(ii) The employer shall provide the employee with a copy of the employee's biological monitoring results and an explanation sheet explaining the results within two weeks after receipt thereof.

(iii) Within 30 days after a request by an employee, the employer shall provide the employee with the information the employer is required to provide the examining physician under paragraph (l)(9) of this section.

(16) Reporting.

In addition to other medical events that are required to be reported on the OSHA Form No. 200, the employer shall report any abnormal condition or disorder caused by occupational exposure to cadmium associated with employment as specified in Chapter (V)(E) of the *Reporting Guidelines for Occupational Injuries and Illnesses.*

(m) Communication of cadmium hazards to employees.

(1) *General.*

In communications concerning cadmium hazards, employers shall comply with the requirements of OSHA's Hazard Communication Standard, 29 CFR 1910.1200, including but not limited to the requirements concerning warning signs and labels, material safety data sheets (MSDS), and employee information and training. In addition, employers shall comply with the following requirements:

(2) *Warning signs.*

(i) Warning signs shall be provided and displayed in regulated areas. In addition, warning signs shall be posted at all approaches to regulated areas so that an employee may read the signs and take necessary protective steps before entering the area.

(ii) Warning signs required by paragraph (m)(2)(i) of this section shall bear the following information:

DANGER
CADMIUM
CANCER HAZARD
CAN CAUSE LUNG AND KIDNEY DISEASE
AUTHORIZED PERSONNEL ONLY
RESPIRATORS REQUIRED IN THIS AREA

(iii) The employer shall assure that signs required by this paragraph are illuminated, cleaned, and maintained as necessary so that the legend is readily visible.

(3) *Warning labels.*

(i) Shipping and storage containers containing cadmium, cadmium compounds, or cadmium contaminated clothing, equipment, waste, scrap, or debris shall bear appropriate warning labels, as specified in paragraph (m)(3)(ii) of this section.

(ii) The warning labels shall include at least the following information:

DANGER
CONTAINS CADMIUM
CANCER HAZARD
AVOID CREATING DUST
CAN CAUSE LUNG AND KIDNEY DISEASE

(iii) Where feasible, installed cadmium products shall have a visible label or other indication that cadmium is present.

(4) *Employee information and training.*

(i) The employer shall institute a training program for all employees who are potentially exposed to cadmium, assure employee participation in the program, and maintain a record of the contents of such program.

(ii) Training shall be provided prior to or at the time of initial assignment to a job involving potential exposure to cadmium and at least annually thereafter.

(iii) The employer shall make the training program understandable to the employee and shall assure that each employee is informed of the following:

(A) The health hazards associated with cadmium exposure, with special attention to the information incorporated in Appendix A to this section;

(B) The quantity, location, manner of use, release, and storage of cadmium in the workplace and the specific nature of operations that could result in exposure to cadmium, especially exposures above the PEL;

(C) The engineering controls and work practices associated with the employee's job assignment;

(D) The measures employees can take to protect themselves from exposure to cadmium, including modification of such habits as smoking and personal hygiene, and specific procedures the employer has implemented to protect employees from exposure to cadmium such as appropriate work practices, emergency procedures, and the provision of personal protective equipment;

(E) The purpose, proper selection, fitting, proper use, and limitations of respirators and protective clothing;

(F) The purpose and a description of the medical surveillance program required by paragraph (l) of this standard;

(G) The contents of this section and its appendices, and,

(H) The employee's rights of access to records under § 1910.20 (e) and (g).

(iv) Additional access to information and training program and materials.

(A) The employer shall make a copy of this section and its appendices readily available without cost to all affected employees and shall provide a copy if requested.

(B) The employer shall provide to the Assistant Secretary or the Director, upon request, all materials relating to the employee information and the training program.

(n) Recordkeeping.

(1) *Exposure Monitoring.*

(i) The employer shall establish and keep an accurate record of all air monitoring for cadmium in the workplace.

(ii) This record shall include at least the following information:

(A) The monitoring date, duration, and results in terms of an 8-hour TWA of each sample taken;

(B) The name, social security number, and job classification of the employees monitored and of all other employees whose exposures the monitoring is intended to represent;

(C) A description of the sampling and analytical methods used and evidence of their accuracy;

(D) The type of respiratory protective device, if any, worn by the monitored employee;

(E) A notation of any other conditions that might have affected the monitoring results.

(iii) The employer shall maintain this record for at least thirty (30) years, in accordance with 29 CFR 1910.20.

(2) *Objective data for exemption from requirement for initial monitoring.*

(i) For purposes of this section, objective data are information demonstrating that a particular product or material containing cadmium or a specific process, operation, or activity involving cadmium cannot release dust or fumes in concentrations at or above the action level even under the worst-case release conditions. Objective data can be obtained from an industry-wide study or from laboratory product test results from manufacturers of cadmium-containing products or materials. The data the employer uses from an industry-wide survey must be obtained under workplace conditions closely resembling the processes, types of material, control methods, work practices and environmental conditions in the employer's current operations.

(ii) The employer shall establish and maintain a record of the objective data for at least 30 years.

(3) *Medical surveillance.*

(i) The employer shall establish and maintain an accurate record for each employee covered by medical surveillance under paragraph (l)(1)(i) of this section.

(ii) The record shall include at least the following information about the employee:

(A) Name, social security number, and description of the duties;

(B) A copy of the physician's written opinions and an explanation sheet for biological monitoring results;

(C) A copy of the medical history, and the results of any physical examination and all test results that are required to be provided by this section, including biological tests, X-rays, pulmonary function tests, etc., or that have been obtained to further evaluate any condition that might be related to cadmium exposure;

(D) The employee's medical symptoms that might be related to exposure to cadmium; and

(E) A copy of the information provided to the physician as required by paragraph (l)(9)(ii)-(v) of this section.

(iii) The employer shall assure that this record is maintained for the duration of employment plus thirty (30) years, in accordance with 29 CFR 1910.20.

(4) *Training.*

The employer shall certify that employees have been trained by preparing a certification record which includes the identity of the person trained, the signature of the employer or the person who conducted the training, and the date the training was completed. The certification records shall be prepared at the completion of training and shall be maintained on file for one (1) year beyond the date of training of that employee.

(5) *Availability.*

(i) Except as otherwise provided for in this section, access to all records required to be maintained by paragraphs (n)(1)-(4) of this section shall be in accordance with the provisions of 29 CFR 1910.20.

(ii) Within 15 days after a request, the employer shall make an employee's medical records required to be kept by paragraph (n)(3) of this section available for examination and copying to the subject employee, to designated representatives, to anyone having the specific written consent of the subject employee, and after the employee's death or incapacitation, to the employee's family members.

(6) *Transfer of records.*

Whenever an employer ceases to do business and there is no successor employer to receive and retain records for the prescribed period or the employer intends to dispose of any records required to be preserved for at least 30 years, the employer shall comply with the requirements concerning transfer of records set forth in 29 CFR 1910.20 (h).

(o) Observation of monitoring.

(1) *Employee observation.*

The employer shall provide affected employees or their designated representatives an opportunity to observe any monitoring of employee exposure to cadmium.

(2) *Observation procedures.*

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 that clothing and equipment and shall assure that the observer uses such clothing and equipment and complies with all other applicable safety and health procedures.

(p) Dates.

(1) *Effective date.*

This section became effective December 14, 1992.

(2) *Start-up dates.*

All obligations of this section commence on the effective date except as follows:

(i) *Exposure monitoring.* Except for small businesses (nineteen (19) or fewer employees), initial monitoring required by paragraph (d)(2) of this section shall be completed as soon as possible and in any event no later than 60 days after the effective date of this standard. For small businesses, initial monitoring required by paragraph (d)(2) of this section shall be completed as soon as possible and in any event no later than 120 days after the effective date of this standard.

(ii) *Regulated areas.* Except for small business, defined under paragraph (p)(2)(i) of this section, regulated areas required to be established by paragraph (e) of this section shall be set up as soon as possible after the results of exposure monitoring are known and in any event no later than 90 days after the effective date of this section. For small businesses, regulated areas required to be established by paragraph (e) of this section shall be set up as soon as possible after the results of exposure monitoring are known and in any event no later than 150 days after the effective date of this section.

(iii) *Respiratory protection.* Except for small businesses, defined under paragraph (p)(2)(i) of this section, respiratory protection required by paragraph (g) of this section shall be provided as soon as possible and in any event no later than 90 days after the effective date of this section. For small businesses, respiratory protection required by paragraph (g) of this section shall be provided as soon as possible and in any event no later than 150 days after the effective date of this section.

(iv) *Compliance program.* Written compliance programs required by paragraph (f)(2) of this section shall be completed and available for inspection and copying as soon as possible and in any event no later than 1 year after the effective date of this section.

(v) *Methods of compliance.* The engineering controls required by paragraph (f)(1) of this section shall be implemented as soon as possible and in any event no later than two (2) years after the effective date of this section. Work practice controls shall be implemented as soon as possible. Work practice controls that are directly related to engineering controls to be implemented in accordance with the compliance plan shall be implemented as soon as possible after such engineering controls are implemented.

(vi) *Hygiene and lunchroom facilities.*

(A) Handwashing facilities, permanent or temporary, shall be provided in accordance with 29 CFR 1910.141(d) (1)and (2) as soon as possible and in any event no later than 60 days after the effective date of this section.

(B) Change rooms, showers, and lunchroom facilities shall be completed as soon as possible and in any event no later than 1 year after the effective date of this section.

(vii) *Employee information and training.* Except for small businesses, defined under paragraph (p)(2)(i) above, employee information and training required by paragraph (m)(4) of this standard shall be provided as soon as possible and in any event no later than 90 days after the effective date of this standard. For small businesses, employee information and training required by paragraph (m)(4) of this standard shall be provided as soon as possible and in any event no later than 180 days after the effective date of this standard.

(viii) *Medical surveillance.* Except for small businesses, defined under paragraph (p)(2)(i) above, initial medical examinations required by paragraph (l) of this standard shall be provided as soon as possible and in any event no later than 90 days after the effective date of this standard. For small businesses, initial medical examinations required by paragraph (l) of this standard shall be provided as soon as possible and in any event no later than 180 days after the effective date of this standard.

(q) Appendices.

(1) Appendix C to this section is incorporated as part of this section, and compliance with its contents is mandatory.

(2) Except where portions of appendices A, B, D, E, and F to this section are expressly incorporated in requirements of this section, these appendices are purely 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
Cadmium

I. Substance Identification

A. Substance: Cadmium.

B. 8-Hour, Time-weighted-average, Permissible Exposure Limit (TWA PEL):

1. TWA PEL: Five micrograms of cadmium per cubic meter of air 5 $\mu g/m^3$, time-weighted average (TWA) for an 8-hour workday.

C. Appearance: Cadmium metal—soft, blue-white, malleable, lustrous metal or grayish-white powder. Some cadmium compounds may also appear as a brown, yellow, or red powdery substance.

II. Health Hazard Data

A. Routes of Exposure.

Cadmium can cause local skin or eye irritation. Cadmium can affect your health if you inhale it or if you swallow it.

B. Effects of Overexposure

1. Short-term (acute) exposure: Cadmium is much more dangerous by inhalation than by ingestion. High exposures to cadmium that may be immediately dangerous to life or health occur in jobs where workers handle large quantities of cadmium dust or fume; heat cadmium-containing compounds or cadmium-coated surfaces; weld with cadmium solders or cut cadmium-containing materials such as bolts.

2. Severe exposure may occur before symptoms appear. Early symptoms may include mild irritation of the upper respiratory tract, a sensation of constriction of the throat, a metallic taste and/or a cough. A period of 1–10 hours may precede the onset of rapidly progressing shortness of breath, chest pain, and flu-like symptoms with weakness, fever, headache, chills, sweating and muscular pain. Acute pulmonary edema usually develops within 24 hours and reaches a maximum by three days. If death from asphyxia does not occur, symptoms may resolve within a week.

3. Long-term (chronic) exposure. Repeated or long-term exposure to cadmium, even at relatively low concentrations, may result in kidney damage and an increased risk of cancer of the lung and of the prostate.

C. Emergency First Aid Procedures

1. Eye exposure: Direct contact may cause redness or pain. Wash eyes immediately with large amounts of water, lifting the upper and lower eyelids. Get medical attention immediately.

2. Skin exposure: Direct contact may result in irritation. Remove contaminated clothing and shoes immediately. Wash affected area with soap or mild detergent and large amounts of water. Get medical attention immediately.

3. Ingestion: Ingestion may result in vomiting, abdominal pain, nausea, diarrhea, headache and sore throat. Treatment for symptoms must be administered by medical personnel. Under no circumstances should the employer allow any person whom he retains, employs, supervises or controls to engage in therapeutic chelation. Such treatment is likely to translocate cadmium from pulmonary or other tissue to renal tissue. Get medical attention immediately.

4. Inhalation: If large amounts of cadmium are inhaled, the exposed person must be moved to fresh air at once. If breathing has stopped, perform cardiopulmonary resuscitation. Administer oxygen if available. Keep the affected person warm and at rest. Get medical attention immediately.

5. Rescue: Move the affected person from the hazardous exposure. If the exposed person has been overcome, attempt rescue only after notifying at least one other person of the emergency and putting into effect established emergency procedures. Do not become a casualty yourself. Understand your emergency rescue procedures and know the location of the emergency equipment before the need arises.

III. Employee Information

A. Protective Clothing and Equipment

1. Respirators: You may be required to wear a respirator for non-routine activities; in emergencies; while your employer is in the process of reducing cadmium exposures through engineering controls; and where engineering controls are not feasible. If respirators are worn in the future, they must have a joint Mine Safety and Health Administration (MSHA) and National Institute for Occupational Safety and Health (NIOSH) label of approval. Cadmium does not have a detectable odor except at levels well above the permissible exposure limits. If you can smell cadmium while wearing a respirator, proceed immediately to fresh air. If you experience difficulty breathing while wearing a respirator, tell your employer.

2. Protective Clothing: You may be required to wear impermeable clothing, gloves, foot gear, a face shield, or other appropriate protective clothing to prevent skin contact with cadmium. Where protective clothing is required, your employer must provide clean garments to you as necessary to assure that the clothing protects you adequately. The employer must replace or repair protective clothing that has become torn or otherwise damaged.

3. Eye Protection: You may be required to wear splash-proof or dust resistant goggles to prevent eye contact with cadmium.

B. Employer Requirements

1. Medical: If you are exposed to cadmium at or above the action level, your employer is required to provide a medical examination, laboratory tests and a medical history according to the medical surveillance provisions under paragraph (l) of this standard. (See summary chart and tables in this Appendix A.) These tests shall be provided without cost to you. In addition, if you are accidentally exposed to cadmium under conditions known or suspected to constitute toxic exposure to cadmium, your employer is required to make special tests available to you.

2. Access to Records: All medical records are kept strictly confidential. You or your

representative are entitled to see the records of measurements of your exposure to cadmium. Your medical examination records can be furnished to your personal physician or designated representative upon request by you to your employer.

3. Observation of Monitoring. Your employer is required to perform measurements that are representative of your exposure to cadmium 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.

C. Employee Requirements

You will not be able to smoke, eat, drink, chew gum or tobacco, or apply cosmetics while working with cadmium in regulated areas. You will also not be able to carry or store tobacco products, gum, food, drinks or cosmetics in regulated areas because these products easily become contaminated with cadmium from the workplace and can therefore create another source unnecessary of cadmium exposure.

Some workers will have to change out of work clothes and shower at the end of the day, as part of their workday, in order to wash cadmium from skin and hair. Handwashing and cadmium-free eating facilities shall be provided by the employer and proper hygiene should always be performed before eating. It is also recommended that you do not smoke or use tobacco products, because among other things, they naturally contain cadmium. For further information, read the labeling on such products.

IV. Physician Information

A. Introduction

The medical surveillance provisions of paragraph (l) generally are aimed at accomplishing three main interrelated purposes: First, identifying employees at higher risk of adverse health effects from excess, chronic exposure to cadmium; second, preventing cadmium-induced disease; and third, detecting and minimizing existing cadmium-induced disease. The core of medical surveillance in this standard is the early and periodic monitoring of the employee's biological indicators of: (a) recent exposure to cadmium; (b) cadmium body burden; and (c) potential and actual kidney damage associated with exposure to cadmium.

The main adverse health effects associated with cadmium overexposure are lung cancer and kidney dysfunction. It is not yet known how to adequately biologically monitor human beings to specifically prevent cadmium-induced lung cancer. By contrast, the kidney can be monitored to provide prevention and early detection of cadmium-induced kidney damage. Since, for non-carcinogenic effects, the kidney is considered the primary target organ of chronic exposure to cadmium, the medical surveillance provisions of this standard effectively focus on cadmium-induced kidney disease. Within that focus, the aim, where possible, is to prevent the onset of such disease and, where necessary, to minimize such disease as may already exist. The by-products of successful prevention of kidney disease are anticipated to be the reduction and prevention of other cadmium-induced diseases.

B. Health Effects

The major health effects associated with cadmium overexposure are described below.

1. Kidney

The most prevalent non-malignant disease observed among workers chronically exposed to cadmium is kidney dysfunction. Initially, such dysfunction is manifested as proteinuria. The proteinuria associated with cadmium exposure is most commonly characterized by excretion of low-molecular weight proteins (15,000 to 40,000 MW) accompanied by loss of electrolytes, uric acid, calcium, amino acids, and phosphate. The compounds commonly excreted include beta-2-microglobulin (β_2-M), retinol binding protein (RBP), immunoglobulin light chains, and lysozyme. Excretion of low molecular weight proteins are characteristic of damage to the proximal tubules of the kidney (Iwao *et al.*, 1980).

It has also been observed that exposure to cadmium may lead to urinary excretion of high-molecular weight proteins such as albumin, immunoglobulin G, and glycoproteins (ex. 29). Excretion of high-molecular weight proteins is typically indicative of damage to the glomeruli of the kidney. Bernard *et al.*, (1979) suggest that damage to the glomeruli and damage to the proximal tubules of the kidney may both be linked mechanisms caused but they may occur independently of each other.

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). Above specific levels of β_2-M associated with cadmium exposure it is unlikely that β_2-M levels return to normal even when cadmium exposure is eliminated by removal of the individual from the cadmium work environment (Friberg, ex. 29, 1990).

Some studies indicate that such proteinuria may be progressive; levels of β_2-M observed in the urine increase with time even after cadmium exposure has ceased. See, for example, Elinder *et al.*, 1985. Such observations, however, are not universal, and it has been suggested that studies in which proteinuria has not been observed to progress may not have tracked persons for a sufficiently long time interval (Jarup, ex. 8–661).

When cadmium exposure continues after the onset of proteinuria, chronic nephrotoxicity may occur (Friberg, ex. 29). Uremia results from the inability of the glomerulus to adequately filter blood. This leads to severe disturbance of electrolyte concentrations and may lead to various clinical complications including kidney stones (L–140–50).

After prolonged exposure to cadmium, glomerular proteinuria, glucosuria, aminoaciduria, phosphaturia, and hypercalciuria may develop (ex. 8–66, 4–28, 14–18). Phosphate, calcium, glucose, and amino acids are essential to life, and under normal conditions, their excretion should be regulated by the kidney. Once low molecular weight proteinuria has developed, these elements dissipate from the human body. Loss of glomerular function may also occur, manifested by decreased glomerular filtration rate and increased serum creatinine. Severe cadmium-induced renal damage may eventually develop into chronic renal failure and uremia (ex. 55).

Studies in which animals are chronically exposed to cadmium confirm the renal effects observed in humans (Friberg *et al.*, 1986). Animal studies also confirm problems with calcium metabolism and related skeletal effects which have been observed among humans exposed to cadmium in addition to the renal effects. 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 co-factors. Hypertension, for example, appears to be associated with diet as well as cadmium exposure. Animals injected with cadmium have also shown testicular necrosis (ex. 8–86B).

2. Biological Markers

It is universally recognized that the best measures of cadmium exposure and its effects are measurements of cadmium in biological fluids, especially urine and blood. Of the two, CdU is conventionally used to determine body burden of cadmium in workers without kidney disease. CdB is conventionally used to monitor for recent exposure to cadmium. In addition, levels of CdU and CdB historically have been used to predict the percent of the population likely to develop kidney disease (Thun *et al.*, Ex. L–140–50; WHO, Ex. 8–674; ACGIH, Ex. 8–667, 140–50).

The third biological parameter upon which OSHA relies for medical surveillance is Beta-2-microglobulin in urine (β_2-M), a low molecular weight protein. Excess β_2-M has been widely accepted by physicians and scientists as a reliable indicator of functional damage to the proximal tubule of the kidney (Exs. 8–447, 144–3–C, 4–47, L–140–45, 19–43–A).

Excess β_2-M is found when the proximal tubules can no longer reabsorb this protein in a normal manner. This failure of the proximal tubules is an early stage of a kind of kidney disease that commonly occurs among workers with excessive cadmium exposure. Used in connection with biological test results indicating abnormal levels of CdU and CdB, the finding of excess β_2-M can establish for an examining physician that any existing kidney disease is probably cadmium-related (Trs. 6/8/90, pp. 82–86, 122, 134). The upper limits of normal levels for cadmium in urine and cadmium in blood are 3 μg Cd/gram creatinine in urine and 5 μgCd/liter whole blood, respectively. These levels were derived from recent population studies.

Three issues confront the physicians in the use of β_2-M as a marker of kidney dysfunction and material impairment. First,

there are a few other causes of elevated levels of β_2-M not related to cadmium exposures, some of which may be rather common diseases and some of which are serious diseases (e.g., myeloma or transient flu, Exs. 29 and 8–686). These can be medically evaluated as alternative causes (Friberg, Ex. 29). Also, there are other factors that can cause β_2-M to degrade so that low levels would result in workers with tubular dysfunction: For example, regarding the degradation of β_2-M, workers with acidic urine (pH > 6) might have β_2M levels that are within the "normal" range when in fact kidney dysfunction has occurred (Ex. L–140–1) and the low molecular weight proteins are degraded in acid urine. Thus, it is very important that the pH of urine be measured, that urine samples be buffered as necessary (See Appendix F.), and that urine samples be handled correctly, i.e., measure the pH of freshly voided urine samples, then if necessary, buffer to pH > 6 (or above for shipping purposes), measure pH again and then, perhaps, freeze the sample for storage and shipping. (See also Appendix F.) Second, there is debate over the pathological significance of proteinuria, however, most world experts believe that β_2-M levels greater than 300 µg/g Cr are abnormal (Elinder, Ex. 55, Friberg, Ex. 29). Such levels signify kidney dysfunction that constitutes material impairment of health. Finally, detection of β_2-M at low levels has often been considered difficult, however, many laboratories have the capability of detecting excess β_2-M using simple kits, such as the Phadebas Delphia test, that are accurate to levels of 100 µg β_2-M/g Cr U (Ex. L–140–1).

Specific recommendations for ways to measure β_2-M and proper handling of urine samples to prevent degradation of β_2-M have been addressed by OSHA in Appendix F, in the section on laboratory standardization. All biological samples must be analyzed in a laboratory that is proficient in the analysis of that particular analyte, under paragraph (l)(1)(iv). (See Appendix F). Specifically, under paragraph (l)(1)(iv), the employer is to assure that the collecting and handling of biological samples of cadmium in urine (CdU), cadmium in blood (CdB), and beta-2 microglobulin in urine (β_2-M) taken from employees is collected in a manner that assures reliability. The employer must also assure that analysis of biological samples of cadmium in urine (CdU), cadmium in blood (CdB), and beta-2 microglobulin in urine (β_2-M) taken from employees is performed in laboratories with demonstrated proficiency for that particular analyte. (See Appendix F.)

3. Lung and Prostate Cancer

The primary sites for cadmium-associated cancer appear to be the lung and the prostate (L–140–50). Evidence for an association between cancer and cadmium exposure derives from both epidemiological studies and animal experiments. Mortality from prostate cancer associated with cadmium is slightly elevated in several industrial cohorts, but the number of cases is small and there is not clear dose-response relationship. More substantive evidence exists for lung cancer.

The major epidemiological study of lung cancer was conducted by Thun *et al.*, (EX. 4–68). Adequate data on cadmium exposures were available 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 observed in this study even when confounding variables such as co-exposure to arsenic and smoking habits were taken into consideration (Ex. L–140–50).

The primary evidence for quantifying a link between lung cancer and cadmium exposure from animal studies derives from two rat bioassay studies: one by Takenaka *et al.*, (1983), which is a study of cadmium chloride and a second study by Oldiges and Glaser (1990) of four cadmium compounds.

Based on the above cited studies, the U.S. Environmental Protection Agency (EPA) classified cadmium as "B1", a probable human carcinogen, in 1985 (Ex. 4–4). The International Agency for Research on Cancer (IARC) in 1987 also recommended that cadmium be listed as "2A", a probable human carcinogen (Ex. 4–15). The American Conference of Governmental Industrial Hygienists (ACGIH) has recently recommended that cadmium be labeled as a carcinogen. Since 1984, NIOSH has concluded that cadmium is possibly a human carcinogen and has recommended that exposures be controlled to the lowest level feasible.

4. Non-carcinogenic Effects

Acute pneumonitis occurs 10 to 24 hours after initial acute inhalation of high levels of cadmium fumes with symptoms such as fever and chest pain (Exs. 30, 8–86B). In extreme exposure cases pulmonary edema may develop and cause death several days after exposure. Little actual exposure measurement data is available on the level of airborne cadmium exposure that causes such immediate adverse lung effects, nonetheless, it is reasonable to believe a cadmium concentration of approximately 1 mg/m^3 over an eight hour period is "immediately dangerous" (55 FR 4052, ANSI; Ex. 8–86B).

In addition to acute lung effects and chronic renal effects, long term exposure to cadmium may cause other severe effects on the respiratory system. Reduced pulmonary function and chronic lung disease indicative of emphysema have been observed in workers who have had prolonged exposure to cadmium dust or fumes (Exs. 4–29, 4–22, 4–42, 4–50, 4–63). In a study of workers conducted by Kazantzis *et al.*, a statistically significant excess of worker deaths due to chronic bronchitis was found, which in his opinion was directly related to high cadmium exposures of 1 mg/m^3 or more (Tr. 6/8/90, pp. 156–157).

Cadmium need not be respirable to constitute a hazard. Inspirable cadmium particles that are too large to be respirable but small enough to enter the tracheobronchial region of the lung can lead to bronchoconstriction, chronic pulmonary disease, and cancer of that portion of the lung. All of these diseases have been associated with occupational exposure to cadmium (Ex. 8–86B). Particles that are constrained by their size to the extra-thoracic regions of the respiratory system such as the nose and maxillary sinuses can be swallowed through mucocillary clearance and be absorbed into the body (ACGIH, Ex. 8–692). The impaction of these particles in the upper airways can lead to anosmia, or loss of sense of smell, which is an early indication of overexposure among workers exposed to heavy metals. This condition is commonly reported among cadmium-exposed workers (Ex. 8–86B).

C. Medical Surveillance

In general, the main provisions of the medical surveillance section of the standard, under paragraphs (l)(1)–(17) of the regulatory text, are as follows:

1. Workers exposed above the action level are covered;

2. Workers with intermittent exposures are not covered;

3. Past workers who are covered receive biological monitoring for at least one year;

4. Initial examinations include a medical questionnaire and biological monitoring of cadmium in blood (CdB), cadmium in urine (CdU), and Beta-2-microglobulin in urine (β_2-M);

5. Biological monitoring of these three analytes is performed at least annually; full medical examinations are performed biennially;

6. Until five years from the effective date of the standard, medical removal is required when CdU is greater than 15 µg/gram creatinine (g Cr), or CdB is greater than 15 µg/liter whole blood (lwb), or β_2-M is greater than 1500 µg/g Cr, and CdB is greater than 5 µg/lwb or CdU is greater than 3 µg/g Cr;

7. Beginning five years after the standard is in effect, medical removal triggers will be reduced;

8. Medical removal protection benefits are to be provided for up to 18 months;

9. Limited initial medical examinations are required for respirator usage;

10. Major provisions are fully described under section (l) of the regulatory text; they are outlined here as follows:

A. Eligibility
B. Biological monitoring
C. Actions triggered by levels of CdU, CdB, and β_2-M (See Summary Charts and Tables in Attachment 1)
D. Periodic medical surveillance
E. Actions triggered by periodic medical surveillance (See Appendix A Summary Chart and Tables in Attachment 1)
F. Respirator usage
G. Emergency medical examinations
H. Termination examination
I. Information to physician
J. Physician's medical opinion
K. Medical removal protection
L. Medical removal protection benefits
M. Multiple physician review
N. Alternate physician review
O. Information employer gives to employee
P. Recordkeeping
Q. Reporting on OSHA form 200

11. The above mentioned summary of the medical surveillance provisions, the summary chart, and tables for the actions triggered at different levels of CdU, CdB and β_2-M (in Appendix A Attachment-1) are included only for the purpose of facilitating understanding of the provisions of paragraphs (l)(3) of the final cadmium standard. The summary of the provisions, the

summary chart, and the tables do not add to or reduce the requirements in paragraph (l)(3).

D. Recommendations to Physicians

1. It is strongly recommended that patients with tubular proteinuria are counseled on: the hazards of smoking; avoidance of nephrotoxins and certain prescriptions and over-the-counter medications that may exacerbate kidney symptoms; how to control diabetes and/or blood pressure; proper hydration, diet, and exercise (Ex. 19–2). A list of prominent or common nephrtoxins is attached. (See Appendix A Attachment-2.)

2. DO NOT CHELATE; KNOW WHICH DRUGS ARE NEPHROTOXINS OR ARE ASSOCIATED WITH NEPHRITIS.

3. The gravity of cadmium-induced renal damage is compounded by the fact there is no medical treatment to prevent or reduce the accumulation of cadmium in the kidney (Ex. 8–619). Dr. Friberg, a leading world expert on cadmium toxicity, indicated in 1992, that there is no form of chelating agent that could be used without substantial risk. He stated that tubular proteinuria has to be treated in the same way as other kidney disorders (Ex. 29).

4. After the results of a workers' biological monitoring or medical examination are received the employer is required to provide an information sheet to the patient, briefly explaining the significance of the results. (See Attachment 3 of this Appendix A.)

5. For additional information the physician is referred to the following additional resources:

a. The physician can always obtain a copy of the preamble, with its full discussion of the health effects, from OSHA's Computerized Information System (OCIS).

b. The Docket Officer maintains a record of the rulemaking. The Cadmium Docket (H–057A), is located at 200 Constitution Ave. NW., Room N–2625, Washington, DC 20210; telephone: 202–523–7894.

c. The following articles and exhibits in particular from that docket (H–057A):

Exhibit number—Author and paper title

8–447.—Lauwerys et. al., Guide for physicians, *Health Maintenance of Workers Exposed to Cadmium* published by the Cadmium Council.

4–67.—Takenaka, S., H. Oldiges, H. Konig, D. Hochrainer, G. Oberdorster. "Carcinogenicity of Cadmium Chloride Aerosols in Wister Rats". *JNCI* 70:367373, 1983. (32)

4–68.—Thun, M.J., T.M. Schnoor, A.B. Smith, W.E. Halperin, R.A. Lemen. "Mortality Among a Cohort of U.S. Cadmium Production Workers—An Update." *JNCI* 74(2):325–33, 1985. (8)

4–25.—Elinder, C.G., Kjellstrom, T., Hogstedt, C., *et al.*, "Cancer Mortality of Cadmium Workers." *Brit. J. Ind. Med.* 42:651–655, 1985. (14)

4–26.—Ellis, K.J. et al., "Critical Concentrations of Cadmium in Human Renal Cortex: Dose Effect Studies to Cadmium Smelter Workers." *J. Toxicol. Environ. Health* 7:691–703, 1981. (76)

4–27.—Ellis, K.J., S.H. Cohn and T.J. Smith. "Cadmium Inhalation Exposure Estimates: Their Significance with Respect to Kidney and Liver Cadmium Burden." *J. Toxicol. Environ. Health* 15:173–187, 1985.

4–28.—Falck, F.Y., Jr., Fine, L.J., Smith, R.G., McClatchey, K.D., Annesley, T., England, B., and Schork, A.M. "Occupational Cadmium Exposure and Renal Status." *Am J. Ind. Med.* 4:541, 1983. (64)

8–86A. Friberg, L., C.G. Elinder, et al., *Cadmium and Health a Toxicological and Epidemiological Appraisal Volume I Exposure, Dose, and Metabolism.* CRC Press, Inc., Boca Raton, FL, 1986. (Available from the OSHA Technical Data Center)

8–86B. Friberg, L., C.G. Elinder, et al. *Cadmium and Health: A Toxicological and Epidemiological Appraisal Volume II Effects and Response.* CRC Press, Inc., Boca Raton, FL, 1986. (Available from the OSHA Technical Data Center)

L–140–45. Elinder, C.G., "Cancer Morality of Cadmium Workers", *Brit. J. Ind. Med.*, 42, 651–655, 1985.

L–140–50. Thun, M., Elinder, C.G., Friberg, L. "Scientific Basis for an Occupational Standard for Cadmium. *Am. J. Ind. Med.*, 20: 629–642, 1991.

V. Information Sheet

The information sheet (Appendix A Attachment-3.) or an equally explanatory one should be provided to you after any biological monitoring results are reviewed by the physician, or where applicable, after any medical examination.

Appendix A—Attachment 1: Summary Chart and Tables A and B of Actions Triggered by Biological Monitoring

Appendix A Summary Chart: Section (1)(3) Medical Surveillance

Categorizing Biological Monitoring Results

(A) Biological monitoring results categories are set forth in Appendix A Table A for the periods ending December 31, 1998 and for the period beginning January 1, 1999.

(B) The results of the biological monitoring for the initial medical exam and the subsequent exams shall determine an employee's biological monitoring result category.

Actions Triggered by Biological Monitoring

(A)(i) The actions triggered by biological monitoring for an employee are set forth in Appendix A Table B.

(ii) The biological monitoring results for each employee under section (1)(3) shall determine the actions required for that employee. That is, for any employee in biological monitoring category C, the employer will perform all of the actions for which there is an X in column C of Appendix A Table B.

(iii) An employee is assigned the alphabetical category ("A" being the lowest) depending upon the test results of the three biological markers.

(iv) An employee is assigned category A if monitoring results for all three biological markers fall at or below the levels indicated in the table listed for category A.

(v) An employee is assigned category B if any monitoring result for any of the three biological markers fall within the range of levels indicated in the table listed for category B, providing no result exceeds the levels listed for category B.

(vi) An employee is assigned category C if any monitoring result for any of the three biological markers are above the levels listed for category C.

(B) The user of Appendix A Tables A and B should know that these tables are provided only to facilitate understanding of the relevant provisions of paragraph (l)(3) of this section. Appendix A Tables A and B are not meant to add to or subtract from the requirements of those provisions.

Appendix A—Table A

Categorization of Biological Monitoring Results

Biological marker	Monitoring result categories		
	A	B	C
Applicable through 1998 only:			
Cadmium in urine (CdU); (µg/g creatinine)	≤ 3	> 3 and ≤ 15	> 15
β_2-microglobulin (β_2-M); (µg/g creatinine)	≤ 300	> 300 and ≤ 1500	[1] > 1500
Cadmium in blood (CdB); (µg/liter whole blood)	≤ 5	> 5 and ≤ 15	> 15
Applicable beginning January 1, 1999:			
Cadmium in urine (CdU); (µg/g creatinine)	≤ 3	> 3 and ≤ 7	> 7
β_2-microglobulin (β_2-M); (µg/g creatinine)	≤ 300	> 300 and ≤ 750	[2] > 750
Cadmium in blood (CdB); (µg/liter whole blood)	≤ 5	> 5 and ≤ 10	> 10

[1] If an employee's β_2-M levels are above 1,500 µg/g creatinine, in order for mandatory medical removal to be required (See Appendix A Table B.), either the employee's CdU level must also be > 3 µg/g creatinine or CdB level must also be > 5 µg/liter whole blood.

[2] If an employee's β_2-M levels are above 750 µg/g creatinine, in order for mandatory medical removal to be required (See Appendix A Table B.), either the employee's CdU level must also be > 3 µg/g creatinine or CdB level must also be > 5 µg/liter whole blood.

Appendix A—Table B

Actions Determined by Biological Monitoring

This table presents the actions required based on the monitoring result in Appendix A Table A. Each item is a separate requirement in citing noncompliance. For example, a medical examination within 90 days for an employee in category B is separate from the requirement to administer a periodic medical examination for category B employees on an annual basis.

Required actions	Monitoring result category		
	A[1]	B[1]	C[1]
(1) Biological monitoring:			
(a) Annual	X		
(b) Semiannual		X	
(c) Quarterly			X
(2) Medical examination:			
(a) Biennial	X		
(b) Annual		X	
(c) Semiannual			X
(d) Within 90 days		X	X
(3) Assess within two weeks:			
(a) Excess cadmium exposure		X	X
(b) Work practices		X	X
(c) Personal hygiene		X	X
(d) Respirator usage		X	X
(e) Smoking history		X	X
(f) Hygiene facilities		X	X
(g) Engineering controls		X	X
(h) Correct within 30 days		X	X
(i) Periodically assess exposures			X
(4) Discretionary medical removal:		X	X
(5) Mandatory medical removal:			[2] X

[1] For all employees covered by medical surveillance exclusively because of exposures prior to the effective date of this standard, if they are in Category A, the employer shall follow the requirements of paragraphs (l)(3)(i)(B) and (l)(4)(v)(A). If they are in Category B or C, the employer shall follow the requirements of paragraphs (l)(4)(v)(B—C).

[2] See footnote Appendix A Table A.

Appendix A—Attachment 2: List of Medications

A list of the more common medications that a physician, and the employee, may wish to review is likely to include some of the following: (1) anticonvulsants: paramethadione, phenytoin, trimethadone; (2) antihypertensive drugs: captopril, methyldopa; (3) antimicrobials: aminoglycosides, amphotericin B, cephalosporins, ethambutol; (4) antineoplastic agents: cisplatin, methotrexate, mitomycin-C, nitrosoureas, radiation; (5) sulfonamide diuretics: acetazolamide, chlorthalidone, furosemide, thiazines; (6) halogenated alkanes, hydrocarbons, and solvents that may occur in some settings: carbon tetrachloride, ethylene glycol, toluene; iodinated radiographic contrast media; nonsteroidal anti-inflammatory drugs; and, (7) other miscellaneous compounds: acetominophen, allopurinol, amphetamines, azathioprine, cimetidine, cyclosporine, lithium, methoxyflurane, methysergide, D-penicillamine, phenacetin, phenendione. A list of drugs associated with acute interstitial nephritis includes: (1) antimicrobial drugs: cephalosporins, chloramphenicol, colistin, erythromycin, ethambutol, isoniazid, paraaminosalicylic acid, penicillins, polymyxin B, rifampin, sulfonamides, tetracyclines, and vancomycin; (2) other

miscellaneous drugs: allopurinol, antipyrene, azathioprine, captopril, cimetidine, clofibrate, methyldopa, phenindione, phenylpropanolamine, phenytoin, probenecid, sulfinpyrazone, sulfonamid diuretics, triamterene; and, (3) metals: bismuth, gold.

This list have been derived from commonly available medical textbooks (e.g., Ex. 14–18). The list has been included merely to facilitate the physician's, employer's, and employee's understanding. The list does not represent an official OSHA opinion or policy regarding the use of these medications for particular employees. The use of such medications should be under physician discretion.

Appendix A—Attachment 3

Biological Monitoring and Medical Examination Results

Employee _____
Testing Date _____

Cadmium in Urine _____μg/g Cr

Cadmium in Blood _____μg/lwb

Beta-2-microglobulin in Urine_____μg/g Cr

Normal Levels: ≤3 μg/g Cr, ≤5 μg/lwb, ≤300 μg/g Cr

Physical Examination Results: N/A_____Satisfactory _____ Unsatisfactory_____(see physician again)

Physician's Review of Pulmonary Function Test: N/A_____Normal _____Abnormal_____

Next biological monitoring or medical examination scheduled for _____

The biological monitoring program has been designed for three main purposes: (1) to identify employees at risk of adverse health effects from excess, chronic exposure to cadmium; (2) to prevent cadmium-induced disease(s); and (3) to detect and minimize existing cadmium-induced disease(s).

The levels of cadmium in the urine and blood provide an estimate of the total amount of cadmium in the body. The amount of a specific protein in the urine (beta-2-microglobulin) indicates changes in kidney function. All three tests must be evaluated together. A single mildly elevated result may not be important if testing at a later time indicates that the results are normal and the workplace has been evaluated to decrease possible sources of cadmium exposure. The levels of cadmium or beta-2-microglobulin may change over a period of days to months and the time needed for those changes to occur is different for each worker.

If the results for biological monitoring are above specific "high levels" [cadmium urine greater than 10 micrograms per gram of creatinine (μg/g Cr), cadmium blood greater than 10 micrograms per liter of whole blood (μg/lwb), or beta-2-microglobulin greater than 1000 micrograms per gram of creatinine (μg/g Cr)], the worker has a much greater chance of developing other kidney diseases.

One way to measure for kidney function is by measuring beta-2-microglobulin in the urine. Beta-2-microglobulin is a protein which is normally found in the blood as it is being filtered in the kidney, and the kidney reabsorbs or returns almost all of the beta-2-microglobulin to the blood. A very small amount (less than 300 μg/g Cr in the urine) of beta-2-microglobulin is not reabsorbed into the blood, but is released in the urine. If cadmium damages the kidney, the amount of beta-2-microglobulin in the urine increases because the kidney cells are unable to reabsorb the beta-2-microglobulin normally. An increase in the amount of beta-2-microglobulin in the urine is a very early sign of kidney dysfunction. A small increase in beta-2-microglobulin in the urine will serve as an early warning sign that the worker may be absorbing cadmium from the air, cigarettes contaminated in the workplace, or eating in areas that are cadmium contaminated.

Even if cadmium causes permanent changes in the kidney's ability to reabsorb beta-2-microglobulin, and the beta-2-microglobulin is above the "high levels", the loss of kidney function may not lead to any serious health problems. Also, renal function naturally declines as people age. The risk for changes in kidney function for workers who have biological monitoring results between the "normal values" and the "high levels" is not well known. Some people are more cadmium-tolerant, while others are more cadmium-susceptible.

For anyone with even a slight increase of beta-2-microglobulin, cadmium in the urine, or cadmium in the blood, it is very important to protect the kidney from further damage. Kidney damage can come from other sources than excess cadmium-exposure so it is also recommended that if a worker's levels are "high" he/she should receive counseling about drinking more water; avoiding cadmium-tainted tobacco and certain medications (nephrotoxins, acetaminophen); controlling diet, vitamin intake, blood pressure and diabetes; etc.

Appendix B—Substance Technical Guidelines for Cadmium

I. Cadmium Metal

A. Physical and Chemical Data

1. *Substance Identification*
Chemical name: Cadmium.
Formula: Cd.
Molecular Weight: 112.4.
Chemical Abstracts Service (CAS) Registry No.: 7440–43–9.
Other identifiers: RETCS EU9800000; EPA D006; DOT 2570 53.
Synonyms: Colloidal Cadmium; Kadmium (German); CI 77180.

2. *Physical data*
Boiling point: (760 mm Hg): 765 degrees C.
Melting point: 321 degrees C.
Specific Gravity: (H_2O=@ 20°C): 8.64.
Solubility: Insoluble in water; soluble in dilute nitric acid and in sulfuric acid.
Appearance: soft, blue-white, malleable, lustrous metal or grayish-white powder.

B. Fire, Explosion and Reactivity Data

1. *Fire*
Fire and Explosion Hazards: The finely divided metal is pyrophoric, that is the dust is a severe fire hazard and moderate explosion hazard when exposed to heat or flame. Burning material reacts violently with extinguishing agents such as water, foam, carbon dioxide, and halons.
Flash point: flamable (dust).
Extinguishing means: Dry sand, dry dolomite, dry graphite, or sodium chloride.

2. *Reactivity*
Conditions contributing to instability: Stable when kept in sealed containers under normal temperatures and pressure, but dust may ignite upon contact with air. Metal tarnishes in moist air.
Incompatibilities: Ammonium nitrate, fused: reacts violently or explosively with cadmium dust below 20°C. Hydrozoic acid: violent explosion occurs after 30 minutes. Acids: reacts violently, forms hydrogen gas. Oxidizing agents or metals: strong reaction with cadmium dust. Nitryl fluoride at slightly elevated temperature: glowing or white incandescence occurs. Selenium: reacts exothermically. Ammonia: corrosive reaction. Sulfur dioxide: corrosive reaction. Fire extinguishing agents (water, foam, carbon dioxide, and halons): reacts violently. Tellurium: incandescent reaction in hydrogen atmosphere.
Hazardous decomposition products: The heated metal rapidly forms highly toxic, brownish fumes of oxides of cadmium.

C. Spill, Leak and Disposal Procedures

1. ***Steps to be taken if the materials is released or spilled***
Do not touch spilled material. Stop leak if you can do it without risk. Do not get water inside container. For large spills, dike spill for later disposal. Keep unnecessary people away. Isolate hazard area and deny entry. The Superfund Amendments and Reauthorization Act of 1986 Section 304 requires that a release equal to or greater than the reportable quantity for this substance (1 pound) must be immediately reported to the local emergency planning committee, the state emergency response commission, and the National Response Center (800) 424–8802; in Washington, D.C. metropolitan area (202) 426–2675.

II. Cadmium Oxide

A. Physical and Chemical Data

1. *Substance identification*
Chemical name: Cadmium Oxide.
Formula: CdO.
Molecular Weight: 128.4.
CAS No.: 1306–19–0.
Other identifiers: RTECS EV1929500.
Synonyms: Kadmu tlenek (Polish).

2. *Physical data*
Boiling point (760 mm Hg): 950 degrees C decomposes.
Melting point: 1500°C.
Specific Gravity: (H_2O = 1 @ 20°oC): 7.0.
Solubility: Insoluble in water; soluble in acids and alkalines.
Appearance: Red or brown crystals.

B. Fire, Explosion and Reactivity Data

1. *Fire*
Fire and Explosion Hazards: Negligible fire hazard when exposed to heat or flame.
Flash point: Nonflammable.
Extinguishing means: Dry chemical, carbon dioxide, water spray or foam.

2. *Reactivity*
Conditions contributing to instability: Stable under normal temperatures and pressures.
Incompatibilities: Magnesium may reduce CdO_2 explosively on heating.

Hazardous decomposition products: Toxic fumes of cadmium.

C. Spill Leak and Disposal Procedures

1. *Steps to be taken if the material is released or spilled*

Do not touch spilled material. Stop leak if you can do it without risk. For small spills, take up with sand or other absorbent material and place into containers for later disposal. For small dry spills, use a clean shovel to place material into clean, dry container and then cover. Move containers from spill area. For larger spills, dike far ahead of spill for later disposal. Keep unnecessary people away. Isolate hazard area and deny entry. The Superfund Amendments and Reauthorization Act of 1986 Section 304 requires that a release equal to or greater than the reportable quantity for this substance (1 pound) must be immediately reported to the local emergency planning committee, the state emergency response commission, and the National Response Center (800) 424–8802; in Washington, D.C. metropolitan area (202) 426–2675.

III. Cadmium Sulfide

A. Physical and Chemical Data

1. *Substance Identification*

Chemical name: Cadmium sulfide.
Formula: CdS.
Molecular weight: 144.5.
CAS No. 1306–23–6.
Other Identifiers: RTECS EV2159000.
Synonyms: Aurora yellow; Cadmium Golden 366; Cadmium Lemon Yellow 527; Cadmium Orange; Cadmium Primrose 819; Cadmium Sulphide; Cadmium Yellow; Cadmium Yellow 000; Cadmium Yellow Conc. Deep; Cadmium Yellow Conc. Golden; Cadmium Yellow Conc. Lemon; Cadmium Yellow Conc. Primrose; Cadmium Yellow Co. Dark; Cadmium Yellow Primrose 47–1400; Cadmium Yellow 10C Conc.; Cadmium Yellow 892; Cadmopur Golden Yellow N; Cadmopur Yellow; Capsebom; C.I. 77199; C.I. Pigment Orange 20; CI Pigment Yellow 37; Ferro Lemon Yellow; Ferro Orange Yellow; Ferro Yellow; Greenockite; NCI–C02711.

2. *Physical data*

Boiling point (760 mm. Hg): sublines in N_2 at 980°C.
Melting point: 1750 degrees C (100 atm).
Specific Gravity: (H_2O= 1@ 20°C): 4.82.
Solubility: Slightly soluble in water; soluble in acid.
Appearance: Light yellow or yellow-orange crystals.

B. Fire, Explosion and Reactivity Data

1. *Fire*

Fire and Explosion Hazards: Neglisible fire hazard when exposed to heat or flame.
Flash point: Nonflamable.
Extinguishing media: Dry chemical, carbon dioxide, water spray or foam.

2. *Reactivity*

Conditions contributing to instability: Generally non-reactive under normal conditions. Reacts with acids to form toxic hydrogen sulfide gas.
Incompatibilities: Reacts vigorously with iodinemonochloride.
Hazardous decomposition products: Toxic fumes of cadmium and sulfur oxides.

C. Spill Leak and Disposal Procedures

1. *Steps to be taken if the material is released or spilled.*

Do not touch spilled material. Stop leak if you can do it without risk. For small, dry spills, with a clean shovel place material into clean, dry container and cover. Move containers from spill area. For larger spills, dike far ahead of spill for later disposal. Keep unnecessary people away. Isolate hazard and deny entry.

IV. Cadmium Chloride

A. Physical and Chemical Data

1. *Substance Identification*

Chemical name: Cadmium chloride.
Formula: $CdCl_2$.
Molecular weight: 183.3.
CAS No. 10108–64–2.
Other Indentifiers: RTECS EY0175000.
Synonyms: Caddy; Cadmium dichloride; NA 2570 (DOT); UI-CAD; dichlorocadmium.

2. *Physical data*

Boiling point (760 mm Hg): 960 degrees C.
Melting point: 568 degrees C.
Specific Gravity: (H_2O = 1 @ 20 °C): 4.05.
Solubility: Soluble in water (140 g/100 cc); soluble in acetone.
Appearance: small, white crystals.

B. Fire, Explosion and Reactivity Data

1. *Fire*

Fire and Explosion Hazards: Negligible fire and negligible explosion hazard in dust form when exposed to heat or flame.
Flash point: Nonflamable.
Extinguishing media: Dry chemical, carbon dioxide, water spray or foam.

2. *Reactivity*

Conditions contributing to instability: Generally stable under normal temperatures and pressures.
Incompatibilities: Bromine trifluoride rapidly attacks cadmium chloride. A mixture of potassium and cadmium chloride may produce a strong explosion on impact.
Hazardous decomposition products: Thermal decomposition may release toxic fumes of hydrogen chloride, chloride, chlorine or oxides of cadmium.

C. Spill Leak and Disposal Procedures

1. *Steps to be taken if the material is released or spiled.*

Do not touch spilled material. Stop leak if you can do it without risk. For small, dry spills, with a clean shovel place material into clean, dry container and cover. Move containers from spill area. For larger spills, dike far ahead of spill for later disposal. Keep unnecessary people away. Isolate hazard and deny entry. The Superfund Amendments and Reauthorization Act of 1986 Section 304 requires that a release equal to or greater than the reportable quantity for this substance (100 pounds) must be immediately reported to the local emergency planning committee, the state emergency response commission, and the National Response Center (800) 424–8802; in Washington, D.C. Metropolitan area (202) 426–2675.

Appendix C—Qualitative and Quantitative Fit Testing Procedures

I. Fit Test Protocols

A. General

The employer shall include the following provisions in the fit test procedures. These provisions apply to both qualitative fit testing (QLFT) and quantitative fit testing (QNFT). All testing is to be conducted annually.

1. The test subject shall be allowed to pick the most comfortable respirator from a selection including respirators of various sizes from different manufacturers. The selection shall include at least three sizes of elastomeric facepieces of the type of respirator that is to be tested, i.e., three sizes of half mask or three sizes of full facepiece. Respirators of each size must be provided from at least two manufacturers.

2. Prior to the selection process, the test subject shall be shown how to put on a respirator, how it should be positioned on the face, how to set strap tension and how to determine a comfortable fit. A mirror shall be available to assist the subject in evaluating the fit and positioning the respirator. This instruction may not constitute the subject's formal training on respirator use; it is only a review.

3. The test subject shall be informed that he/she is being asked to select the respirator which provides the most comfortable fit. Each respirator represents a different size and shape, and if fitted, maintained and used properly, will provide substantial protection.

4. The test subject shall be instructed to hold each facepiece up to the face and eliminate those which obviously do not give a comfortable fit.

5. The more comfortable facepieces are noted; the most comfortable mask is donned and worn at least five minutes to assess comfort. Assistance in assessing comfort can be given by discussing the points in item 6 below. If the test subject is not familiar with using a particular respirator, the test subject shall be directed to don the mask several times and to adjust the straps each time to become adept at setting proper tension on the straps.

6. Assessment of comfort shall include reviewing the following points with the test subject and allowing the test subject adequate time to determine the comfort of the respirator:

(a) Position of the mask on the nose;
(b) Room for eye protection;
(c) Room to talk; and
(d) Position of mask on face and cheeks.

7. The following criteria shall be used to help determine the adequacy of the respirator fit:

(a) Chin properly placed;
(b) Adequate strap tension, not overly tightened;
(c) Fit across nose bridge;
(d) Respirator of proper size to span distance from nose to chin;
(e) Tendency of respirator to slip; and
(f) Self-observation in mirror to evaluate fit and respirator position.

8. The test subject shall conduct the negative and positive pressure fit checks as described below or in ANSI Z88.2–1980. Before conducting the negative or positive pressure test, the subject shall be told to seat the mask on the face by moving the head from side-to-side and up and down slowly

while taking in a few slow deep breaths. Another facepiece shall be selected and retested if the test subject fails the fit check tests.

(a). *Positive pressure test.* Close off the exhalation valve and exhale gently onto the facepiece. The face fit is considered satisfactory if a slight positive pressure can be built up inside the facepiece without any evidence of outward leakage of air at the seal. For most respirators this method of leak testing requires the wearer to first remove the exhalation valve cover before closing off the exhalation valve and then carefully replacing it after the test.

(b). *Negative pressure test.* Close off the inlet opening of the canister or cartridge(s) by covering with the palm of the hand(s) or by replacing the filter seal(s). Inhale gently so that the facepiece collapses slightly, and hold the breath for ten seconds. If the facepiece remains in its slightly collapsed condition and no inward leakage of air is detected, the tightness of the respirator is considered satisfactory.

9. The test shall not be conducted if there is any hair growth between the skin and the facepiece sealing surface, such as stubble beard growth, beard, or long sideburns which cross the respirator sealing surface. Any type of apparel which interferes with a satisfactory fit shall be altered or removed.

10. If a test subject exhibits difficulty in breathing during the tests, she or he shall be referred to a physician trained in respiratory disease or pulmonary medicine to determine, in accordance with paragraph (1), (2) and (3) of this standard, whether the test subject can wear a respirator while performing her or his duties.

11. The test subject shall be given the opportunity to wear the successfully fitted respirator for a period of two weeks. If at any time during this period the respirator becomes uncomfortable, the test subject shall be given the opportunity to select a different facepiece and to be retested.

12. The employer shall maintain a record of the fit test administered to an employee. The record shall contain at least the following information:

(a) Name of employee;

(b) Type of respirator;

(c) Brand, size of respirator;

(d) Date of test; and

(e) Where QNFT is used, the fit factor and strip chart recording or other recording of the results of the test. The record shall be maintained until the next fit test is administered.

13. Exercise regimen. Prior to the commencement of the fit test, the test subject shall be given a description of the fit test and the test subject's responsibilities during the test procedure. The description of the process shall include a description of the test exercises that the subject will be performing. The respirator to be tested shall be worn for at least 5 minutes before the start of the fit test.

14. Test Exercises. The test subject shall perform exercises, in the test environment, in the manner described below:

(a) Normal breathing. In a normal standing position, without talking, the subject shall breathe normally.

(b) Deep breathing. In a normal standing position, without talking, the subject shall breathe slowly and deeply, taking care so as to not hyperventilate.

(c) Turning head side to side. Standing in place, the subject shall slowly turn his/her head from side to side between the extreme positions on each side. The head shall be held at each extreme momentarily so the subject can inhale at each side.

(d) Moving head up and down. Standing in place, the subject shall slowly move his/her head up and down. The subject shall be instructed to inhale in the up position (i.e., when looking toward the ceiling).

(e) Talking. The subject shall talk out loud slowly and loud enough so as to be heard clearly by the test conductor. The subject can read from a prepared text such as the Rainbow Passage, count backward from 100, or recite a memorized poem or song.

(f) Grimace. The test subject shall grimace by smiling or frowning.

(g) Bending over. The test subject shall bend at the waist as if he/she were to touch his/her toes. Jogging in place shall be substituted for this exercise in those test environments such as shroud type QNFT units which prohibit bending at the waist.

(h) Normal breathing. Same as exercise 1.

Each test exercise shall be performed for one minute except for the grimace exercise which shall be performed for 15 seconds. The test subject shall be questioned by the test conductor regarding the comfort of the respirator upon completion of the protocol. If it has become uncomfortable, another model of respirator shall be tried.

B. Qualitative Fit Test (QLFT) Protocols

1. General

(a) The employer shall assign specific individuals who shall assume full responsibility for implementing the respirator qualitative fit test program.

(b) The employer shall assure that persons administering QLFTs are able to prepare test solutions, calibrate equipment and perform tests properly, recognize invalid tests, and assure that test equipment is in proper working order.

(c) The employer shall assure that QLFT equipment is kept clean and well maintained so as to operate within the parameters for which it was designed.

2. Isoamyl Acetate Protocol

(a) Odor threshold screening. The odor threshold screening test, performed without wearing a respirator, is intended to determine if the individual tested can detect the odor of isoamyl acetate.

(1) Three 1-liter glass jars with metal lids are required.

(2) Odor free water (e.g. distilled or spring water) at approximately 25 degrees C shall be used for the solutions.

(3) The isoamyl acetate (IAA) (also known as isopentyl acetate) stock solution is prepared by adding 1 cc of pure IAA to 800 cc of odor free water in a 1 liter jar and shaking for 30 seconds. A new solution shall be prepared at least weekly.

(4) The screening test shall be conducted in a room separate from the room used for actual fit testing. The two rooms shall be well ventilated and shall not be connected to the same recirculating ventilation system.

(5) The odor test solution is prepared in a second jar by placing 0.4 cc of the stock solution into 500 cc of odor free water using a clean dropper or pipette. The solution shall be shaken for 30 seconds and allowed to stand for two to three minutes so that the IAA concentration above the liquid may reach equilibrium. This solution shall be used for only one day.

(6) A test blank shall be prepared in a third jar by adding 500 cc of odor free water.

(7) The odor test and test blank jars shall be labeled 1 and 2 for jar identification. Labels shall be placed on the lids so they can be periodically peeled, dried off and switched to maintain the integrity of the test.

(8) The following instruction shall be typed on a card and placed on the table in front of the two test jars (i.e., 1 and 2): "The purpose of this test is to determine if you can smell banana oil at a low concentration. The two bottles in front of you contain water. One of these bottles also contains a small amount of banana oil. Be sure the covers are on tight, then shake each bottle for two seconds. Unscrew the lid of each bottle, one at a time, and sniff at the mouth of the bottle. Indicate to the test conductor which bottle contains banana oil."

(9) The mixtures used in the IAA odor detection test shall be prepared in an area separate from where the test is performed, in order to prevent olfactory fatigue in the subject.

(10) If the test subject is unable to correctly identify the jar containing the odor test solution, the IAA qualitative fit test shall not be performed.

(11) If the test subject correctly identifies the jar containing the odor test solution, the test subject may proceed to respirator selection and fit testing.

(b) Isoamyl acetate fit test

(1) The fit test chamber shall be similar to a clear 55-gallon drum liner suspended inverted over a 2-foot diameter frame so that the top of the chamber is about 6 inches above the test subject's head. The inside top center of the chamber shall have a small hook attached.

(2) Each respirator used for the fitting and fit testing shall be equipped with organic vapor cartridges or offer protection against organic vapors. The cartridges or masks shall be changed at least weekly.

(3) After selecting, donning, and properly adjusting a respirator, the test subject shall wear it to the fit testing room. This room shall be separate from the room used for odor threshold screening and respirator selection, and shall be well ventilated, as by an exhaust fan or lab hood, to prevent general room contamination.

(4) A copy of the test exercises and any prepared text from which the subject is to read shall be taped to the inside of the test chamber.

(5) Upon entering the test chamber, the test subject shall be given a 6-inch by 5-inch piece of paper towel, or other porous, absorbent, single-ply material, folded in half and wetted with 0.75 cc of pure IAA. The test subject shall hang the wet towel on the hook at the top of the chamber.

(6) Allow two minutes for the IAA test concentration to stabilize before starting the fit test exercises. This would be an appropriate time to talk with the test subject: to explain the fit test, the importance of his/her cooperation, and the purpose for the head exercises; and to demonstrate some of the exercises.

(7) If at any time during the test, the subject detects the banana like odor of IAA, the respirator fit is inadequate. The subject shall quickly exit from the test chamber and leave the test area to avoid olfactory fatigue.

(8) If the respirator fit was inadequate, the subject shall return to the selection room and remove the respirator, repeat the odor sensitivity test, select and put on another respirator, return to the test chamber and again begin the procedure described in paragraph (I)(B)(2)(b) (1) through (7) of this appendix. The process continues until a respirator that fits well has been found. Should the odor sensitivity test be failed, the subject shall wait about 5 minutes before retesting. Odor sensitivity will usually have returned by this time.

(9) When a respirator is found that passes the test, its efficiency shall be demonstrated for the subject by having the subject break the face seal and take a breath before exiting the chamber.

(10) When the test subject leaves the chamber, the subject shall remove the saturated towel and return it to the person conducting the test. To keep the test area from becoming contaminated, the used towels shall be kept in a self sealing bag so there is no significant IAA concentration build-up in the test chamber during subsequent tests.

3. Irritant Fume Protocol

(a) The respirator to be tested shall be equipped with high-efficiency particulate air (HEPA) filters.

(b) The test subject shall be allowed to smell a weak concentration of the irritant smoke before the respirator is donned to become familiar with its characteristic odor.

(c) Break both ends of a ventilation smoke tube containing stannic oxychloride, such as the MSA part No. 5645, or equivalent. Attach one end of the smoke tube to a low flow air pump set to deliver 200 milliliters per minute.

(d) Advise the test subject that the smoke can be irritating to the eyes and instruct the subject to keep his/her eyes closed while the test is performed.

(e) The test conductor shall direct the stream of irritant smoke from the smoke tube towards the face seal area of the test subject. He/She shall begin at least 12 inches from the facepiece and gradually move to within one inch, moving around the whole perimeter of the mask.

(f) The exercises identified in section I. A. 14 above shall be performed by the test subject while the respirator seal is being challenged by the smoke.

(g) Each test subject passing the smoke test without evidence of a response shall be given a sensitivity check of the smoke from the same tube once the respirator has been removed to determine whether he/she reacts to the smoke. Failure to evoke a response shall void the fit test.

(h) The fit test shall be performed in a location with exhaust ventilation sufficient to prevent general contamination of the testing area by the test agent.

4. Saccharin Solution Aerosol Protocol

The entire screening and testing procedure shall be explained to the test subject prior to the conduct of the screening test.

(a) Taste threshold screening. The saccharin taste threshold screening, performed without wearing a respirator, is intended to determine whether the individual being tested can detect the taste of saccharin.

(1) Threshold screening as well as fit testing subjects shall wear an enclosure about the head and shoulders that is approximately 12 inches in diameter by 14 inches tall with at least the front portion clear and that allows free movements of the head when a respirator is worn. An enclosure substantially similar to the 3M hood assembly, parts # FT 14 and # FT 15 combined, is adequate.

(2) The test enclosure shall have a ¾ inch hole in front of the test subject's nose and mouth area to accommodate the nebulizer nozzle.

(3) The test subject shall don the test enclosure. Throughout the threshold screening test, the test subject shall breathe through his/her wide open mouth with tongue extended.

(4) Using a DeVilbiss Model 40 Inhalation Medication Nebulizer the test conductor shall spray the threshold check solution into the enclosure. This nebulizer shall be clearly marked to distinguish it from the fit test solution nebulizer.

(5) The threshold check solution consists of 0.83 grams of sodium saccharin USP in 1 cc of warm water. It can be prepared by putting 1 cc of the fit test solution (see (b)(5) below) in 100 cc of distilled water.

(6) To produce the aerosol, the nebulizer bulb is firmly squeezed so that it collapses completely, then released and allowed to fully expand.

(7) Ten squeezes are repeated rapidly and then the test subject is asked whether the saccharin can be tasted.

(8) If the first response is negative, ten more squeezes are repeated rapidly and the test subject is again asked whether the saccharin is tasted.

(9) If the second response is negative, ten more squeezes are repeated rapidly and the test subject is again asked whether the saccharin is tasted.

(10) The test conductor will take note of the number of squeezes required to solicit a taste response.

(11) If the saccharin is not tasted after 30 squeezes (step 10), the test subject may not perform the saccharin fit test.

(12) If a taste response is elicited, the test subject shall be asked to take note of the taste for reference in the fit test.

(13) Correct use of the nebulizer means that approximately 1 cc of liquid is used at a time in the nebulizer body.

(14) The nebulizer shall be thoroughly rinsed in water, shaken dry, and refilled at least each morning and afternoon or at least every four hours.

(b) Saccharin solution aerosol fit test procedure

(1) The test subject may not eat, drink (except plain water), or chew gum for 15 minutes before the test.

(2) The fit test uses the same enclosure described in (a) above.

(3) The test subject shall don the enclosure while wearing the respirator selected in section (a) above. The respirator shall be properly adjusted and equipped with a particulate filter(s).

(4) A second DeVilbiss Model 40 Inhalation Medication Nebulizer is used to spray the fit test solution into the enclosure. This nebulizer shall be clearly marked to distinguish it from the screening test solution nebulizer.

(5) The fit test solution is prepared by adding 83 grams of sodium saccharin to 100 cc of warm water.

(6) As before, the test subject shall breathe through the open mouth with tongue extended.

(7) The nebulizer is inserted into the hole in the front of the enclosure and the fit test solution is sprayed into the enclosure using the same number of squeezes required to elicit a taste response in the screening test.

(8) After generating the aerosol the test subject shall be instructed to perform the exercises in section I.A. 14 above.

• (9) Every 30 seconds the aerosol concentration shall be replenished using one half the number of squeezes as initially.

(10) The test subject shall indicate to the test conductor if at any time during the fit test the taste of saccharin is detected.

(11) If the taste of saccharin is detected, the fit is deemed unsatisfactory and a different respirator shall be tried".

C. Quantitative Fit Test (QNFT) Protocol

1. General

(a) The employer shall assign specific individuals who shall assume full responsibility for implementing the respirator quantitative fit test program.

(b) The employer shall ensure that persons administering QNFT are able to calibrate equipment and perform tests properly, recognize invalid tests, calculate fit factors properly and assure that test equipment is in proper working order.

(c) The employer shall assure that QNFT equipment is kept clean and well maintained so as to operate at the parameters for which it was designed.

2. Definitions

(a) Quantitative fit test. The test is performed in a test chamber. The normal air-purifying element of the respirator is replaced by a high-efficiency particulate air (HEPA) filter in the case of particulate QNFT aerosols or a sorbent offering contaminant penetration protection equivalent to high-efficiency filters where the QNFT test agent is a gas or vapor.

(b) Challenge agent means the aerosol, gas or vapor introduced into a test chamber so that its concentration inside and outside the respirator may be measured.

(c) Test subject means the person wearing the respirator for quantitative fit testing.

(d) Normal standing position means standing erect and straight with arms down along the sides and looking straight ahead.

(e) Maximum peak penetration method means the method of determining test agent penetration in the respirator as determined by strip chart recordings of the test. The highest peak penetration for a given exercise is taken to be representative of average penetration into the respirator for that exercise.

(f) Average peak penetration method means the method of determining test agent penetration into the respirator utilizing a strip chart recorder, integrator, or computer. The agent penetration is determined by an average of the peak heights on the graph or by computer integration, for each exercise except the grimace exercise. Integrators or computers which calculate the actual test agent penetration into the respirator for each exercise will also be considered to meet the requirements of the average peak penetration method.

(g) "Fit Factor" means the ratio of challenge agent concentration outside with respect to the inside of a respirator mist covering (facepiece or enclosure).

3. Apparatus

(a) Instrumentation. Aerosol generation, dilution, and measurement systems using corn oil or sodium chloride as test aerosols shall be used for quantitative fit testing.

(b) Test chamber. The test chamber shall be large enough to permit all test subjects to perform freely all required exercises without disturbing the challenge agent concentration or the measurement apparatus. The test chamber shall be equipped and constructed so that the challenge agent is effectively isolated from the ambient air, yet uniform in concentration throughout the chamber.

(c) When testing air-purifying respirators, the normal filter or cartridge element shall be replaced with a high-efficiency particulate filter supplied by the same manufacturer.

(d) The sampling instrument shall be selected so that a strip chart record may be made of the test showing the rise and fall of the challenge agent concentration with each inspiration and expiration at fit factors of at least 2,000. Integrators or computers which integrate the amount of test agent penetration leakage into the respirator for each exercise may be used provided a record of the readings is made.

(e) The combination of substitute air-purifying elements, challenge agent and challenge agent concentration in the test chamber shall be such that the test subject is not exposed in excess of an established exposure limit for the challenge agent at any time during the testing process.

(f) The sampling port on the test specimen respirator shall be placed and constructed so that no leakage occurs around the port (e.g. where the respirator is probed), a free air flow is allowed into the sampling line at all times and so that there is no interference with the fit or performance of the respirator.

(g) The test chamber and test set up shall permit the person administering the test to observe the test subject inside the chamber during the test.

(h) The equipment generating the challenge atmosphere shall maintain the concentration of challenge agent inside the test chamber constant to within a 10 percent variation for the duration of the test.

(i) The time lag (interval between an event and the recording of the event on the strip chart or computer or integrator) shall be kept to a minimum. There shall be a clear association between the occurrence of an event inside the test chamber and its being recorded.

(j) The sampling line tubing for the test chamber atmosphere and for the respirator sampling port shall be of equal diameter and of the same material. The length of the two lines shall be equal.

(k) The exhaust flow from the test chamber shall pass through a high-efficiency filter before release.

(l) When sodium chloride aerosol is used, the relative humidity inside the test chamber shall not exceed 50 percent.

(m) The limitations of instrument detection shall be taken into account when determining the fit factor.

(n) Test respirators shall be maintained in proper working order and inspected for deficiencies such as cracks, missing valves and gaskets, etc.

4. Procedural Requirements

(a) When performing the initial positive or negative pressure test the sampling line shall be crimped closed in order to avoid air pressure leakage during either of these tests.

(b) An abbreviated screening isoamyl acetate test or irritant fume test may be utilized in order to quickly identify poor fitting respirators which passed the positive and/or negative pressure test and thus reduce the amount of QNFT time. When performing a screening isoamyl acetate test, combination high-efficiency organic vapor cartridges/canisters shall be used.

(c) A reasonably stable challenge agent concentration shall be measured in the test chamber prior to testing. For canopy or shower curtain type of test units the determination of the challenge agent stability may be established after the test subject has entered the test environment.

(d) Immediately after the subject enters the test chamber, the challenge agent concentration inside the respirator shall be measured to ensure that the peak penetration does not exceed 5 percent for a half mask or 1 percent for a full facepiece respirator.

(e) A stable challenge concentration shall be obtained prior to the actual start of testing.

(f) Respirator restraining straps shall not be overtightened for testing. The straps shall be adjusted by the wearer without assistance from other persons to give a reasonable comfortable fit typical of normal use.

(g) The test shall be terminated whenever any single peak penetration exceeds 5 percent for half masks and 1 percent for full facepiece respirators. The test subject shall be refitted and retested. If two of the three required tests are terminated, the fit shall be deemed inadequate.

(h) In order to successfully complete a QNFT, three successful fit tests are required. The results of each of the three independent fit tests must exceed the minimum fit factor needed for the class of respirator (e.g. half mask respirator, full facepiece respirator).

(i) Calculation of fit factors.

(1) The fit factor shall be determined for the quantitative fit test by taking the ratio of the average chamber concentration to the concentration inside the respirator.

(2) The average test chamber concentration is the arithmetic average of the test chamber concentration at the beginning and of the end of the test.

(3) The concentration of the challenge agent inside the respirator shall be determined by one of the following methods:

(i) Average peak concentration.

(ii) Maximum peak concentration.

(iii) Integration by calculation of the area under the individual peak for each exercise. This includes computerized integration.

(j) Interpretation of test results. The fit factor established by the quantitative fit testing shall be the lowest of the three fit factor values calculated from the three required fit tests.

(k) The test subject shall not be permitted to wear a half mask, or full facepiece respirator unless a minimum fit factor equivalent to at least 10 times the hazardous exposure level is obtained.

(l) Filters used for quantitative fit testing shall be replaced at least weekly, or whenever increased breathing resistance is encountered, or when the test agent has altered the integrity of the filter media. Organic vapor cartridges/canisters shall be replaced daily (when used) or sooner if there is any indication of breakthrough by a test agent.

Appendix D—Occupational Health History Interview With Reference to Cadmium Exposure

Directions

(To be read by employee and signed prior to the interview)

Please answer the questions you will be asked as completely and carefully as you can. These questions are asked of everyone who works with cadmium. You will also be asked to give blood and urine samples. The doctor will give your employer a written opinion on whether you are physically capable of working with cadmium. Legally, the doctor cannot share personal information you may tell him/her with your employer. The following information is considered strictly confidential. The results of the tests will go to you, your doctor and your employer. You will also receive an information sheet explaining the results of any biological monitoring or physical examinations performed.

If you are just being hired, the results of this interview and examination will be used to:

(1) Establish your health status and see if working with cadmium might be expected to cause unusual problems.

(2) Determine your health status today and see if there are changes over time.

(3) See if you can wear a respirator safely.

If you are not a new hire:

OSHA says that everyone who works with cadmium can have periodic medical examinations performed by a doctor. The reasons for this are:

(a) If there are changes in your health, either because of cadmium or some other reason, to find them early.

(b) To prevent kidney damage.

Please sign below.

I have read these directions and understand them:

Employee signature

Date

Thank you for answering these questions. (Suggested Format)

Name

Age

Social Security #

Company

Job

Type of Preplacement Exam:
[ ] Periodic
[ ] Termination
[ ] Initial
[ ] Other

Blood Pressure

Pulse Rate

1. How long have you worked at the job listed above?
[ ] not yet hired
[ ] number of months
[ ] number of years

2. Job Duties Etc.

3. Have you ever been told by a doctor that you had bronchitis?
[ ] yes
[ ] no

If yes, how long ago?
[ ] number of months
[ ] number of years

4. Have you ever been told by a doctor that you had emphysema?
[ ] yes
[ ] no

If yes, how long ago?
[ ] number of years
[ ] number of months

5. Have you ever been told by a doctor that you had other lung problems?
[ ] yes
[ ] no

If yes, please describe type of lung problems and when you had these problems.

6. In the past year, have you had a cough?
[ ] yes
[ ] no

If yes, did you cough up sputum?
[ ] yes
[ ] no

If yes, how long did the cough with sputum production last?
[ ] less than 3 months
[ ] 3 months or longer

If yes, for how many years have you had episodes of cough with sputum production lasting this long?
[ ] less than one
[ ] 1
[ ] 2
[ ] longer than 2

7. Have you ever smoked cigarettes?
[ ] yes
[ ] no

8. Do you now smoke cigarettes?
[ ] yes
[ ] no

9. If you smoke or have smoked cigarettes, for how many years have you smoked, or did you smoke?
[ ] less than 1 year
[ ] number of years

What is or was the greatest number of packs per day that you have smoked?
[ ] number of packs

If you quit smoking cigarettes, how many years ago did you quit?
[ ] less than 1 year
[ ] number of years

How many packs a day do you now smoke?
[ ] number of packs per day

10. Have you ever been told by a doctor that you had a kidney or urinary tract disease or disorder?
[ ] yes
[ ] no

11. Have you ever had any of these disorders?

Kidney stones
[ ] yes [ ] no

Protein in urine
[ ] yes [ ] no

Blood in urine
[ ] yes [ ] no

Difficulty urinating
[ ] yes [ ] no

Other kidney/Urinary disorders
[ ] yes [ ] no

Please describe problems, age, treatment, and follow up for any kidney or urinary problems you have had:

12. Have you ever been told by a doctor or other health care provider who took your blood pressure that your blood pressure was high?
[ ] yes
[ ] no

13. Have you ever been advised to take any blood pressure medication?
[ ] yes
[ ] no

14. Are you presently taking any blood pressure medication?
[ ] yes
[ ] no

15. Are you presently taking any other medication?
[ ] yes
[ ] no

16. Please list any blood pressure or other medications and describe how long you have been taking each one:

Medicine	How long taken

Medicine	How long taken

17. Have you ever been told by a doctor that you have diabetes? (sugar in your blood or urine)
[ ] yes
[ ] no

If yes, do you presently see a doctor about your diabetes?
[ ] yes
[ ] no

If yes, how do you control your blood sugar?
[ ] diet alone
[ ] diet plus oral medicine
[ ] diet plus insulin (injection)

18. Have you ever been told by a doctor that you had:

anemia
[ ] yes [ ] no

a low blood count?
[ ] yes [ ] no

19. Do you presently feel that you tire or run out of energy sooner than normal or sooner than other people your age?
[ ] yes
[ ] no

If yes, for how long have you felt that you tire easily?
[ ] less than 1 year
[ ] number of years

20. Have you given blood within the last year?
[ ] yes
[ ] no

If yes, how many times?
[ ] number of times

How long ago was the last time you gave blood?
[ ] less than 1 month
[ ] number of months

21. Within the last year have you had any injuries with heavy bleeding?
[ ] yes
[ ] no

If yes, how long ago?
[ ] less than 1 month
[ ] number of months

Describe:

22. Have you recently had any surgery?
[ ] yes
[ ] no

If yes, please describe:

23. Have you seen any blood lately in your stool or after a bowel movement?
[ ] yes
[ ] no

24. Have you ever had a test for blood in your stool?
[ ] yes
[ ] no

If yes, did the test show any blood in the stool?
[ ] yes
[ ] no

What further evaluation and treatment were done?

The following questions pertain to the ability to wear a respirator. Additional information for the physician can be found in The Respiratory Protective Devices Manual.

25. Have you ever been told by a doctor that you have asthma?
[ ] yes
[ ] no

If yes, are you presently taking any medication for asthma? Mark all that apply.
[ ] shots
[ ] pills
[ ] inhaler

26. Have you ever had a heart attack?
[ ] yes
[ ] no

If yes, how long ago?
[ ] number of years
[ ] number of months

27. Have you ever had pains in your chest?
[ ] yes
[ ] no

If yes, when did it usually happen?
While resting [ ]
While working [ ]
While exercising [ ]
Activity didn't matter [ ]

28. Have you ever had a thyroid problem?
[ ] yes
[ ] no

29. Have you ever had a seizure or fits?
[ ] yes
[ ] no

30. Have you ever had a stroke (cerebrovascular accident)?
[ ] yes
[ ] no

31. Have you ever had a ruptured eardrum or a serious hearing problem?
[ ] yes
[ ] no

32. Do you now have a claustrophobia, meaning fear of crowded or closed in spaces or any psychological problems that would make it hard for you to wear a respirator?
[ ] yes
[ ] no

The following questions pertain to reproductive history.

33. Have you or your partner had a problem conceiving a child?
[ ] yes
[ ] no

If yes, specify:
[ ] self
[ ] present mate
[ ] previous mate

34. Have you or your partner consulted a physician for a fertility or other reproductive problem?
[ ] yes
[ ] no

If yes, specify who consulted the physician:
[ ] self
[ ] spouse/partner
[ ] self and partner

If yes, specify diagnosis made: _____

35. Have you or your partner ever conceived a child resulting in a miscarriage, still birth or deformed offspring?
[ ] yes
[ ] no

If yes, specify:
[ ] miscarriage
[ ] still birth
[ ] deformed offspring

If outcome was a deformed offspring, please specify type: _____

36. Was this outcome a result of a pregnancy of:
[ ] yours with present partner
[ ] yours with a previous partner

37. Did the timing of any abnormal pregnancy outcome coincide with present employment?
[ ] yes
[ ] no

List dates of occurrences: _____

38. What is the occupation of your spouse or partner?

For Women Only

39. Do you have menstrual periods?
[ ] yes
[ ] no

Have you had menstrual irregularities?
[ ] yes
[ ] no

If yes, specify type: _____

If yes, what was the approximated date this problem began? _____

Approximate date problem stopped? _____

For Men Only

40. Have you ever been diagnosed by a physician as having prostate gland problem(s)?
[ ] yes
[ ] no

If yes, please describe type of problem(s) and what was done to evaluate and treat the problem(s):

Appendix E—Cadmium in Workplace Atmospheres

Method Number: ID–189.

Matrix: Air.

OSHA Permissible Exposure Limits: 5 µg/m³ (TWA) .2.5 µg/m³ (Action Level TWA).

Collection Procedure: A known volume of air is drawn through a 37-mm diameter filter cassette containing a 0.8-µm mixed cellulose ester membrane filter (MCEF).

Recommended Air Volume: 960 L.

Recommended Sampling Rate: 2.0 L/min.

Analytical Procedure: Air filter samples are digested with nitric acid. After digestion, a small amount of hydrochloric acid is added. The samples are then diluted to volume with deionized water and analyzed by either flame atomic absorption spectroscopy (AAS) or flameless atomic absorption spectroscopy using a heated graphite furnace atomizer (AAS–HGA).

Detection Limits:

Qualitative: 0.2 µg/m³ for a 200 L sample by Flame AAS; 0.007 µg/m³ for a 60 L sample by AAS–HGA

Quantitative: 0.70 µg/m³ for a 200 L sample by Flame AAS; 0.025 µg/m³ for a 60 L sample by AAS–HGA

Precision and Accuracy: *Flame AAS Analysis, AAS–HGA Analysis.*

VALIDATION LEVEL

	2.5 to 10 µg/m³ for a 400 L air vol.	1.25 to 5.0 µg/m³ for a 60 L air vol.
CV_T (pooled)	0.010	0.043
Analytical Bias	+4.0%	−5.8%
Overall Analytical Error	±6.0%	±14.2%

Method Classification: Validated.

Date: June, 1992.

Inorganic Service Branch II, OSHA Salt Lake Technical Center, Salt Lake City, Utah.

Commercial manufacturers and products mentioned in this method are for descriptive use only and do not constitute endorsements by USDOL-OSHA. Similar products from other sources can be substituted.

1. Introduction

1.1. Scope—This method describes the collection of airborne elemental cadmium and cadmium compounds on 0.8-μm mixed cellulose ester membrane filters and their subsequent analysis by either flame atomic absorption spectroscopy (AAS) or flameless atomic absorption spectroscopy using a heated graphite furnace atomizer (AAS-HGA). It is applicable for both TWA and Action Level TWA Permissible Exposure Level (PEL) measurements. The two atomic absorption analytical techniques included in the method do not differentiate between cadmium fume and cadmium dust samples. They also do not differentiate between elemental cadmium and its compounds.

1.2. Principle—Airborne elemental cadmium and cadmium compounds are collected on a 0.8-μm mixed cellulose ester membrane filter (MCEF). The air filter samples are digested with concentrated nitric acid to destroy the organic matrix and dissolve the cadmium analytes. After digestion, a small amount of concentrated hydrochloric acid is added to help dissolve other metals which may be present. The samples are diluted to volume with deionized water and then aspirated into the oxidizing air/acetylene flame of an atomic absorption spectrophotometer for analysis of elemental cadmium. If the concentration of cadmium in a sample solution is too low for quantitation by this flame AAS analytical technique, and the sample is to be averaged with other samples for TWA calculations, aliquots of the sample and a matrix modifier are later injected onto a L'vov platform in a pyrolytically-coated graphite tube of a Zeeman atomic absorption spectrophotometer/graphite furnace assembly for analysis of elemental cadmium. The matrix modifier is added to stabilize the cadmium metal and minimize sodium chloride as an interference during the high temperature charring step of the analysis (5.1., 5.2.).

1.3. History—Previously, two OSHA sampling and analytical methods for cadmium were used concurrently (5.3., 5.4.). Both of these methods also required 0.8-μm mixed cellulose ester membrane filters for the collection of air samples. These cadmium air filter samples were analyzed by either flame atomic absorption spectroscopy (5.3.) or inductively coupled plasma/atomic emission spectroscopy (ICP-AES) (5.4.). Neither of these two analytical methods have adequate sensitivity for measuring workplace exposure to airborne cadmium at the new lower TWA and Action Level TWA PEL levels when consecutive samples are taken on one employee and the sample results need to be averaged with other samples to determine a single TWA.

The inclusion of two atomic absorption analytical techniques in the new sampling and analysis method for airborne cadmium permits quantitation of sample results over a broad range of exposure levels and sampling periods. The flame AAS analytical technique included in this method is similar to the previous procedure given in the General Metals Method ID-121 (5.3.) with some modifications. The sensitivity of the AAS-HGA analytical technique included in this method is adequate to measure exposure levels at 1/10 the Action Level TWA, or lower, when less than full-shift samples need to be averaged together.

1.4. Properties (5.5.)—Elemental cadmium is a silver-white, blue-tinged, lustrous metal which is easily cut with a knife. It is slowly oxidized by moist air to form cadmium oxide. It is insoluble in water, but reacts readily with dilute nitric acid. Some of the physical properties and other descriptive information of elemental cadmium are given below:

CAS No.7440-43-9

Atomic Number—48
Atomic Symbol—Cd
Atomic Weight—112.41
Melting Point—321 °C
Boiling Point—765 °C
Density—8.65 g/mL (25 °C)

The properties of specific cadmium compounds are described in reference 5.5.

1.5. Method Performance—A synopsis of method performance is presented below. Further information can be found in Section 4.

1.5.1. The qualitative and quantitative detection limits for the flame AAS analytical technique are 0.04 μg (0.004 μg/mL) and 0.14 μg (0.014 μg/mL) cadmium, respectively, for a 10 mL solution volume. These correspond, respectively, to 0.2 $\mu g/m^3$ and 0.70 $\mu g/m^3$ for a 200 L air volume.

1.5.2. The qualitative and quantitative detection limits for the AAS-HGA analytical technique are 0.44 ng (0.044 ng/mL) and 1.5 ng (0.15 ng/mL) cadmium, respectively, for a 10 mL solution volume. These correspond, respectively, to 0.007 $\mu g/m^3$ and 0.025 $\mu g/m^3$ for a 60 L air volume.

1.5.3. The average recovery by the flame AAS analytical technique of 17 spiked MCEF samples containing cadmium in the range of 0.5 to 2.0 times the TWA target concentration of 5 $\mu g/m^3$ (assuming a 400 L air volume) was 104.0% with a pooled coefficient of variation (CV_1) of 0.010. The flame analytical technique exhibited a positive bias of +4.0% for the validated concentration range. The overall analytical error (OAE) for the flame AAS analytical technique was ±8.0%.

1.5.4. The average recovery by the AAS-HGA analytical technique of 18 spiked MCEF samples containing cadmium in the range of 0.5 to 2.0 times the Action Level TWA target concentration of 2.5 $\mu g/m^3$ (assuming a 60 L air volume) was 94.2% with a pooled coefficient of variation (CV_1) of 0.043. The AAS-HGA analytical technique exhibited a negative bias of −5.8% for the validated concentration range. The overall analytical error (OAE) for the AAS-HGA analytical technique was ±14.2%.

1.5.5. Sensitivity in flame atomic absorption is defined as the characteristic concentration of an element required to produce a signal of 1% absorbance (0.0044 absorbance units). Sensitivity values are listed for each element by the atomic absorption spectrophotometer manufacturer and have proved to be a very valuable diagnostic tool to determine if instrumental parameters are optimized and if the instrument is performing up to specification. The sensitivity of the spectrophotometer used in the validation of the flame AAS analytical technique agreed with the manufacturer specifications (5.6.); the 2 μg/mL cadmium standard gave an absorbance reading of 0.350 abs. units.

1.5.6. Sensitivity in graphite furnace atomic absorption is defined in terms of the characteristic mass, the number of picograms required to give an integrated absorbance value of 0.0044 absorbance-second (5.7.). Data suggests that under Stabilized Temperature Platform Furnace (STPF) conditions (see Section 1.6.2.), characteristic mass values are transferable between properly functioning instruments to an accuracy of about 20% (5.2.). The characteristic mass for STPF analysis of cadmium with Zeeman background correction listed by the manufacturer of the instrument used in the validation of the AAS-HGA analytical technique was 0.35 pg. The experimental characteristic mass value observed during the determination of the working range and detection limits of the AAS-HGA analytical technique was 0.41 pg.

1.6. Interferences

1.6.1. High concentrations of silicate interfere in determining cadmium by flame AAS (5.6.). However, silicates are not significantly soluble in the acid matrix used to prepare the samples.

1.6.2. Interferences, such as background absorption, are reduced to a minimum in the AAS-HGA analytical technique by taking full advantage of the Stabilized Temperature Platform Furnace (STPF) concept. STPF includes all of the following parameters (5.2.):

a. Integrated Absorbance,
b. Fast Instrument Electronics and Sampling Frequency,
c. Background Correction,
d. Maximum Power Heating,
e. Atomization off the L'vov platform in a pyrolytically coated graphite tube,
f. Gas Stop during Atomization,
g. Use of Matrix Modifiers.

1.7. Toxicology (5.14.)

Information listed within this section is synopsis of current knowledge of the physiological effects of cadmium and is not intended to be used as the basis for OSHA policy.

IARC classifies cadmium and certain of its compounds as Group 2A carcinogens (probably carcinogenic to humans). Cadmium fume is intensely irritating to the respiratory tract. Workplace exposure to cadmium can cause both chronic and acute effects. Acute effects include tracheobronchitis, pneumonitis, and pulmonary edema. Chronic effects include anemia, rhinitis/anosmia, pulmonary emphysema, proteinuria and lung cancer. The primary target organs for chronic disease are the kidneys (non-carcinogenic) and the lungs (carcinogenic).

2. Sampling

2.1. Apparatus

2.1.1. Filter cassette unit for air sampling: A 37-mm diameter mixed cellulose ester membrane filter with a pore size of 0.8-μm contained in a 37-mm polystyrene two- or three-piece cassette filter holder (part no. MAWP 037 A0, Millipore Corp., Bedford,

MA). The filter is supported with a cellulose backup pad. The cassette is sealed prior to use with a shrinkable gel band.

2.1.2. A calibrated personal sampling pump whose flow is determined to an accuracy of ±5% at the recommended flow rate with the filter cassette unit in line.

2.2. Procedure

2.2.1. Attach the prepared cassette to the calibrated sampling pump (the backup pad should face the pump) using flexible tubing. Place the sampling device on the employee such that air is sampled from the breathing zone.

2.2.2. Collect air samples at a flow rate of 2.0 L/min. If the filter does not become overloaded, a full-shift (at least seven hours) sample is strongly recommended for TWA and Action Level TWA measurements with a maximum air volume of 960 L. If overloading occurs, collect consecutive air samples for shorter sampling periods to cover the full workshift.

2.2.3. Replace the end plugs into the filter cassettes immediately after sampling. Record the sampling conditions.

2.2.4. Securely wrap each sample filter cassette end-to-end with an OSHA Form 21 sample seal.

2.2.5. Submit at least one blank sample with each set of air samples. The blank sample should be handled the same as the other samples except that no air is drawn through it.

2.2.6. Ship the samples to the laboratory for analysis as soon as possible in a suitable container designed to prevent damage in transit.

3. Analysis

3.1. Safety Precautions

3.1.1. Wear safety glasses, protective clothing and gloves at all times.

3.1.2. Handle acid solutions with care. Handle all cadmium samples and solutions with extra care (see Sect. 1.7.). Avoid their direct contact with work area surfaces, eyes, skin and clothes. Flush acid solutions which contact the skin or eyes with copious amounts of water.

3.1.3. Perform all acid digestions and acid dilutions in an exhaust hood while wearing a face shield. To avoid exposure to acid vapors, do not remove beakers containing concentrated acid solutions from the exhaust hood until they have returned to room temperature and have been diluted or emptied.

3.1.4. Exercise care when using laboratory glassware. Do not use chipped pipets, volumetric flasks, beakers or any glassware with sharp edges exposed in order to avoid the possibility of cuts or abrasions.

3.1.5. Never pipet by mouth.

3.1.6. Refer to the instrument instruction manuals and SOPs (5.8., 5.9.) for proper and safe operation of the atomic absorption spectrophotometer, graphite furnace atomizer and associated equipment.

3.1.7. Because metallic elements and other toxic substances are vaporized during AAS flame or graphite furnace atomizer operation, it is imperative that an exhaust vent be used. Always ensure that the exhaust system is operating properly during instrument use.

3.2. Apparatus for Sample and Standard Preparation

3.2.1. Hot plate, capable of reaching 150° C, installed in an exhaust hood.

3.2.2. Phillips beakers, 125 mL.

3.2.3. Bottles, narrow-mouth, polyethylene or glass with leakproof caps: used for storage of standards and matrix modifier.

3.2.4. Volumetric flasks, volumetric pipets, beakers and other associated general laboratory glassware.

3.2.5. Forceps and other associated general laboratory equipment.

3.3. Apparatus for Flame AAS Analysis

3.3.1. Atomic absorption spectrophotometer consisting of a(an):

Nebulizer and burner head.

Pressure regulating devices capable of maintaining constant oxidant and fuel pressures.

Optical system capable of isolating the desired wavelength of radiation (228.8 nm).

Adjustable slit.

Light measuring and amplifying device.

Display, strip chart, or computer interface for indicating the amount of absorbed radiation.

Cadmium hollow cathode lamp or electrodeless discharge lamp (EDL) and power supply.

3.3.2. Oxidant: compressed air, filtered to remove water, oil and other foreign substances.

3.3.3. Fuel: standard commercially available tanks of acetylene dissolved in acetone; tanks should be equipped with flash arresters. CAUTION: Do not use grades of acetylene containing solvents other than acetone because they may damage the PVC tubing used in some instruments.

3.3.4. Pressure-reducing valves: two gauge, two-stage pressure regulators to maintain fuel and oxidant pressures somewhat higher than the controlled operating pressures of the instrument.

3.3.5. Exhaust vent installed directly above the spectrophotometer burner head.

3.4. Apparatus for AAS–HGA Analysis

3.4.1. Atomic absorption spectrophotometer consisting of a(an):

Heated graphite furnace atomizer (HGA) with argon purge system.

Pressure-regulating devices capable of maintaining constant argon purge pressure.

Optical system capable of isolating the desired wavelength of radiation (228.8 nm).

Adjustable slit.

Light measuring and amplifying device.

Display, strip chart, or computer interface for indicating the amount of absorbed radiation (as integrated absorbance, peak area).

Background corrector: Zeeman or deuterium arc. The Zeeman background corrector is recommended.

Cadmium hollow cathode lamp or electrodeless discharge lamp (EDL) and power supply.

Autosampler capable of accurately injecting 5 to 20 µL sample aliquots onto the L'vov Platform in a graphite tube.

3.4.2. Pyrolytically-coated graphite tubes containing solid, pyrolytic L'vov platforms.

3.4.3. Polyethylene sample cups, 2.0 to 2.5 mL, for use with the autosampler.

3.4.4. Inert purge gas for graphite furnace atomizer: compressed gas cylinder of purified argon.

3.4.5. Two gauge, two-stage pressure regulator for the argon gas cylinder.

3.4.6. Cooling water supply for graphite furnace atomizer.

3.4.7. Exhaust vent installed directly above the graphite furnace atomizer.

3.5. Reagents

All reagents should be ACS analytical reagent grade or better.

3.5.1. Deionized water with a specific conductance of less than 10 µS.

3.5.2. Concentrated nitric acid, HNO_3.

3.5.3. Concentrated hydrochloric acid, HCl.

3.5.4. Ammonium phosphate, monobasic, $NH_4H_2PO_4$.

3.5.5. Magnesium nitrate, $Mg(NO_3)_2 \cdot 6H_2O$.

3.5.6. Diluting solution (4% HNO_3, 0.4% HCl): Add 40 mL HNO_3 and 4 mL HCl carefully to approximately 500 mL deionized water and dilute to 1 L with deionized water.

3.5.7. Cadmium standard stock solution, 1,000 µg/mL: Use a commercially available certified 1,000 µg/mL cadmium standard or, alternatively, dissolve 1.0000 g of cadmium metal in a minimum volume of 1:1 HCl and dilute to 1 L with 4% HNO_3. Observe expiration dates of commercial standards. Properly dispose of commercial standards with no expiration dates or prepared standards one year after their receipt or preparation date.

3.5.8. Matrix modifier for AAS–HGA analysis: Dissolve 1.0 g $NH_4H_2PO_4$ and 0.15 g $Mg(NO_3)_2 \cdot 6H_2O$ in approximately 200 mL deionized water. Add 1 mL HNO_3 and dilute to 500 mL with deionized water.

3.5.9 Nitric Acid, 1:1 HNO_3/DI H_2O mixture: Carefully add a measured volume of concentrated HNO_3 to an equal volume of DI H_2O.

3.5.10. Nitric acid, 10% v/v: Carefully add 100 mL of concentrated HNO_3 to 500 mL of DI H_2O and dilute to 1 L.

3.6. Glassware Preparation

3.6.1. Clean Phillips beakers by refluxing with 1:1 nitric acid on a hot plate in a fume hood. Thoroughly rinse with deionized water and invert the beakers to allow them to drain dry.

3.6.2. Rinse volumetric flasks and all other glassware with 10% nitric acid and deionized water prior to use.

3.7. Standard Preparation for Flame AAS Analysis

3.7.1. Dilute stock solutions: Prepare 1, 5, 10 and 100 µg/mL cadmium standard stock solutions by making appropriate serial dilutions of 1,000 µg/mL cadmium standard stock solution with the diluting solution described in Section 3.5.6.

3.7.2. Working standards: Prepare cadmium working standards in the range of 0.02 to 2.0 µg/mL by making appropriate serial dilutions of the dilute stock solutions with the same diluting solution. A suggested method of preparation of the working standards is given below.

Working standard (µg/mL)	Std solution (µg/mL)	Aliquot (mL)	Final vol (mL)
0.02	1	10	500
.05	5	5	500
.1	10	5	500
.2	10	10	500
.5	10	25	500
1	100	5	500
2	100	10	500

Store the working standards in 500-mL, narrow-mouth polyethylene or glass bottles with leakproof caps. Prepare every twelve months.

3.8. Standard Preparation for AAS–HGA Analysis

3.8.1. Dilute stock solutions: Prepare 10, 100 and 1,000 ng/mL cadmium standard stock solutions by making appropriate ten-fold serial dilutions of the 1,000 µg/mL cadmium standard stock solution with the diluting solution described in Section 3.5.6.

3.8.2. Working standards: Prepare cadmium working standards in the range of 0.2 to 20 ng/mL by making appropriate serial dilutions of the dilute stock solutions with the same diluting solution. A suggested method of preparation of the working standards is given below.

Working standard (ng/mL)	Std solution (ng/mL)	Aliquot (mL)	Final vol (mL)
0.2	10	2	100
.5	10	5	100
1	10	10	100
2	100	2	100
5	100	5	100
10	100	10	100
20	1,000	2	100

Store the working standards in narrow-mouth polyethylene or glass bottles with leakproof caps. Prepare monthly.

3.9. Sample Preparation

3.9.1. Carefully transfer each sample filter with forceps from its filter cassette unit to a clean, separate 125-mL Phillips beaker along with any loose dust found in the cassette. Label each Phillips beaker with the appropriate sample number.

3.9.2. Digest the sample by adding 5 mL of concentrated nitric acid (HNO_3) to each Phillips beaker containing an air filter sample. Place the Phillips beakers on a hot plate in an exhaust hood and heat the samples until approximately 0.5 mL remains. The sample solution in each Phillips beaker should become clear. If it is not clear, digest the sample with another portion of concentrated nitric acid.

3.9.3. After completing the HNO_3 digestion and cooling the samples, add 40 µL (2 drops) of concentrated HCl to each air sample solution and then swirl the contents. Carefully add about 5 mL of deionized water by pouring it down the inside of each beaker.

3.9.4. Quantitatively transfer each cooled air sample solution from each Phillips beaker to a clean 10-mL volumetric flask. Dilute each flask to volume with deionized water and mix well.

3.10. Flame AAS Analysis

Analyze all of the air samples for their cadmium content by flame atomic absorption spectroscopy (AAS) according to the instructions given below.

3.10.1. Set up the atomic absorption spectrophotometer for the air/acetylene flame analysis of cadmium according to the SOP (5.8.) or the manufacturer's operational instructions. For the source lamp, use the cadmium hollow cathode or electrodeless discharge lamp operated at the manufacturer's recommended rating for continuous operation. Allow the lamp to warm up 10 to 20 min or until the energy output stabilizes. Optimize conditions such as lamp position, burner head alignment, fuel and oxidant flow rates, etc. See the SOP or specific instrument manuals for details. Instrumental parameters for the Perkin-Elmer Model 603 used in the validation of this method are given in Attachment 1.

3.10.2. Aspirate and measure the absorbance of a standard solution of cadmium. The standard concentration should be within the linear range. For the instrumentation used in the validation of this method a 2 µg/mL cadmium standard gives a net absorbance reading of about 0.350 abs. units (see Section 1.5.5.) when the instrument and the source lamp are performing to manufacturer specifications.

3.10.3. To increase instrument response, scale expand the absorbance reading of the aspirated 2 µg/mL working standard approximately four times. Increase the integration time to at least 3 seconds to reduce signal noise.

3.10.4. Autozero the instrument while aspirating a deionized water blank. Monitor the variation in the baseline absorbance reading (baseline noise) for a few minutes to insure that the instrument, source lamp and associated equipment are in good operating condition.

3.10.5. Aspirate the working standards and samples directly into the flame and record their absorbance readings. Aspirate the deionized water blank immediately after every standard or sample to correct for and monitor any baseline drift and noise. Record the baseline absorbance reading of each deionized water blank. Label each standard and sample reading and its accompanying baseline reading.

3.10.6. It is recommended that the entire series of working standards be analyzed at the beginning and end of the analysis of a set of samples to establish a concentration-response curve, ensure that the standard readings agree with each other and are reproducible. Also, analyze a working standard after every five or six samples to monitor the performance of the spectrophotometer. Standard readings should agree within ±10 to 15% of the readings obtained at the beginning of the analysis.

3.10.7. Bracket the sample readings with standards during the analysis. If the absorbance reading of a sample is above the absorbance reading of the highest working standard, dilute the sample with diluting solution and reanalyze. Use the appropriate dilution factor in the calculations.

3.10.8. Repeat the analysis of approximately 10% of the samples for a check of precision.

3.10.9. If possible, analyze quality control samples from an independent source as a check on analytical recovery and precision.

3.10.10. Record the final instrument settings at the end of the analysis. Date and label the output.

3.11. AAS–HGA Analysis

Initially analyze all of the air samples for their cadmium content by flame atomic absorption spectroscopy (AAS) according to the instructions given in Section 3.10. If the concentration of cadmium in a sample solution is less than three times the quantitative detection limit (0.04 µg/mL (40 ng/mL) for the instrumentation used in the validation) and the sample results are to be averaged with other samples for TWA calculations, proceed with the AAS–HGA analysis of the sample as described below.

3.11.1. Set up the atomic absorption spectrophotometer and HGA for flameless atomic absorption analysis of cadmium according to the SOP (5.9.) or the manufacturer's operational instructions and allow the instrument to stabilize. The graphite furnace atomizer is equipped with a pyrolytically coated graphite tube containing a pyrolytic platform. For the source lamp, use a cadmium hollow cathode or electrodeless discharge lamp operated at the manufacturer's recommended setting for graphite furnace operation. The Zeeman background corrector and EDL are recommended for use with the L'vov platform. Instrumental parameters for the Perkin-Elmer Model 5100 spectrophotometer and Zeeman HGA–600 graphite furnace used in the validation of this method are given in Attachment 2.

3.11.2. Optimize the energy reading of the spectrophotometer at 228.8 nm by adjusting the lamp position and the wavelength according to the manufacturer's instructions.

3.11.3. Set up the autosampler to inject a 5-µL aliquot of the working standard, sample or reagent blank solution onto the L'vov platform along with a 10−µL overlay of the matrix modifier.

3.11.4. Analyze the reagent blank (diluting solution, Section 3.5.6.) and then autozero the instrument before starting the analysis of a set of samples. It is recommended that the reagent blank be analyzed several times during the analysis to assure the integrated absorbance (peak area) reading remains at or near zero.

3.11.5. Analyze a working standard approximately midway in the linear portion of the working standard range two or three times to check for reproducibility and sensitivity (see Sections 1.5.5. and 1.5.6.) before starting the analysis of samples. Calculate the experimental characteristic mass value from the average integrated absorbance reading and injection volume of the analyzed working standard. Compare this value to the manufacturer's suggested value as a check of proper instrument operation.

3.11.6. Analyze the reagent blank, working standard, and sample solutions. Record and label the peak area (abs-sec) readings and the peak and background peak profiles on the printer/plotter.

3.11.7. It is recommended the entire series of working standards be analyzed at the beginning and end of the analysis of a set of samples. Establish a concentration-response curve and ensure standard readings agree with each other and are reproducible. Also, analyze a working standard after every five or six samples to monitor the performance of the system. Standard readings should agree within ±15% of the readings obtained at the beginning of the analysis.

3.11.8. Bracket the sample readings with standards during the analysis. If the peak area reading of a sample is above the peak area reading of the highest working standard, dilute the sample with the diluting solution and reanalyze. Use the appropriate dilution factor in the calculations.

3.11.9. Repeat the analysis of approximately 10% of the samples for a check of precision.

3.11.10. If possible, analyze quality control samples from an independent source as a check of analytical recovery and precision.

3.11.11. Record the final instrument settings at the end of the analysis. Date and label the output.

3.12. Calculations

Note: Standards used for HGA analysis are in ng/mL. Total amounts of cadmium from calculations will be in ng (not µg) unless a prior conversion is made.

3.12.1. Correct for baseline drift and noise in flame AAS analysis by subtracting each baseline absorbance reading from its corresponding working standard or sample absorbance reading to obtain the net absorbance reading for each standard and sample.

3.12.2. Use a least squares regression program to plot a concentration-response curve of net absorbance reading (or peak area for HGA analysis) versus concentration (µg/mL or ng/mL) of cadmium in each working standard.

3.12.3. Determine the concentration (µg/mL or ng/mL) of cadmium in each sample from the resulting concentration-response curve. If the concentration of cadmium in a sample solution is less than three times the quantitative detection limit (0.04 µg/mL (40 ng/mL) for the instrumentation used in the validation of the method) and if consecutive samples were taken on one employee and the sample results are to be averaged with other samples to determine a single TWA, reanalyze the sample by AAS–HGA as described in Section 3.11. and report the AAS–HGA analytical results.

3.12.4. Calculate the total amount (µg or ng) of cadmium in each sample from the sample solution volume (mL):

$$W = (C)(\text{sample vol, mL})(DF)$$

Where:

W = Total cadmium in sample
C = Calculated concentration of cadmium
DF = Dilution Factor (if applicable)

3.12.5. Make a blank correction for each air sample by subtracting the total amount of cadmium in the corresponding blank sample from the total amount of cadmium in the sample.

3.12.6. Calculate the concentration of cadmium in an air sample (mg/m³ or µg/m³) by using one of the following equations:

$$\text{mg/m}^3 = W_{bc}/(\text{Air vol sampled, L})$$

or

$$\mu\text{g/m}^3 = (W_{bc})(1{,}000\ \text{ng/}\mu\text{g})/(\text{Air vol sampled, L})$$

Where:

W_{bc} = blank corrected total µg cadmium in the sample. (1µg = 1,000 ng)

4. Backup Data

4.1. Introduction

4.1.1. The purpose of this evaluation is to determine the analytical method recovery, working standard range, and qualitative and quantitative detection limits of the two atomic absorption analytical techniques included in this method. The evaluation consisted of the following experiments:

1. An analysis of 24 samples (six samples each at 0.1, 0.5, 1 and 2 times the TWA–PEL) for the analytical method recovery study of the flame AAS analytical technique.

2. An analysis of 18 samples (six samples each at 0.5, 1 and 2 times the Action Level (TWA–PEL) for the analytical method recovery study of the AAS–HGA analytical technique.

3. Multiple analyses of the reagent blank and a series of standard solutions to determine the working standard range and the qualitative and quantitative detection limits for both atomic absorption analytical techniques.

4.1.2. The analytical method recovery results at all test levels were calculated from concentration-response curves and statistically examined for outliers at the 99% confidence level. Possible outliers were determined using the Treatment of Outliers test (5.10.). In addition, the sample results of the two analytical techniques, at 0.5, 1.0 and 2.0 times their target concentrations, were tested for homogeneity of variances also at the 99% confidence level. Homogeneity of the coefficients of variation was determined using the Bartlett's test (5.11.). The overall analytical error (OAE) at the 95% confidence level was calculated using the equation (5.12.):

$$OAE = \pm\left[|\text{Bias}| + (1.96)(CV_1(\text{pooled}))(100\%)\right]$$

4.1.3. A derivation of the International Union of Pure and Applied Chemistry (IUPAC) detection limit equation (5.13.) was used to determine the qualitative and quantitative detection limits for both atomic absorption analytical techniques:

$$C_{ld} = k(sd)/m \qquad \text{(Equation 1)}$$

Where:

C_{ld}=the smallest reliable detectable concentration an analytical instrument can determine at a given confidence level.

k=3 for the Qualitative Detection Limit at the 99.86% Confidence Level.

=10 for the Quantitative Detection Limit at the 99.99% Confidence Level.

sd=standard deviation of the reagent blank (Rbl) readings.

m=analytical sensitivity or slope as calculated by linear regression.

4.1.4. Collection efficiencies of metallic fume and dust atmospheres on 0.8-µm mixed cellulose ester membrane filters are well documented and have been shown to be excellent (5.11.). Since elemental cadmium and the cadmium component of cadmium compounds are nonvolatile, stability studies of cadmium spiked MCEF samples were not performed.

4.2. Equipment

4.2.1. A Perkin-Elmer (PE) Model 603 spectrophotometer equipped with a manual gas control system, a stainless steel nebulizer, a burner mixing chamber, a flow spoiler and a 10 cm. (one-slot) burner head was used in the experimental validation of the flame AAS analytical technique. A PE cadmium hollow cathode lamp, operated at the manufacturer's recommended current setting for continuous operation (4 mA), was used as the source lamp. Instrument parameters are listed in Attachment 1.

4.2.2. A PE Model 5100 spectrophotometer, Zeeman HGA–600 graphite furnace atomizer and AS–60 HGA autosampler were used in

the experimental validation of the AAS-HGA analytical technique. The spectrophotometer was equipped with a PE Series 7700 professional computer and Model PR-310 printer. A PE System 2 cadmium electrodeless discharge lamp, operated at the manufacturer's recommended current setting for modulated operation (170 mA), was used as the source lamp. Instrument parameters are listed in Attachment 2.

4.3. Reagents

4.3.1. J.T. Baker Chem. Co. (Analyzed grade) concentrated nitric acid, 69.0–71.0%, and concentrated hydrochloric acid, 36.5–38.0%, were used to prepare the samples and standards.

4.3.2. Ammonium phosphate, monobasic, $NH_4H_2PO_4$ and magnesium nitrate, $Mg(NO_3)_2 \cdot 6H_2O$, both manufactured by the Mallinckrodt Chem. Co., were used to prepare the matrix modifier for AAS–HGA analysis.

4.4. Standard Preparation for Flame AAS Analysis

4.4.1. Dilute stock solutions: Prepared 0.01, 0.1, 1, 10 and 100 µg/mL cadmium standard stock solutions by making appropriate serial dilutions of a commercially available 1,000 µg/mL cadmium standard stock solution (FISCA Chemical Co., Lot # A102) with the diluting solution (4% HNO_3, 0.4% HCl).

4.4.2. Analyzed Standards: Prepared cadmium standards in the range of 0.001 to 2.0 µg/mL by pipetting 2 to 10 mL of the appropriate dilute cadmium stock solution into a 100-mL volumetric flask and diluting to volume with the diluting solution. (See Section 3.7.2.)

4.5. Standard Preparation for AAS–HGA Analysis

4.5.1. Dilute stock solutions: Prepared 1, 10, 100 and 1,000 µg/mL cadmium standard stock solutions by making appropriate serial dilutions of a commercially available 1,000 µg/mL cadmium standard stock solution (J.T. Baker Chemical Co., Instra-analyzed, Lot # D22642) with the diluting solution (4% HNO_3, 0.4% HCl).

4.5.2. Analyzed Standards: Prepared cadmium standards in the range of 0.1 to 40 ng/mL by pipetting 2 to 10 mL of the appropriate dilute cadmium stock solution into a 100-mL volumetric flask and diluting to volume with the diluting solution. (See Section 3.8.2.)

4.6. Detection Limits and Standard Working Range for Flame AAS Analysis

4.6.1. Analyzed the reagent blank solution and the entire series of cadmium standards in the range of 0.001 to 2.0 µg/mL three to six times according to the instructions given in Section 3.10. The diluting solution (4% HNO_3, 0.4% HCl) was used as the reagent blank. The integration time on the PE 603 spectrophotometer was set to 3.0 seconds and a four-fold expansion of the absorbance reading of the 2.0 µg/mL cadmium standard was made prior to analysis. The 2.0 µg/mL standard gave a net absorbance reading of 0.350 abs. units prior to expansion in agreement with the manufacturer's specifications (5.6.).

4.6.2. The net absorbance readings of the reagent blank and the low concentration Cd standards from 0.001 to 0.1 µg/mL and the statistical analysis of the results are shown in Table I. The standard deviation, sd, of the six net absorbance readings of the reagent blank is 1.05 abs. units. The slope, m, as calculated by a linear regression plot of the net absorbance readings (shown in Table II) of the 0.02 to 1.0 µg/mL cadmium standards versus their concentration is 772.7 abs. units/(µg/mL).

4.6.3. If these values for sd and the slope, m, are used in Eqn. 1 (Sect. 4.1.3.), the qualitative and quantitative detection limits as determined by the IUPAC Method are:

$$C_{ld} = (3)(1.05 \text{ abs. units}) / (772.7 \text{ abs. units}/(\mu g/mL))$$
$$= 0.0041 \ \mu g/mL \text{ for the qualitative detection limit.}$$

$$C_{ld} = (10)(1.05 \text{ abs. units}) / (772.7 \text{ abs. units}/(\mu g/mL))$$
$$= 0.014 \ \mu g/mL \text{ for the quantitative detection limit.}$$

The qualitative and quantitative detection limits for the flame AAS analytical technique are 0.041 µg and 0.14 µg cadmium, respectively, for a 10 mL solution volume. These correspond, respectively, to 0.2 µg/m³ and 0.70 µg/m³ for a 200 L air volume.

4.6.4. The recommended Cd standard working range for flame AAS analysis is 0.02 to 2.0 µg/mL. The net absorbance readings of the reagent blank and the recommended working range standards and the statistical analysis of the results are shown in Table II. The standard of lowest concentration in the working range, 0.02 µg/mL, is slightly greater than the calculated quantitative detection limit, 0.014 µg/mL. The standard of highest concentration in the working range, 2.0 µg/mL, is at the upper end of the linear working range suggested by the manufacturer (5.6.). Although the standard net absorbance readings are not strictly linear at concentrations above 0.5 µg/mL, the deviation from linearity is only about 10% at the upper end of the recommended standard working range. The deviation from linearity is probably caused by the four-fold expansion of the signal suggested in the method. As shown in Table II, the precision of the standard net absorbance readings are excellent throughout the recommended working range; the relative standard deviations of the readings range from 0.009 to 0.064.

4.7. Detection Limits and Standard Working Range for AAS-HGA Analysis

4.7.1. Analyzed the reagent blank solution and the entire series of cadmium standards in the range of 0.1 to 40 ng/mL according to the instructions given in Section 3.11. The diluting solution (4% HNO_3, 0.4% HCl) was used as the reagent blank. A fresh aliquot of the reagent blank and of each standard was used for every analysis. The experimental characteristic mass value was 0.41 pg, calculated from the average peak area (abs-sec) reading of the 5 ng/mL standard which is approximately midway in the linear portion of the working standard range. This agreed within 20% with the characteristic mass value, 0.35 pg, listed by the manufacturer of the instrument (5.2.).

4.7.2. The peak area (abs-sec) readings of the reagent blank and the low concentration Cd standards from 0.1 to 2.0 ng/mL and statistical analysis of the results are shown in Table III. Five of the reagent blank peak area readings were zero and the sixth reading was 1 and was an outlier. The near lack of a blank signal does not satisfy a strict interpretation of the IUPAC method for determining the detection limits. Therefore, the standard deviation of the six peak area readings of the 0.2 ng/mL cadmium standard, 0.75 abs-sec, was used to calculate the detection limits by the IUPAC method. The slope, m, as calculated by a linear regression plot of the peak area (abs-sec) readings (shown in Table IV) of the 0.2 to 10 ng/mL cadmium standards versus their concentration is 51.5 abs-sec/(ng/mL).

4.7.3. If 0.75 abs-sec (sd) and 51.5 abs-sec/(ng/mL) (m) are used in Eqn. 1 (Sect. 4.1.3.), the qualitative and quantitative detection limits as determined by the IUPAC method are:

$$C_{lq} = (3)(0.75 \text{ abs-sec}) / (51.5 \text{ abs-sec/(ng/mL)})$$
$$= 0.044 \text{ ng/mL for the qualitative detection limit.}$$

$$C_{lq} = (10)(0.75 \text{ abs-sec}) / (51.5 \text{ abs-sec/(ng/mL)})$$
$$= 0.15 \text{ ng/mL for the quantitative detection limit.}$$

The qualitative and quantitative detection limits for the AAS–HGA analytical technique are 0.44 ng and 1.5 ng cadmium, respectively, for a 10 mL solution volume. These correspond, respectively, to 0.007 µg/m³ and 0.025 µg/m³ for a 60 L air volume.

4.7.4. The peak area (abs-sec) readings of the Cd standards from 0.2 to 40 ng/mL and the statistical analysis of the results are given in Table IV. The recommended standard working range for AAS–HGA analysis is 0.2 to 20 ng/mL. The standard of lowest concentration in the recommended working range is slightly greater than the calculated quantitative detection limit, 0.15 ng/mL. The deviation from linearity of the peak area readings of the 20 ng/mL standard, the highest concentration standard in the recommended working range, is approximately 10%. The deviations from linearity of the peak area readings of the 30 and 40 ng/mL standards are significantly greater than 10%. As shown in Table IV, the precision of the peak area readings are satisfactory throughout the recommended working range; the relative standard deviations of the readings range from 0.025 to 0.083.

4.8. Analytical Method Recovery for Flame AAS Analysis

4.8.1. Four sets of spiked MCEF samples were prepared by injecting 20 µL of 10, 50, 100 and 200 µg/mL dilute cadmium stock solutions on 37 mm diameter filters (part no. AAWP 037 00, Millipore Corp., Bedford, MA) with a calibrated micropipet. The dilute stock solutions were prepared by making appropriate serial dilutions of a commercially available 1,000 ug/mL cadmium standard stock solution (RICCA Chemical Co., Lot #A102) with the diluting solution (4% HNO_3, 0.4% HCl). Each set contained six samples and a sample blank. The amount of cadmium in the prepared sets were equivalent to 0.1, 0.5, 1.0 and 2.0 times the TWA PEL target concentration of 5 µg/m³ for a 400 L air volume.

4.8.2. The air-dried spiked filters were digested and analyzed for their cadmium content by flame atomic absorption spectroscopy (AAS) following the procedure described in Section 3. The 0.02 to 2.0 ug/mL cadmium standards (the suggested working range) were used in the analysis of the spiked filters.

4.8.3. The results of the analysis are given in Table V. One result at 0.5 times the TWA PEL target concentration was an outlier and was excluded from statistical analysis. Experimental justification for rejecting it is that the outlier value was probably due to a spiking error. The coefficients of variation for the three test levels at 0.5 to 2.0 times the TWA PEL target concentration passed the Bartlett's test and were pooled.

4.8.4. The average recovery of the six spiked filter samples at 0.1 times the TWA PEL target concentration was 118.2% with a coefficient of variation (CV_t) of 0.128. The average recovery of the spiked filter samples in the range of 0.5 to 2.0 times the TWA target concentration was 104.0% with a pooled coefficient of variation (CV_t) of 0.010. Consequently, the analytical bias found in these spiked sample results over the tested concentration range was +4.0% and the OAE was ±6.0%. #

4.9. Analytical Method Recovery for AAS–HGA Analysis

4.9.1. Three sets of spiked MCEF samples were prepared by injecting 15 µL of 5, 10 and 20 µg/mL dilute cadmium stock solutions on 37 mm diameter filters (part no. AAWP 037 00, Millipore Corp., Bedford, MA) with a calibrated micropipet. The dilute stock solutions were prepared by making appropriate serial dilutions of a commercially available certified 1.000 µg/mL cadmium standard stock solution (Fisher Chemical Co., Lot #913438–24) with the diluting solution (4% HNO_3, 0.4% HCl). Each set contained six samples and a sample blank. The amount of cadmium in the prepared sets were equivalent to 0.5, 1 and 2 times the Action Level TWA target concentration of 2.5 µg/m³ for a 60 L air volume.

4.9.2. The air-dried spiked filters were digested and analyzed for their cadmium content by flameless atomic absorption spectroscopy using a heated graphite furnace atomizer following the procedure described in Section 3. A five-fold dilution of the spiked filter samples at 2 times the Action Level TWA was made prior to their analysis. The 0.05 to 20 ng/mL cadmium standards were used in the analysis of the spiked filters.

4.9.3. The results of the analysis are given in Table VI. There were no outliers. The coefficients of variation for the three test levels at 0.5 to 2.0 times the Action Level TWA PEL passed the Bartlett's test and were pooled. The average recovery of the spiked filter samples was 94.2% with a pooled coefficient of variation (CV_t) of 0.043. Consequently, the analytical bias was −5.8% and the OAE was ±14.2%.

4.10. Conclusions

The experiments performed in this evaluation show the two atomic absorption analytical techniques included in this method to be precise and accurate and have sufficient sensitivity to measure airborne cadmium over a broad range of exposure levels and sampling periods.

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TABLE I.—CO DETECTION LIMIT STUDY

[Flame AAS Analysis]

STD (µg/mL)	Absorbance reading at 228.8 nm		Statistical analysis
Reagent Blank	5	2	n = 6.
	4	3	mean = 3.50.
	4	3	std dev = 1.05.
			CV = 0.30.
0.001	6	6	n = 6.
	2	4	mean = 5.00.
	6	6	std dev = 1.67.
			CV = 0.335.
0.002	5	7	n = 6.
	7	3	mean = 5.50.
	7	4	std dev = 1.76.
			CV = 0.320.
0.005	7	7	n = 6.
	8	8	mean = 7.33.
	8	6	std dev = 0.817.
			CV = 0.111.
0.010	10	9	n = 6.
	10	13	mean = 10.3.
	10	10	std dev = 1.37.
			CV = 0.133.
0.020	20	23	n = 6.
	20	22	mean = 20.8.
	20	20	std dev = 1.33.
			CV = 0.064.
0.050	42	42	n = 6.
	42	42	mean = 42.5.
	42	45	std dev = 1.22.
			CV = 0.029.
0.10	84		n = 3.
	80		mean = 82.3.
	83		std dev = 2.08.
			CV = 0.025.

TABLE II.—CO STANDARD WORKING RANGE STUDY

[Flame AAS Analysis]

STD(µg/mL)	Absorbance reading at 228.8 nm		Statistical anaysis
Reagent Blank	5	2	n=6.
	4	3	mean=3.50.
	4	3	std dev=1.05.
			CV=0.30.
0.020	20	23	n=6.
	20	22	mean=20.8.
	D20	20	std dev=1.33.
			CV=0.064.
0.050	42	42	n=6.
	42	42	mean=42.5.
	42	45	std dev=1.22.
			CV=0.029
0.10	84		n=3.
	80		mean=82.3.
	83		std dev=2.08.
			CV=0.025.
0.20	161		n=3.
	161		mean=160.0.
	158		std dev=1.73.
			CV=0.011.
0.50	391		n=3.
	389		mean=391.0.

TABLE II.—CD STANDARD WORKING RANGE STUDY—Continued

[Flame AAS Analysis]

STD(µg/mL)	Absorbance reading at 228.8 nm	Statistical analysis
1.00	393 760 748 752	std dev=2.00. CV=0.005. n=3. mean=753.3. std dev=6.11. CV=0.008.
2.00	1416 1426 1401	n=3. mean=1414.3. std dev=12.6. CV=0.009.

TABLE III.—CD DETECTION LIMIT STUDY

[AAS-HGA Analysis]

STD (ng/mL)	Peak area readings X 10^3 at 228.8 nm		Statistical analysis
Reagent Blank	0	0	n = 6.
	0	1	mean = 0.167.
	0	0	std dev = 0.41.
			CV = 2.45.
0.1	8	6	n = 6.
	5	7	mean = 7.7.
	13	7	std dev = 2.8.
			CV = 0.366.
0.2	11	13	n = 6.
	11	12	mean = 11.8.
	12	12	std dev = 0.75.
			CV = 0.064.
0.5	28	33	n = 6.
	26	28	mean = 28.8.
	28	30	std dev = 2.4.
			CV = 0.083.
1.0	52	55	n = 6.
	56	58	mean = 54.8.
	54	54	std dev = 2.0.
			CV = 0.037.
2.0	101	112	n = 6.
	110	110	mean = 108.8.
	110	110	std dev = 3.9.
			CV = 0.036.

TABLE IV.—CD STANDARD WORKING RANGE STUDY

[AAS-HGA Analysis]

STD (ng/mL)	Peak area readings x 10^3 at 228.8 nm		Statistical analysis
0.2	11	13	n=6.
	11	12	mean=11.8.
	12	12	std dev=0.75.
			CV=0.064.
0.5	28	33	n=6.
	26	28	mean=28.8.
	28	30	std dev=2.4.
			CV=0.083.
1.0	52	55	n=6.
	56	58	mean=54.8.
	54	54	std dev=2.0.
			CV=0.037.
2.0	101	112	n=6
	110	110	mean=108.8.
	110	110	std dev=3.9.
			CV=0.036.
5.0	247	265	n=6.
	268	275	mean=265.5.
	259	279	std dev=11.5.
			CV=0.044.

TABLE IV.—CD STANDARD WORKING RANGE STUDY—Continued

(AAS-HGA Anaysis)

STD (ng/mL)	Peak area readings x 10^3 at 228.8 nm		Statistical anaysis
10.0	495	520	n=6.
	523	513	mean=516.7.
	516	533	std dev=12.7.
			CV=0.025.
20.0	950	953	n=6.
	951	958	mean=941.8.
	949	890	std dev=25.5.
			CV=0.027.
30.0	1269	1291	n=6.
	1303	1307	mean=1293.
	1295	1290	std dev=13.3.
			CV=0.010.
40.0	1505	1567	n=6.
	1535	1567	mean=1552.
	1566	1572	std dev=26.6.
			CV=0.017.

TABLE V.—ANALYTICAL METHOD RECOVERY [FLAME AAS ANALYSIS]

Test level								
0.5x			1.0x			2.0x		
µg taken	µg found	Percent rec.	µg taken	µg found	Percent rec.	µg taken	µg found	Percent rec.
1.00	1.0715	107.2	2.00	2.0688	103.4	4.00	4.1504	103.8
1.00	1.0842	108.4	2.00	2.0174	100.9	4.00	4.1108	102.8
1.00	1.0842	108.4	2.00	2.0431	102.2	4.00	4.0581	101.5
1.00	*1.0081	*100.8	2.00	2.0431	102.2	4.00	4.0844	102.1
1.00	1.0715	107.2	2.00	2.0174	100.9	4.00	4.1504	103.8
1.00	1.0842	108.4	2.00	2.0045	100.2	4.00	4.1899	104.7
n=	5			6			6	
mean=	107.9			101.6			103.1	
std dev=	0.657			1.174			1.189	
CV_1=	0.006			0.011			0.012	
				CV_1(pooled)=0.010				

*—Rejected as an outlier—this value did not pass the outlier T-test at the 99% confidence level.

Test level		
0.1x		
µg taken	µg found	Percent Rec.
0.200	0.2509	125.5
0.200	0.2509	125.5
0.200	0.2761	138.1
0.200	0.2258	112.9
0.200	0.2253	112.9
0.200	0.1881	94.1
n=	6	
mean=	118.2	
std dev=	15.1	
CV=	0.128	

TABLE VI.—ANALYTICAL METHOD RECOVERY

(AAS-HGA Anaysis)

Test Level								
0.5x			1.0x			2.0x		
ng taken	ng found	Percent rec.	ng taken	ng found	Percent rec.	ng taken	ng found	Percent rec.
75	71.23	95.0	150	138.00	92.0	300	258.43	86.1
75	71.47	95.3	150	138.29	92.2	300	258.46	86.2
75	70.02	93.4	150	136.30	90.9	300	280.55	93.5
75	77.34	103.1	150	146.62	97.7	300	288.34	96.1

TABLE VII.—ANALYTICAL METHOD RECOVERY—Continued

(AAS-HGA Analysis)

Test Level								
0.5x			1.0x			2.0x		
ng taken	ng found	Percent rec.	ng taken	ng found	Percent rec.	ng taken	ng found	Percent rec.
75	78.32	104.4	150	145.17	96.8	300	261.74	87.2
75	71.96	95.9	150	144.88	96.6	300	277.22	92.4
n=	6			6			6	
mean=	97.9			94.4			90.3	
std dev=	4.68			2.98			4.30	
CV1=	0.048			0.032			0.048	
CV1 (pooled) = 0.043								

Attachment 1

Instrumental Parameters for Flame AAS Analysis

Atomic Absorption Spectrophotometer (Perkin-Elmer Model 603)
Flame: Air/Acetylene—lean, blue
Oxidant Flow: 55
Fuel Flow: 32
Wavelength: 228.8 nm
Slit: 4 (0.7 nm)
Range: UV
Signal: Concentration (4 exp)
Integration Time: 3 sec

Attachment 2

Instrumental Parameters for HGA Analysis

Atomic Absorption Spectrophotometer (Perkin-Elmer Model 5100)

Signal Type: Zeeman AA
Slitwidth: 0.7 nm
Wavelength: 228.8 nm
Measurement: Peak Area
Integration Time: 6.5 sec
BOC Time: 5 sec
BOC = Background Offset Correction

ZEEMAN GRAPHITE FURNACE

(Perkin-Elmer Model HGA-600)

Step	Ramp Time (sec)	Hold Time (sec)	Temp. (°C)	Argon Flow mL/min)	Read (sec)
(1)Predry	5	10	90	300	—
(2)Dry	30	10	140	300	—
(3)Char	10	20	900	300	—
(4)Cool Down	1	8	30	300	—
(5)Atomize	0	5	1600	0	−1
(6)Burnout	1	8	2500	300	—

Appendix F—Nonmandatory Protocol for Biological Monitoring 1.0 Introduction

Under the final OSHA cadmium rule (29 CFR 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 which employees may continue to work in locations exhibiting airborne-cadmium concentrations at or above defined actions levels (see paragraphs (1)(3) and (1)(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 which 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 (which 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 analyses 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 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 nonmandatory 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 idiosyncracy 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 which the concentration of analyte in the sample 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 which 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 predifined level of confidence, this is the lowest measured value at which 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 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 (±) 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 which are unknown to anyone at a participating laboratory, and which 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 which 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 which 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 µg/l. For CDU, the target values are 3, 7 and 15 µg/g CRTU. For B2MU, the target value are 300, 750 and 1500 µg/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	0.5 µg/l		±1 µg/l or 15% of the mean.
≤2 µg/l		40%	
>2 µg/l		20%	
Cadmium in urine	0.5 µg/g creatinine		±1 µg/l or 15% of the mean.
≤2 µg/l creatinine		40%	
>2 µg/l creatinine		20%	
β-2-Microglobulin in urine	100 µg/g creatinine		± 15% of the mean.
100 µg/g creatinine		5%	

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 Stoeppler 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 which 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 which 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 which will be provided to the laboratory on the initial confirmation form, along with identification of the specific analytes for which 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 which 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 which the laboratory conducts determinations.

To continue participation for CDU and/or B2MU analyses, 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 which satisfies these requirements (or which can provide documentation of accreditation/participation in an equivalent program).

The performance requirement for CDB analysis is defined as an analytical result within ±1µg/l blood or 15% of the consensus mean (whichever is greater). For samples

exhibiting a consensus mean less than 1 µg/l, the performance requirement is defined as a concentration between the detection limit of the analysis and a maximum of 2 µg/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 µg/l.

The performance requirement for CDU analysis is defined as an analytical result within ±1µg/l urine or 15% of the consensus mean (whichever is greater). For samples exhibiting a consensus mean less than 1 µg/l urine, the performance requirement is defined as a concentration between the detection limit of the analysis and a maximum of 2 µg/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 µg/g CRTU.

The performance requirement for B2MU is defined as analytical results within ±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 µg/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 which 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 which 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 which 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, which 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 ±1 µg/l or 15% of the consensus mean (whichever is greater). For samples exhibiting a consensus mean less than 1 µg/l, the performance requirement is defined as a concentration between the detection limit of the analysis and a maximum of 2 µg/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 µg/l.

The performance requirement for CDU analysis is defined as an analytical result within ±1 µg/l urine or 15% of the consensus mean (whichever is greater). For samples exhibiting a consensus mean less than 1 µg/l urine, the performance requirement is defined as a concentration that falls between the detection limit of the analysis and a maximum of 2 µg/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 (i.e., compliance samples), 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 µg/g CRTU.

The performance requirement for B2MU is defined as an analytical result within ± 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 two sets of results should be combined to provide a measure of B2MU in units of µg/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 which 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 which determinations are to be made.

Reevaluation of these laboratories is discretionary on the part of the responsible physician. Reevaluation, which normally takes about 6 months, may be expected 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 which 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 which 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 which 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 nonmandatory 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 which 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 ±15% of its theoretical value. If a standard is more than ±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, which 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 two 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 which 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 which 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$\bar{S}$ from the laboratory mean recovery), or on proficiency testing limits (e.g., ±1 µg or 15% of the mean, whichever is greater).

Statistical limits that exceed ±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 which 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 µg 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 Bl CBM–1 at 5.37 µg Cd/l, and Bl CBM–2 at 12.38 µg 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 µg/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 verses 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 which 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 which 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.
4 Analytical Data Report	For all reports of data results	Results of the 100 most recent QC samples incorporated into regular runs for each instrument. Date the sample was received. Date the sample was analyzed. Appropriate chain-of-custody information. Types of analyses performed. Results of the requested analyses. 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 $\bar{X}\pm2\hat{\sigma}$ (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, σ, for these measurements is derived using the following equation (note that 2σ is twice this value):

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

The accompanying 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 which 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 this 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, $(1/N)\Sigma T_i$, with T_i being a consensus mean for the sample;
3. Mean of the measurements, $(1/N)\Sigma M_i$, with M_i being a sample measurement;
4. A measure of error defined by:

$$(1/N)\sum\left(T_i - M_i\right)^2$$

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 $X\pm2\hat{\sigma}$, with X being the measured value and $2\hat{\sigma}$ the standard deviation calculated as described above.

For CDU or B2MU results, which 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:

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

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 anticoagulant; and, styrofoam vacutainer shipping containers.

Whole blood samples are taken by venipuncture. Each bluecapped 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 µl 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°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 which 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 which 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 which absorption is estimated at 4–7% (Kowai et al. 1979). An additional nonoccupational 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 which 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 which 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 1968).

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 coexposure 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), retinolbinding 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 (Friberg 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 which 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 μg-years/m³ 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 proteinurial, chronic nephrotoxicity may occur (Meridian Research, Inc. 1989; Roth Associates, Inc. 1989). Uremia, which 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 which 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 unchallenged 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, nonexposed 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, which 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 2σ 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 which 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, exhit 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 which the repeated measurements of the same sample vary within that laboratory. The accuracy of the data provides an indication of the extent to which those 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 which 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 which 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 which 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 unexposed 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 techniques most suitable for medical monitoring for cadmium is atomic absorption spectroscopy (AAS).

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).	0.05	Urine	Pruszkowska et al. (1983).	Methods of choice for routine cadmium analyses.
	≥ 0.20	Blood	Stoeppler and Brandt (1980).	
Inductively-Coupled Argon-Plasma Atomic Emission Spectroscopy (ICAP AES).	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	Stoeppler and Brandt (1980).	Suitable for absolute determination of cadmium in reference materials; efficient method to check accuracy of analytical method.

To obtain a measurement using AAS, a light source (i.e., hollow cathode or lectrode-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 monochrometer 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.

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, which 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 (which 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 quants of emitted light passing through a monochrometer 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 which 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, which 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 Bievre 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 diphenylthiocarbazone 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 forcadmium 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 which 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 which 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 bloodborne 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 which the method was developed.

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

The APHA (1988) reports a range of 1.0–25 µg/l, with a CV of 7.3% (concentration not stated). Insufficient documentation was available to critique this method.

Stoeppler 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 which 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 16 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 ± 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: ± 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 which 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± (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± (0.05X+0.2 for a concentration range of 0.3–5.0 µg 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 µg/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 ± 10% of the true value at CDB concentrations ≥ 5.0 µg/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.

TABLE 4.—BLOOD CADMIUM CONCENTRATIONS OF U.S. POPULATION NOT OCCUPATIONALLY EXPOSED TO CADMIUM[a]

Study No.	Number in study (n)	Sex	Age	Smoking habits[b]	Arithmetic mean (±S.D.)[c]	Absolute range or (95% CI)[d]	Geometric mean (±GSD)[e]	Lower 95th percentile of distribution[f]	Upper 95th percentile of distribution[f]	Reference
1	80	M	4–69	NS, S	1.13	0.35–3.3	0.96±1.71	0.4	2.4	Kowal et al. (1979).
	88	F	4–69	NS, S	1.03	0.21–3.3	0.91±1.63	0.4	2.0	
	115	M/F	4–69	NS	0.95	0.21–3.3	0.85±1.59	0.4	1.8	
	31	M/F	4–69	S	1.54	0.4–3.3	1.37±1.65	0.6	3.2	
2	10	M	Adults	7	2.0±2.1	(0.5–5.0)		[g](0)	[g](5.8)	Ellis et al. (1983).
3	24	M	Adults	NS			0.6±1/87	0.2	1.8	Friberg and Vahter (1983).
	20	M	Adults	S			1.2±2.13	0.3	4.4	
	64	F	Adults	NS			0.5±1.85	0.2	1.4	
	39	F	Adults	S			0.8±2.22)	0.2	3.1	
4	32	M	Adults	S, NS			1.2±2.0	0.4	3.9	Thun et al. (1989).
5	35	M	Adults	?	2.1±2.1	(0.5–7.3)		[g](0)	[g](5.6)	Mueller et al. (1989).

a—Concentrations reported n µg Cd/l blood unless otherwise stated
b—NS never smoked; S-current cigarette smoker
c—S.D.—Arithmetic Standard Deviation
d—C.I.—Confidence Interval
e—GSD—Geometric Standard Deviation
f—Based on an assumed lognormal distribution
g—Based on an assumed normal distribution

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 µg/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 µg/l.

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

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 in which a mean and corresponding standard deviation were reported.

TABLE 5—BLOOD CADMIUM IN WORKERS EXPOSED TO CADMIUM IN THE WORK PLACE

[Concentrations of Cadmium in Blood[a]]

Study number	Work environment (worker population monitored)	Number in study	Employment in years (mean)	Mean concentration of cadmium in air (µg/mg³)	Arithmetic mean (±S.D.)[b]	Absolute range or (95% C.I.)[c]	Geometric mean (±GSD)[d]	Lower 95th percentile of range[e] ([f]	Upper 95th percentile of range[e] P ([f]	Reference
1	Ni-Cd Battery Plant and Cd Production.		3–40	≥90						Lauwerys et al.
	Plant	98			21.4±1.9			(18)	(25)	1976.
	(Workers without Kidney Lesions).	25			38.8±3.8			(32)	(45)	
	(Workers with Kidney Lesions).									
2	Ni-Cd Battery Plant									Adamsson et al.
	(Smokers)	7	(5)	10.1	22.7	7.3–67.2				(1979).
	(Nonsmokers)	8	(9)	7.0	7.0	4.9–10.5				

TABLE 5—BLOOD CADMIUM IN WORKERS EXPOSED TO CADMIUM IN THE WORK PLACE—Continued

[Concentrations of Cadmium in Blood[a]]

Study number	Work environment (worker population monitored)	Number in study	Employment in years (mean)	Mean concentration of cadmium in air (μg/mg³)	Arithmetic mean (±S.D.)[b]	Absolute range or (95% C.I.)[c]	Geometric mean (±GSD)[d]	Lower 95th percentile of range[e] ( )[f]	Upper 95th percentile of range[e] P ( )[f]	Reference
3	Cadmium Alloy Plant.									Sukuri et al. 198.
	(High Exposure Group).	7	(10.6)	[1,000– ..	20.8±7.1			(7.3)	(34)	
	(Low Exposure Group).	9	(7.3)	5 yrs; 40–5 yrs].	7.1±1.1			(5.1	(9.1)	
4	Retrospective Study of Workers with Renal Problems.	19	15–41							Roels et al. 1982.
	(Before Removal).		(27.2)		39.9±3.7	11–179		(34)	(46)	
	(After Removal) .		(4.2)[g]		14.1±5.6	5.7–27.4		(4.4)	(24)	
5	Cadmium Production Plant.									Ellis et al. 1983.
	(Workers without Renal Dysfunction).	33	1–34		15±5.7	7–31		(5.4)	(25)	
	(Workers with Renal Dysfunction).	18	10–34		24±8.5	10–34		(9.3)	(39)	
6	Cd-Cu Alloy Plant .	75	Up to 39 ..				8.8±1.1	7.5	10	Mason et al. 1988.
7	Cadmium Recovery Operation.	45	(19.0)				7.9±2.0	2.5	25	Thun et al. 1989.
	(Current [19] and Former [26] Workers.									
8	Cadmium Recovery Operation.	40			10.2±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] GDS—Geometric Standard Deviation
[e] Based on an assumed lognormal distribution
[f] Based on an assumed normal distribution
[g] Years following removal.

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 which includes former workers in the sample group tested), the lower 95th percentile for CDB levels among exposed workers are greater than 5 μg/l, which 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 which significant work place exposure to cadmium may be occurring.

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 (HNO_3 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 80% 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 nonmandatory 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., µg Cd/l urine), "corrected" concentrations of cadmium per volume of urine at a standard specific gravity (i.e., µg Cd/l urine at a specific gravity of 1.020), or "corrected" mass concentration per unit mass of creatinine (i.e., µg 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 nmoles of cadmium=10 µg.)

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 (µg/g CTRU).

Reporting CDU as µg/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 µg 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 (1957) 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 nonexposed 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 HNO_3, to achieve accurate low-level determinations of CDU.

In the method described by Pruszkowska et al. (1983), which has become the preferred method for CDU analysis, urine samples were diluted at a ratio of 1:5 with water; diammonium hydrogenphosphate in dilute HNO_3 was used as a matrix modifier. The matrix modifier allows for a higher charring temperature without loss of cadmium through volatilization during prestomization. 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 which 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 which 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 which 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 µ/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 which 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, which 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 which only 60% of the laboratories reported acceptable results. For each of the last 15 samples, approximately 50% 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 1985).

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 lognormally 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 (1986) 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 SEX [1]

	Geometric means (and geometric standard deviations)		
	Unadjusted (µg/l)	SG-adjusted [2] µg/l at 1.020)	Creatine-adjusted (µg/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	Unadjusted (µg/l) percent	SG-adjusted (µg/l at 1.020) percent	Creatine-adjusted (µg/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
10.0–20.0	99.8	99.8	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 µ/g Cd/l urine (unadjusted), with a geometric standard deviation of 3.0. Normalized for creatinine, the geometric mean for the population is 0.66 µ/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 µ/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 which 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 µ/g CRTU, unless otherwise stated.

TABLE 8—URINE CADMIUM CONCENTRATIONS IN WORKERS EXPOSED TO CADMIUM IN THE WORKPLACE

Study number and work environment (worker population monitored)	Number in study (n)	Employment in years (mean)	Mean concentration of cadmium in air (μg/m³)	Concentration of cadmium in urine[a]					Reference
				Arithmetic mean (±S.D.)[b]	Absolute range or (95 percent C.I.)[c]	Geometric mean (±GSD)[d]	Lower 95th percentile of range[e] ( )	Upper 95th percentile of range[e] ( )	
1. Ni-Cd Battery Plant and Cd Production Plant.		3–40	≤30						Lauwerys et al. 1976.
(Workers without Kidney Lesions).	96			16.3±16.7			(0)	(44)	
(Workers with Kidney Lesions).	25			48.2±42.6			(0)	(120)	
2. Ni-Cd Battery Plant.									
(Smokers)	7	(5)	10.1	5.5	1.0–14.7				Adamsson et al. (1979).
(Non-smokers).	6	(9)	7.0	3.6	0.5–9.3				
3. Cadmium Salts Production Facility.	148	(15.4)		15.8	2–150				Botchet et al. 1990.
4. Retrospective Study of Workers with Renal Problems.	19	15–41							Roels et al. 1982.
(Before Removal).		(27.2)		39.4±28.1	10.8–117		(0)	(88)	
(After Removal).		(4.2)[g]		16.4±9.9	99–42.2		(1.9)	(32)	
5. Cadmium Production Plant.									Ellis et al. 1983.
(Workers without Renal Dysfunction).	33	1–36		9.4±6.9	2–27		(0)	(21)	
(Workers with Renal Dysfunction).	16	10–34		22.3±12.7	9–55		(1)	(45)	
6. Cd-Cu Alloy Plant.	75	Up to 39	Note [h].	6.9±9.4			(0)	(23)	Mason et al. 1988.
7. Cadmium Recovery Operation.	45	(19)	87	9.3±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±2.45	0.3	5	Kawada et al. 1990.

a—Concentrations are reported in ug/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

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 which 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, which are to be reported as an unadjusted µg 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 µg/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 µg/l (i.e., corresponding to a detection limit of 0.5 µg/g CRTU, assuming 1 g CRT/l urine) should be achievable. Pruszkowska et al. (1983) achieved a limit of detection of 0.04 µg/l for CDU based on the slope of the curve for their working standards (0.35 pg Cd/0.0044, A signal=1% absorbance using GF-AAS).

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 (which 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 (which 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 nonmandatory 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 nonmandatory program, and which 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 precipition rings are measured. The diameter of a ring is related to the concentration of the consutuent 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 which 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, which 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, nonexposed population falls between 60 and 300 µg/g CRTU. The upper 95th percentile of distributions, derived from studies in Table 9 which reported standard deviations, range between 180 and 1,140 µg 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 to what extent to which 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 B2MU 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 which 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 adaptation 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 B2MU 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 (which 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).

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 ng/g CRTU. B2MU values in the study by Thun et al. (1989), however, appear high in comparison to the other 3 studies.

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

Study No.	No. in study	Geometric mean	Geometric 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. 1988.
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[a]	320 µg/gr Cr[a]	Kowal 1983.
8	87	71 µg/g[f]		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[i]	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[a]	Falck et al. 1983.
14	35[n]	67				Roels et al. 1991.
15	31[d]	63				Roels et al. 1991.
16	36[d]	77[j]				Miksche et al. 1991.
17	18[n]	130				Kawada et al. 1989.
18	32[p]	122				Kawada et al. 1989.
19	18[d]	235	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 male.
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.

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.—B-2-MICROGLOBULIN CONCENTRATIONS OBSERVED IN URINE AMONG OCCUPATIONALLY-EXPOSED WORKERS

Study No.	N	Concentration of B-2-Microglobulin in urine				Reference
		Geometric mean (µg/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., 1969.

[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 (µg/gr Cr); for Roels, 1991, range = 31 – 35, 170 µgβ2/gr Cr and geometric mean = 63 among healthy workers; for Mason β_2 > 300 µg/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 µgβ2/gr Cr for first survey; second survey = 1,600; third survey = 2,600; fourth survey = 2,600; fifth survey = 2,600.

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.

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 is 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 ±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 µg Cd/g CRTU, while B2MU should be reported as µg 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 analysise 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 which 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 which 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 which 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 (±) 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, which 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 ± 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 µg/l, (the target value is 10 µg/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 which 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 which 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 σ. Thus, for the control limit for a pool, $\bar{X}$ is calculated as:

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

and σ 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 3 standard deviations ($\bar{X} \pm 3\sigma$).

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 which will mean repeating the running 20 quality control samples from each pool over 20 days.

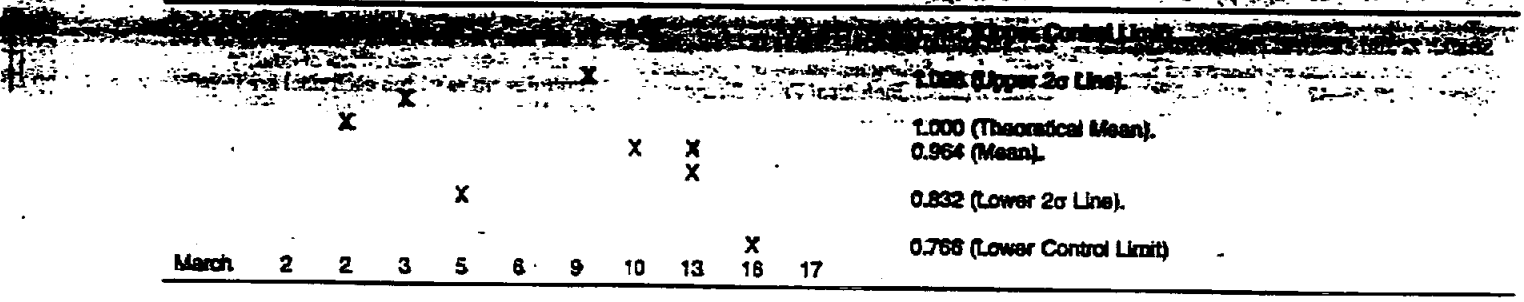
Internal Quality Control Analyses and Maintaining Control

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 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, which 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



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 two 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 µg 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

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

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 (JAFFE 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 spiked 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.

$$\text{Creatinine} + \text{Picrate} \xrightarrow{\text{NaOH}} \text{Red chromophore (absorbs at 510 nm)}$$

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 1910.1030).

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

FOR IN VITRO DIAGNOSTIC USE

MIXING & 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	60	3000	10	500

Storage of Unprocessed Packs: Store at 2–8°C. Do not freeze. Do not expose to temperatures above 35°C 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 Substances[3]

• 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][4] 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 endrogenous 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	5.0
Cephalexin	0.6–2.0	0.2–0.6	25	7.2
Cephamandole	1.3–2.5	0.3–0.5	25	4.9
Cephapirin	2.0	D0.4	25	5.6
Cephazolne	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 that 0.1 mg/dL [8.84 µmol/L] at CREA concentrations of:

Antibiotic	Peak serum level[a,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	710815901	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: 200 uL
- 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][a].
- Reference Material: Protein containing primary standards[f] or secondary calibrators such as Du Pont Elevated Chemistry Control (Cat. #790035903) and Normal Chemistry Control (Cat.e#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 Du Pont Representative.

g. If the Du Pont 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) ..... [Five (5)]	NA
Decimal Point.	0.0 mg/dL	000.0 mg/dL
Location	[000.0 µmol/L].	[000 µmol/L]
Assigned Slanting.	999.8	−1.000 E1
Point or Offset C_0.	[9823.]	[−8.840 E2]
Scale Factor or Assigned.	0.2000 ..... mg/dL/count[e]	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 Analyzerinstrument 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].

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	0.8–2.5 g/24 hr [53–221 mmol/24 hr]
Females	0.6–1.5 g/24 hr [53–133 mmol/24 hr]

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

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

Specific Performance Characteristics[j]

REPRODUCIBILITY[k]

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

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

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

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 which 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 clean-up. 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-methylglycocyamidine, 1-methylhydantoin-2-imide

Structure: see Figure #1

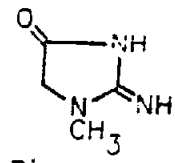


Figure #1

1.2. Advantages

1.2.1. This method offers a simple, straightforward, 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

STORAGE DATA—Continued

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
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.

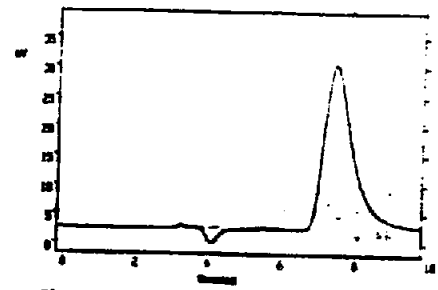
Detector: Dual wavelength UV: 229 nm (primary) 254 nm (secondary)

Flow rate: 0.7 mL/ minute

Retention time: 7.2 minutes

Sensitivity: 0.05 AUFS

Injection volume: 20µl



Chromatogram of a creatinine standard

Figure #2

3.6. Interferences

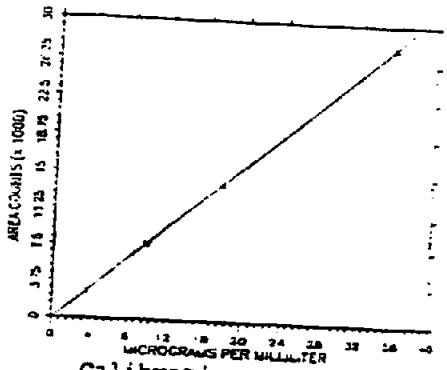
3.6.1. Any compound that has the same retention time as creatinine and absorbs at 229 nm is an interference.

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).



Calibration curve for creatinine
Figure #3

3.7.3. The ug/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:

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

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.

$$\mu g\ A/g\ creatinine = \frac{\mu g\ A/L\ (experimental)}{g/L\ creatinine}$$

Where A is the desired analyte. The protocol of reporting such normalized results is µg A/g creatinine.

3.8. Safety precautions See section 2.7.

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.

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Signed at Washington, DC, this 13th day of April, 1993.

David Zeiglar,

Acting Assistant Secretary of Labor.

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