

these methods are applied, a matched group of unexposed people has to be studied concurrently.

It is difficult to interpret cytogenetic changes, although several carcinogens induce chromosome damage. There is suggestive evidence that groups of people with chromosome damage may have an increased risk of cancer (97), and such a relationship is apparent after exposure to ionizing radiation. However, after exposure to chemicals, it is not known whether the persons who show the highest frequencies of chromosome aberrations, micronuclei, or sister-chromatid exchanges are at a higher risk than the average person. Even on a group basis, no quantitative estimate of the cancer risk can be made. Neither can the kind of cancer to be expected be predicted (ie, the validation of cytogenetic monitoring as far as the health outcome is concerned is still lacking). On the other hand, observed cytogenetic damage gives no clue of the type of chemical exposure, and cytogenetic changes cannot be assessed in quantitative exposure terms. Thus the only way of estimating the results of cytogenetic monitoring results is to compare the results observed in similar industries — and even such data are scant. At present, cytogenetic examinations are best suitable for ad hoc studies, rather than for routine monitoring programs.

Quality management

Many studies have shown that the quality of biological monitoring analyses is often mediocre (98—105). What is positive is that, in continuously running external quality assessment schemes, improved analytical quality has often been observed (13, 98—100, 106, 107). The other positive development is that several international quality assessment schemes are currently available, in addition to the schemes limited to blood lead, such as those of the United States Public Health Services (Centers for Disease Control), the State of New York Department of Health, the Commonwealth of Pennsylvania Department of Health, the College of American Pathologists, the United States Public Health Service (Health Care Financing Administration), the United States Occupational Safety and Health Administration, the Commission of the European Communities, and the Chinese Academy of Preventive Medicine (108, 109).

The German Society of Occupational Medicine has offered intercomparison programs for toxic chemicals in blood or serum since 1982. The program consists of one annual round, and the number of participants is approximately 90 (12, 99). In the rounds in 1991 and 1992, the program was expanded to include four chlorinated solvents in blood, six polychlorinated biphenyl isomers, and six other chlorinated environmental contaminants.

The Centre de Toxicologie du Québec has operated an interlaboratory comparison program for cad-

mium and lead in blood; aluminum, selenium, copper, and zinc in serum; and arsenic, fluoride, mercury, cadmium, and chromium in urine (106).

In Japan, an industrial health regulation obliges the employers to monitor biologically all workers exposed to lead, toluene, xylene, trichloroethylene, tetrachloroethylene, 1,1,1-trichloroethane, styrene, dimethylformamide, or n-hexane. Since 1980, the Japan Federation of Occupational Health Organization has conducted an annual quality assurance round among the laboratories performing such analyses. In 1991, 36 to 67 laboratories participated in 10 types of such analyses (lead in blood; free protoporphyrin in blood; aminolevulinic acid, hippuric acid, methylhippuric acid, total trichloro compounds, trichloroacetic acid, and mandelic acid in urine; monomethylformamide; and 2,5-hexanedione) (13, 100, 110).

The Occupational Medicine and Hygiene Laboratories of the Health and Safety Executive in the United Kingdom has run an external quality assurance scheme for the analysis of mercury in urine since 1983; the number of participating laboratories is 15—20 (111). As a part of this external quality assessment scheme, a program for the quality assurance of lead in blood was started in 1973. Currently, some 80 laboratories take part in these analyses, and about 40 laboratories participate in the blood cadmium analyses (98).

The Robens Institute of Health and Safety runs an external quality assurance scheme for copper, zinc, gold, aluminum, and selenium in serum; lead and cadmium in blood; and mercury and cadmium in urine. The number of participating laboratories is 20—110 for different elements (98, 107, 112).

The Finnish Institute of Occupational Health has arranged a quality assurance scheme for metabolites of organic solvents in urine. Currently, four sets of specimens are sent annually for the analysis of methylhippuric acids, hexanedione, trichloroacetic acid, mandelic acid, and phenol (102).

Thus, at present, an external quality assessment scheme is available for most important analytes. (Volatile solvents in blood and aluminum, nickel and speciated arsenic analysis in urine are still exceptions.) [Note added to proof: From 1994 on, the German quality assurance scheme also includes samples for the analysis of some volatile organic solvents in blood (K-H Schaller, personal communication).] Therefore, no laboratory should do biological monitoring without external quality assessment — and it is foreseeable that the analytical performance in biological monitoring will improve.

In the early 1980s, the Organisation for Economic Cooperation and Development (OECD) established principles of good laboratory practice in order to facilitate mutual acceptance of test data on the harmful effects of chemicals, and thus to limit unnecessary duplicate testing, with the aim of avoiding technical barriers to free international trade. The principles are concerned with the organizational process

and the conditions under which laboratory studies are planned, performed, monitored, recorded, and reported (113). These principles then developed into recommendations on quality systems (ie, organizational structure, responsibilities, procedures, processes, and resources for implementing quality management) that are generally applicable to laboratories doing analyses, chemical or other (114, 115). These recommendations were recently adapted for use in clinical chemistry laboratories (116), whose functions closely resemble those of biological monitoring laboratories. It is thus apparent that quality systems will be required from biological monitoring laboratories also. This requirement will probably assist in improving analytical performance by drawing the attention of personnel to quality. One should, however, be aware that the quality system is, in principle, a framework that guarantees only that the laboratory can achieve acceptable results, not that it does so. The actual achievement can only be attained through functioning quality assurance, in other words, a thorough investigation of the performance of every new analytical method and continuous follow-up of all methods through internal quality control and external quality assessment to ascertain that the adopted methods continuously perform in an acceptable way.

Analytical methods in biological monitoring

In biological monitoring, several different approaches and analytical methods may be selected that are widely different as to practicability and cost. Often, more accurate results are obtained when more expensive methodology and instrumentation are selected. Especially, the limit of detection is dependent on the cost involved. The selection of approach and methodology must be made according to the requirements of the user of the results, that is, occupational health care. The methods chosen must be accurate enough, but must not involve unnecessary detectability, accuracy, sophistication, or cost.

It is thus apparent that while, for example, flameless atomic absorption spectrometry and gas and liquid chromatographic methods are the mainstream in biological monitoring, there is still space for colorimetric methods where levels of exposure is high.

On the other hand, it is likely that mass spectrometric analysis, combined with gas and liquid chromatographic separation, will gain further use in biological monitoring. There are also indications that, as in clinical pharmacology — which in scope is very similar to biological monitoring — immunologic methods will become routine in biological monitoring. Immunologic methods have already been published for the analysis of cotinine, some pesticides, and even mercury (68, 117—119).

Acknowledgments

I wish to thank Professor V Riihimäki for his interesting and useful discussions on biological monitoring during the last few years and during the preparation of this manuscript.

References

1. Berlin A, Yodaiken RE, Henman BA, editors. Assessment of toxic agents at the workplace: roles of ambient and biological monitoring. The Hague: Nijhoff Publishers, 1984.
2. Leake JP, et al. The use of tetraethyl lead gasoline in its relation to public health. US Public Health Bull 1926;163. (Cited in: Kehoe RA, Thamann F, Cholak J. Lead absorption and excretion in certain trades. J Ind Hyg 1933;15:306—19.)
3. Badham C, Taylor HB. Lead poisoning. Report of Director General of Public Health, New South Wales, for year 1925. 1927; studies in industrial hygiene no 7. (Cited in: Kehoe RA, Thamann F, Cholak J. Lead absorption and excretion in certain trades. J Ind Hyg 1933;15:306—19.)
4. Litzner ST, Weyrauch F. Untersuchungen über den Bleigehalt des Blutes und Harns, seine Beziehungen zum Auftreten klinischer Krankheitserscheinungen sowie seine diagnostische Bedeutung. Arch Gewerbepath Gewerbehyg 1932;4:74—100.
5. Kehoe RA, Thamann F, Cholak J. Lead absorption and excretion in certain trades. J Ind Hyg 1933;15:306—19.
6. Lauwerys RR, Hoet P. Industrial chemical exposure: guidelines for biological monitoring. 2nd ed. Boca Raton, Ann Arbor, London, Tokyo: Lewis Publishers, 1993.
7. Council of the European Communities. Council directive of 27 November 1980 on the protection of workers from the risks related to exposure to chemical, physical and biological agents at work (80/1107/EEC). Off J Eur Communities 1980;L327:8—13.
8. Spee T. Loodbesluit in werking getreden. Arbvisie 1989;5:1—3.
9. American Conference of Governmental Industrial Hygienists (ACGIH). 1992—1993 threshold limit values for chemical substances and physical agents and biological exposure indices. Cincinnati, OH: ACGIH, 1992.
10. Health and Safety Executive OM and HL. Guidance on laboratory techniques in occupational medicine. 5th ed. London: Health and Safety Executive, 1991.
11. Deutsche Forschungsgemeinschaft (DFG). MAK- und BAT-Werte-Liste 1992. Senatskommission zur Prüfung gesundheitsschädlicher Arbeitsstoffe. 28th ed. Weinheim: VCH Verlagsgesellschaft mbH, 1992.
12. Schaller KH, Angerer J, Lehnert G. First results of two external intercomparison programmes for the determination of organochlorine compounds in blood specimens relevant in environmental and occupational medicine. Fresenius J Anal Chem 1993;346:830—2.
13. Sakurai H. Quality assurance of biological monitoring in view of risk management. Int Arch Occup Environ Health 1993;65:S77—82.
14. Council of the European Communities. Council directive of 29 July 1982 on the protection of workers from the risks related to exposure to metallic lead and its ionic compounds at work (82/605/EEC). Off J Eur Communities 1982;247:12—21.
15. Valtioneuvosto. No 356: valtioneuvoston päätös lyijyn käytöstä johtuvien haittavaikutusten torjunnasta

- ja valvonnasta. Annettu Helsingissä 14. päivänä toukokuuta 1982 [No 356: Council of State resolution for the prevention and control of harmful effects induced by exposure to use of lead. Issued in Helsinki on May 14, 1982]. Helsinki: Suomen Säädoskok, 1982.
16. Valtioneuvosto. No 920: valtioneuvoston päätös työntekijöiden suojelemisesta kemiallisille tekijöille altistumiseen liittyviltä vaaroilta. Annettu Helsingissä 8. päivänä lokakuuta 1992 [No 920: Council of State resolution for the protection of workers against hazards caused by exposure to chemicals. Issued in Helsinki on October 8, 1992]. Helsinki: Suomen Säädoskok, 1992:2399—404.
17. Aitio A, Riihimäki V, Järvisalo J, Liesivuori J, Hernberg S. Biological monitoring. In: Zenz C, editor. Occupational medicine. 3rd ed. Saint Louis, MO: Mosby Year Book, Inc. In press.
18. Solberg HE. Approved recommendation (1987) on the theory of reference values part V: statistical treatment of collected reference values: determination of reference limits. *J Clin Chem Clin Biochem* 1987; 25:645—56.
19. Vahter M, Slorach S, editors. Exposure monitoring of lead and cadmium: an international pilot study within the WHO/UNEP human exposure assessment location (HEAL) program. Nairobi (Kenya): Global Environment Monitoring System, World Health Organization, United Nations Environmental Program, 1990.
20. International Program on Chemical Safety. Cadmium. Geneva: World Health Organization, 1992. Environmental health criteria 134.
21. Schütz A, Attewell R, Skerfving S. Decreasing blood lead in Swedish children, 1978—1988. *Arch Environ Health* 1989;44:391—4.
22. Heinzow B, Jessen H, Mohr S, Riemer D. Heavy metals in the general population: trend evaluation and interrelation with trace elements. In: Aitio A, Aro A, Järvisalo J, Vainio H, editors. Trace elements in health and disease. Cambridge (United Kingdom): The Royal Society of Chemistry, 1991:75—81.
23. Grobler SR, Maresky LS, Kotze TJvW. Lead reduction of petrol and blood lead concentrations of athletes. *Arch Environ Health* 1992;47:139—42.
24. Hinton D, Coope PA, Malpess WA, Janus ED. Trends in blood lead levels in Christchurch (NZ) and environs 1978—1985. *J Epidemiol Community Health* 1986;40:244—8.
25. Pekari K, Vainiotalo S, Heikkilä P, Palotie A, Luotamo M, Riihimäki V. Biological monitoring of occupational exposure to low levels of benzene. *Scand J Work Environ Health* 1992;18:317—22.
26. Minoia C, Sabbioni E, Apostoli P, Pietra R, Pozzoli L, Gallorini M, et al. Trace element reference values in tissues from inhabitants of the European Community I: a study of 46 elements in urine, blood and serum of Italian subjects. *Sci Total Environ* 1990;95: 89—105.
27. Nordberg G, Brune D, Gerhardsson L, Grandjean P, Vesterberg O, Wester PO. The ICOH and IUPAC international program for establishing reference values of metals. *Sci Total Environ* 1992;120:17—21.
28. Sabbioni E, Minoia C, Pietra R, Fortaner S, Gallorini M. Trace element reference values in tissues from inhabitants of the European Community II: examples of strategy adopted and trace element analysis of blood, lymph nodes and cerebrospinal fluid of Italian subjects. *Sci Total Environ* 1992;120:39—62.
29. World Health Organization (WHO). Guidelines on biological monitoring of chemical exposure in the workplace. Geneva: WHO. In press.
30. Roels H, Bernard AM, Cárdenas A, Buchet JP, Lawwerys RR, Hotter G, et al. Markers of early renal changes induced by industrial pollutants: III application to workers exposed to cadmium. *Br J Ind Med* 1993;50:37—48.
31. International Agency for Research on Cancer (IARC). Cadmium and cadmium compounds. In: IARC. Some metals and metal compounds, and occupational exposures in the glass industry. Lyon: IARC. In press. IARC monographs on the evaluation of carcinogenic risks to humans, vol 58.
32. Pekari K, Nylander-French L, Pfaffli P, Sorsa M, Aitio A. Biological monitoring of exposure to styrene — assessment of different approaches. *J Occup Med Toxicol* 1993;2:115—26.
33. Sunderman FW Jr, Aitio A, Morgan LG, Norseth T. Biological monitoring of nickel. *Toxicol Ind Health* 1986;2:17—78.
34. Hartung M, Schaller K-H, Kentner M, Weltle D, Valentin H. Untersuchungen zur cobalt-Belastung in verschiedenen Gewerbezeigen. *Arbeitsmed Sozialmed Praeventivmed* 1983;18:73.
35. Aitio A, Järvisalo J, Kiilunen M, Kalliomäki P-L, Kalliomäki K. Chromium. In: Clarkson TW, Friberg L, Nordberg GF, Sager PR, editors. Biological monitoring of toxic metals. New York, London: Plenum Publishing Corporation, 1988:369—82.
36. Aitio A, Kiilunen M, Kivistö H, Luotamo M, Pekari K, Valkonen S, editors. Kemikaalialtistumisen biologinen monitorointi: näytteenotto-ohjeet [Biological monitoring of exposure to chemicals: guideline for sample collection]. 2nd ed. Helsinki: Työterveyslaitos, 1993.
37. International Program on Chemical Safety. Environmental health criteria for biomarkers and risk assessment: concepts and principles. Geneva: World Health Organization. In press.
38. Angerer J, Amin W, Heinrich-Ramm R, Szadkowski D, Lehnert G. Occupational chronic exposure to metals I: chromium exposure of stainless steel welders — biological monitoring. *Int Arch Occup Environ Health* 1987;59:503—12.
39. Kiilunen M, Palotie A, Aitio A. Chromium in whole blood, serum and blood cells of workers exposed to different chromium compounds [abstract]. In: International conference on lead, chromium and thallium: toxicity, environmental and health impact, regulation, Milan, Italy 7—9 April 1986. Milan: National Research Council of Italy, 1986:24.
40. Ehrenberg L. Covalent binding of genotoxic agents to proteins and nucleic acids. In: Berlin A, Draper M, Hemminki K, Vainio H, editors. Monitoring human exposure to carcinogenic and mutagenic agents, vol 59. Lyon: International Agency for Research on Cancer, 1984:247—58.
41. Hemminki K. Significance of DNA and protein adducts. In: Vainio H, Magee P, McGregor D, McMichael AJ, editors. Mechanisms of carcinogenesis in risk identification. Lyon: International Agency for Research on Cancer; 1992:525—34. IARC scientific publication, vol 116.
42. Perera F, Brenner D, Jeffrey A, Mayer J, Tang D, Warburton D, et al. DNA adducts and related biomarkers in populations exposed to environmental carcinogens. *Environ Health Perspect* 1992;98:133—7.
43. Neumann H-G, Birner G, Kowallik P, Schütze D, Zwirner-Baier I. Hemoglobin adducts of N-substituted aryl compounds in exposure control and risk assessment. *Environ Health Perspect* 1993;99:65—9.
44. Kriek E, Van Schooten FJ, Hillebrand MJX, Van Leeuwen FE, Den Engelse L, De Looft AJA, et al. DNA adducts as a measure of lung cancer in humans exposed to polycyclic aromatic hydrocarbons. *Environ Health Perspect* 1993;99:71—5.
45. Mumford JL, Lee X, Lewtas J, Young TL, Santella RM. DNA adducts as biomarkers for assessing ex-

- posure to polycyclic aromatic hydrocarbons in tissues from Xyan Wei women with high exposure to coal combustion emissions and high lung cancer mortality. *Environ Health Perspect* 1993;99:83—7.
46. Pergal M, Vukovic N, Cirin-Popov N, Djuric D, Bojovic T. Carbon disulfide metabolites excreted in the urine of exposed workers: 1. isolation and identification of 2-mercapto-2-thiazolinone-5. *Arch Environ Health* 1972;25:38—41.
47. Pergal M, Vukovic N, Djuric D. Carbon disulfide metabolites excreted in the urine of exposed workers: 2. isolation and identification of thiocarbamide. *Arch Environ Health* 1972;25:42—4.
48. Aringer L, Lidums V. Influence of diet and other factors on urinary levels of thioethers. *Int Arch Occup Environ Health* 1988;61:123—30.
49. Aringer L, Löf A, Elinder C-G. The applicability of the measurement of urinary thioethers: a study of humans exposed to styrene during diet standardization. *Int Arch Occup Environ Health* 1991;63:341—6.
50. Jongeneelen FJ, Dirven HAAM, Leijdekkers C-M, Henderson PT. S-Phenyl-N-acetylcysteine in urine of rats and workers after exposure to benzene. *J Anal Toxicol* 1987;11:100—4.
51. Vansittert NJ, Boogaard PJ, Beulink GDJ. Application of the urinary s-phenylmercapturic acid test as a biomarker for low levels of exposure to benzene in industry. *Br J Ind Med* 1993;50(5):460—9.
52. Vainio H, Sorsa M, Falck K. Bacterial urinary assay in monitoring exposure to mutagens and carcinogens. In: Berlin A, Draper M, Hemminki K, Vainio H, editors. *Monitoring human exposure to carcinogenic and mutagenic agents*, vol 59. Lyon: International Agency for Research on Cancer, 1984:247—58.
53. Clonfero E, Jongeneelen F, Zordan M, Levis AG. Biological monitoring of human exposure to coal tar: urinary mutagenicity assays and analytical determination of polycyclic aromatic hydrocarbon metabolites in urine. In: Vainio H, Sorsa M, McMichael AJ, editors. *Complex mixtures and cancer risk*. Lyon: International Agency for Research on Cancer, 1990: 215—22. IARC scientific publications, vol 104.
54. Zhao Z-H, Quan W-I, Tian D-H. Urinary 1-hydroxypyrene as an indicator of human exposure to ambient polycyclic aromatic hydrocarbons in a coal-burning environment. *Sci Total Environ* 1990;92:145—54.
55. Sherson D, Sabro P, Sigsgaard T, Jonansen F, Astrup H. Biological monitoring of foundry workers exposed to polycyclic aromatic hydrocarbons. *Br J Ind Med* 1990;47:448—53.
56. Buchet JP, Gennart JP, Mercado-Calderon F, Delavignette JP, Cupers L, Lauwerys R. Evaluation of exposure to polycyclic aromatic hydrocarbons in a coke production and a graphite electrode manufacturing plant: assessment of urinary excretion of 1-hydroxypyrene as a biological indicator of exposure. *Br J Ind Med* 1992;49:761—8.
57. Buckley TJ, Liroy PJ. An examination of the time course from human dietary exposure to polycyclic aromatic hydrocarbons to urinary elimination of 1-hydroxypyrene. *Br J Ind Med* 1992;49:113—24.
58. Burgaz S, Borm PJA, Jongeneelen FJ. Evaluation of urinary excretion of 1-hydroxypyrene and thioethers in workers exposed to bitumen fumes. *Int Arch Occup Environ Health* 1992;63:397—401.
59. Jongeneelen FJ. Biological exposure limit for occupational exposure to coal tar pitch volatiles at coke ovens. *Int Arch Occup Environ Health* 1992;63: 511—6.
60. Jongeneelen FJ, van Leeuwen FE, Oosterink S, Anzion RBM, van der Loop F, Bos RP, et al. Ambient and biological monitoring of cokeoven workers: determinants of the internal dose of polycyclic aromatic hydrocarbons. *Br J Ind Med* 1990; 47:454—61.
61. Dell'Omo M, Lauwerys RR. Adducts to macromolecules in the biological monitoring of workers exposed to polycyclic aromatic hydrocarbons. *Crit Rev Toxicol* 1993;23(2):111—26.
62. Van Hummelen P, Gennart JP, Buchet JP, Lauwerys R, Kirsch-Volders M. Biological markers in PAH exposed workers and controls. *Mutat Res* 1993;300(3—4):231—9.
63. Grimmer G, Dettbarn G, Jacob J. Biomonitoring of polycyclic aromatic hydrocarbons in highly exposed coke plant workers by measurement of urinary phenanthrene and pyrene metabolites (phenols and dihydrodiols). *Int Arch Occup Environ Health* 1993; 65(3):189—99.
64. Waage H, Silsand T, Urdal P, Langård S. Discrimination of smoking status by thiocyanate and cotinine in serum, and carbon monoxide in expired air. *Int J Epidemiol* 1992;21:488—93.
65. Pré J, Vassy R. Urinary thiocyanate: creatinine ratio as a reliable indicator of cigarette smoking. *Clin Chim Acta* 1991;204:87—94.
66. Ehrlich R, Kattan M, Godbold J, Saltzberg DS, Grimm KT, Landrigan PJ, et al. Childhood asthma and passive smoking: urinary cotinine as a biomarker of exposure. *Am Rev Respir Dis* 1992; 145: 594—9.
67. Coultas DB, Stidley CA, Samet JM. Cigarette yields of tar and nicotine and markers of exposure to tobacco smoke. *Am Rev Respir Dis* 1993;148(2):435—40.
68. Miwa K, Miyagi Y, Asanoi H, Fujita M, Sasayama S. Augmentation of smoking cessation education by urinary cotinine measurement. *Jpn Circ J* 1993;57(8): 775—80.
69. Lerman C, Orleans CT, Engstrom PF. Biological markers in smoking cessation treatment. *Semin Oncol* 1993;20(4):359—67.
70. Murray RP, Connett JE, Lauger GG, Voelker HT. Error in smoking measures — effects of intervention on relations of cotinine and carbon monoxide to self-reported smoking. *Am J Public Health* 1993;83(9): 1251—7.
71. Franklin DM, Guthrie CJ, Chettle DR, Scott MC, Mason HJ, Davison AG, et al. In vivo neutron activation analysis of organ cadmium burdens: referent levels in liver and kidney and the impact of smoking. *Biol Trace Elem Res* 1990;26—27:401—6.
72. Armstrong R, Chettle DR, Scott MC, Blindt M, Mason HJ. Longitudinal studies of exposure to cadmium. *Br J Ind Med* 1992;49:556—9.
73. Erkkilä J, Armstrong R, Riihimäki V, Chettle DR, Paakkari A, Scott M, et al. In vivo measurements of lead in bone at four anatomical sites: long term occupational and consequent endogenous exposure. *Br J Ind Med* 1992;49:631—44.
74. Wielopolski L, Rosen JF, Slatkin DN, et al. In vivo measurement of cortical bone lead using polarized x rays. *Med Physics* 1989;16:521—8.
75. Gerhardsson R, Attewell R, Chettle DR, Englyst V, Lundström NG, Nordberg GF, et al. In vivo measurements of lead in bone in long-term exposed lead smelter workers. *Arch Environ Health* 1993;48: 147—56.
76. Chung C. In vivo partial body activation analysis using filtered neutron beam. *Int J Rad Appl Instrum A* 1988;39:P93—6.
77. Mattson S, Alpsten M, Borjesson J, Jonson R, Larsson L, Tolli J. Experiences in the field of elemental analysis in vivo. *Radiobiol Radiother* 1990;31:203—7.
78. Green S, Chettle DR. A feasibility study of the in vivo measurement of aluminium in peripheral bone. *Physics Med Biol* 1992;37:2287—96.

79. Guyader D, Gandon Y, Robert JY, Heautot JF, Jouanolle H, Jacquelinet C, et al. Magnetic resonance imaging and assessment of liver iron content in genetic hemochromatosis. *J Hepatol* 1992;15: 304—8.
80. Kacpersek A, Ryde SJ, Evans CJ, Dutton J, Morgan WD, Sivyer A. The measurement of silicon in a lung phantom — a comparison of two nuclear reactions for in vivo activation analysis. *Physics Med Biol* 1993;38:689—98.
81. International Program on Chemical Safety. Carbon monoxide. Geneva: World Health Organization; 1979. Environmental health criteria 13.
82. Nutley B, Cocker J. Biological monitoring of workers occupationally exposed to organophosphorus pesticides. *Pestic Sci* 1993;38:315—22.
83. Grandjean P, Jensen BM, Sando SH, Jogensen PJ, Antonsen S. Delayed blood regeneration in lead exposure: an effect on reserve capacity. *Am J Public Health* 1989;79(10):1385—8.
84. Cárdenas A, Roels H, Bernard A, Barbon R, Buchet JP, Lauwerys RR, et al. Markers of early renal changes induced by industrial pollutants: I. application to workers exposed to mercury vapour. *Br J Ind Med* 1993;50:17—27.
85. Cárdenas A, Roels H, Bernard A, Barbon R, Buchet JP, Lauwerys RR, et al. Markers of early renal changes induced by industrial pollutants: II. application to workers exposed to lead. *Br J Ind Med* 1993;50:28—36.
86. Järup L, Persson B, Edling C, Elinder CG. Renal function impairment in workers previously exposed to cadmium. *Nephron* 1993;64(1):75—81.
87. Kido T, Nogawa K, Ohmichi M, Honda R, Tsuritani I, Yamada Y. Significance of urinary cadmium concentration in a Japanese population environmentally exposed to cadmium. *Arch Environ Health* 1992;47:196—202.
88. Iwata K, Saito H, Nakano A. Association between cadmium-induced renal dysfunction and mortality: further evidence. *Tohoku J Exp Med* 1991;164:319—30.
89. Roels HA, Lauwerys RR, Bernard AM, Buchet JP, Vos A, Oversteyns M. Assessment of the filtration reserve capacity of the kidney in workers exposed to cadmium. *Br J Ind Med* 1991;48:365—74.
90. Iwata K, Saito H, Moriyama M, Nakano A. Follow up study of renal dysfunction and mortality in residents of an area polluted with cadmium. *Br J Ind Med* 1992;49:736—7.
91. Ellekilde G, von Eyben FE, Holm J, Hemmingsen L. Above-normal urinary excretion of albumin and retinol-binding protein in patients with acute myocardial infarction. *Clin Chem* 1993;39:2350—1.
92. Ellekilde G, von Eyben FE, Holm J, Hemmingsen L. Above-normal urinary excretion of retinol-binding protein and albumin in Albustix-negative hypertensive patients. *Clin Chem* 1991;37:1446—7.
93. Ellekilde G, Holm J, von Eyben FE, Hemmingsen L. Above-normal urinary excretion of retinol-binding protein and albumin in chronic heart failure. *Clin Chem* 1992;38:593—4.
94. Holm J, Hemmingsen L, Vesti NV, Thomsen M. Increased urinary excretion of the retinol-binding protein in insulin-dependent diabetes mellitus in the absence of microalbuminuria. *Clin Chim Acta* 1987;170:345—50.
95. Forni A. Chromosomal aberrations in monitoring exposure to mutagens-carcinogens. In: Berlin A, Draper M, Hemminki K, Vainio H, editors. Monitoring human exposure to carcinogenic and mutagenic agents, vol 59. Lyon: International Agency for Research on Cancer, 1984:247—58.
96. Sorsa M. Monitoring of sister chromatid exchange and micronuclei as biological endpoints. In: Berlin A, Draper M, Hemminki K, Vainio H, editors. Monitoring human exposure to carcinogenic and mutagenic agents, vol 59. Lyon: International Agency for Research on Cancer, 1984:247—58.
97. Sorsa M, Wilbourn J, Vainio H. Human cytogenetic damage as a predictor of cancer risk. In: Vainio H, Magee P, McGregor D, McMichael AJ, editors. Mechanisms of carcinogenesis in risk identification. Lyon: International Agency for Research on Cancer; 1992:543—54. IARC scientific publication, vol 116.
98. Bullock DG, Smith NJ, Whitehead TP. External quality assessment of assays of lead in blood. *Clin Chem* 1986;32:1884—9.
99. Schaller K-H, Angerer J, Lehnert G. Internal and external quality control in the toxicological analysis of blood and urine samples in the Federal Republic of Germany. *Int Arch Occup Environ Health* 1991;62:537—42.
100. Sugita M, Harada A, Taniguchi M, Saito M, Imai-zumi K, Kitamura M, et al. Quality control program on biological monitoring by Japan Federation of Occupational Health Organizations. *Int Arch Occup Environ Health* 1991;62:569—77.
101. Morisi G, Patriarca M, Taggi F. Evaluation of the performance of Italian laboratories in the determination of cadmium levels in blood. *Ann Ist Super Sanità* 1989;25:449—56.
102. Valkonen S, Palotie A, Aitio A. A quality control program for biological monitoring of organic compounds in urine. In: Foá V, Emmett EA, Maroni M, Colombi A, editors. Occupational and environmental chemical hazards: cellular and biochemical indices for monitoring toxicity. Chichester (England): Ellis Horwood Limited, 1987:91—5.
103. Aitio A. Laboratory quality control: interim document 4. Copenhagen: World Health Organization, Regional Office for Europe; 1981. Health aspects of chemical safety.
104. Sunderman FWJ, Brown SS, Stoeppeler M, Tonks DB. Interlaboratory evaluations of nickel and cadmium analyses in body fluids. In: Egan H, West TS, editors. IUPAC collaborative interlaboratory studies in chemical analysis. Oxford, New York: Pergamon Press, 1982:25—35.
105. Anglov T, Holst E, Christensen JM. Danish external quality assessment scheme — an interlaboratory comparison study on lead, cadmium and chromium in lyophilized human blood concentrate. *Int Arch Occup Environ Health* 1993;64(6):431—8.
106. Weber J-P. An interlaboratory comparison program for several toxic substances in blood and urine. *Sci Total Environ* 1988;71:111—23.
107. Taylor A, Briggs RJ. An external quality assessment scheme for trace elements in biological fluids. *Anal Atomic Spectr* 1986;1:391—5.
108. Wu YQ, Tang XY, Li XL, Lu YF, Tang J. Quality assurance in the biological monitoring of lead exposure in China. *Int Arch Occup Environ Health* 1993;65(1):S231—4.
109. Parsons PJ. Monitoring human exposure to lead: an assessment of current laboratory performance for the determination of blood lead. *Environ Res* 1992;57:149—62.
110. Harada A. Quality control of analytical procedures used in biological monitoring in Japan. In: Fisero-va-Bergerova V, Ogata M, editors. Biological monitoring of exposure to industrial chemicals. Cincinnati, OH: American Conference of Governmental Industrial Hygienists, 1990:199—202.
111. Lewis PJ, Wright AL. Analysis of mercury in urine: operation of an external quality assurance scheme. *Ann Occup Hyg* 1988;32:83—93.
112. Taylor A, Starkey B, Walker AB. Determination of aluminum in serum: findings of an external quality

- assurance scheme. *Ann Clin Biochem* 1985;22:351—8.
113. Organisation for Economic Cooperation and Development. Decision of the Council concerning the mutual acceptance of data in the assessment of chemicals. Council decision adopted at its 535th meeting on 12th May 1981.
114. International Organization for Standardization (ISO). General requirements for the competence of calibration and testing laboratories. 3rd ed. Geneva: ISO, 1990. ISO guide 25.
115. CEN/CENELEC. General criteria for the operation of testing laboratories. Brussels: CEN/CENELEC The Joint European Standards Institution, 1989. European standard EN 45001.
116. Dybkaer R, Jordal R, Jørgensen PJ, Hansson P, Hjelm M, Kaihola HL, et al. A quality manual for the clinical laboratory including the elements of a quality system: proposed guidelines. *Scand J Clin Lab Invest* 1993;53 suppl 212:60—84.
117. Knopp D, Glass S. Biological monitoring of 2,4-dichlorophenoxyacetic acid-exposed workers in agriculture and forestry. *Int Arch Occup Environ Health* 1991;63:329—33.
118. Wylie DE, Carlson LD, Carlson R, Wagner FW, Schuster SM. Detection of mercuric ions in water by ELISA with a mercury-specific antibody. *Anal Biochem* 1991;194:381—7.
119. Schuster SM, Wylie DE, Bertholf RL, Soderholm KJ. Mercury specific monoclonal antibodies as an analytical reagent for measurement of both soluble mercury and potential anti-mercury antibodies. In: Galteau M-M, Siest G, Henny J, editors. *Comptes rendus du 8e colloque de Pont-à-Mousson: biologie prospective*. Montrouge (France): John Libbey Eurotext, 1993:371—6.