

Carcinogenicity of trace elements

Report of a panel discussion in Stockholm 25 May 1992¹

The panel discussed the problem of multiple exposures in most epidemiologic studies addressing the carcinogenic risk from metals and other trace elements. In fact, it seems extremely difficult to identify and study sizable occupational groups exposed to substantial levels of elements such as antimony, manganese, zinc, or vanadium but not concomitantly exposed to other known or suspected risk factors.

The presentation by O Axelson, in which a series of studies among Swedish glass workers was presented, clearly showed the difficulty of disentangling the contribution of individual chemicals in exposure to complex mixtures. The uncertainties as to the carcinogenic role of cadmium in humans, presented during the symposium by G Nordberg and CG Elinder, provide another such example, since most of the problems arise from concomitant exposure to cadmium and nickel in the nickel-cadmium battery industry or to arsenic in cadmium refining and smelting.

Two major points on which there was agreement among the panel members were raised during the discussion. First, in several situations it is simply not possible to separate the individual effects of different exposures, which therefore need to be treated as "blocks." If "blocks" of exposures that remain reasonably fixed across time and space can be identified, then it might be possible to attempt an evaluation in terms of carcinogenic risk to humans, and to test the "blocks" in experimental systems, as one step in the process of identifying individual agents.

Second, the need for definitive evidence of carcinogenicity before appropriate action is taken to protect both workers and the general public was questioned. In particular, the problem of cadmium carcinogenicity was discussed. The panel noted that there is evidence (1) that long-term occupational exposure to cadmium contributes to the development of cancer of the lung, but that observations on exposed workers have been difficult to interpret because of confounding factors. It was also noted that Sir Richard Doll has concluded, on the basis of the

data currently available, that the carcinogenicity of cadmium in humans has not been proved because of possible confounding factors (2). In light of all the evidence, the panel agreed that it is prudent that cadmium be treated, from a practical point of view, as if it presented a carcinogenic risk for humans.²

Another point which was raised and discussed with respect to cancer epidemiology studies on trace elements concerns the opportunities which have recently become available for research in several central and eastern European countries. While it is obviously desirable that hygienic conditions improve quickly in these countries, they may well provide an opportunity to study the effects of the very high exposure levels that occurred in the recent past. International organizations, such as the International Agency for Research on Cancer (IARC) and the International Commission on Occupational Health (ICOH), might play a unique role in the promotion and coordination of this type of research. The problems involved in studying the health effects of elements widely used in the manufacture of semiconductors and superconductors, such as the complexity of the exposure pattern, the instability of the work force in many situations (eg, Silicon Valley in the United States), and the transfer of manufacturing processes to developing countries to avoid environmental regulation, were highlighted.

Current knowledge of mechanisms of metal carcinogenicity was reviewed. There are strong indications that some metals, such as chromium, act directly on deoxyribonucleic acid (adduct formation), whereas others, such as nickel and possibly also cadmium and lead, interact primarily with proteins. However, an effect of the latter group of metals on genetic material, for example, through the formation of hydroxy radicals, cannot be excluded. There was agreement that the current state of knowledge does not allow any general conclusion to be reached with respect to the mechanism of the carcinogenicity of metals. In particular, no general conclusion can be reached as to the slope of the dose-response curve in humans at low exposure levels, nor as to the interaction between the essentiality and toxicity of

¹ Panel members: P Boffetta, International Agency for Research on Cancer (chairman and rapporteur); O Axelson, Sweden; M Berlin, Sweden; M Costa, the United States; CG Elinder, Sweden; B Fowler, the United States; L Gerhardsson, Sweden; P Grandjean, Denmark; GF Nordberg, Sweden; FW Sunderman, Jr, the United States.

² Cadmium and cadmium compounds were evaluated in February 1993 by IARC to be carcinogenic to humans. The results will be published in the IARC monograph series (vol 58).

elements. There is a need for a better understanding of the possible essential biochemical role (eg, of bivalent nickel, trivalent chromium and arsenic) and of how (or whether) such essential biochemical roles are related to the process of carcinogenesis.

Finally, the problems of occupational and environmental exposure to potentially toxic trace elements in developing countries were pointed out. The health effects following exposure to similar doses of trace elements are likely to be different from those observed in developed countries, where practically all the studies on humans have been conducted, because of the lower dietary intake of essential elements in developing countries and the increased possibility of interaction with other carcinogenic factors in such countries. Two aspects of this problem were addressed. On the one hand, there are opportunities for

dietary intervention and dietary intervention studies, but, on the other, care should be taken in applying exposure limits, such as occupational limit values, which have been established on the basis of studies conducted in developed countries, to developing countries.

References

1. International Programme on Chemical Safety (IPCS). Cadmium. Geneva: World Health Organization, 1992. (Environmental health criteria; vol 134.)
2. Doll R. Cadmium in the human environment: closing remarks. In: Nordberg GF, Alessio L, Herber RFM, ed. Cadmium in the human environment: toxicity and carcinogenicity. Lyon: International Agency for Research on Cancer, 1992: 459—464. (IARC scientific publications; no 118.)