

Effects and dose-response relationships of toxic metals

A report from an international meeting¹

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At previous meetings in Bulgaria and Argentina the Subcommittee on the Toxicology of Metals under the Permanent Commission and International Association of Occupational Health discussed questions on the accumulation of toxic metals. This work was continued in a third meeting at which specific questions concerning the effects and dose-response relationships of toxic metals were discussed. Thirty-six experts in metal toxicology and epidemiology from 12 countries participated in the meeting,² which was held in Tokyo on November 18-23, 1974. Dr. Lars Friberg was elected chairman of the meeting, Dr. Kenzaburo Tsuchiya was elected vice-chairman, and Dr. Gunnar Nordberg was elected rapporteur. The participants at the meeting had prepared working papers dealing with specific aspects of the chosen topic; these papers were circulated in advance. Based on the working papers, a draft report was then prepared and circulated. The discussions at the meeting centered on the draft report, which was periodically revised. A final report, of which this is a summary, was approved by the participants as a group. The full report will be published elsewhere (42).

CONCEPTUAL CONSIDERATIONS

Much discussion was devoted to definitions, and it was pointed out that the resulting concepts might clarify some problems involved in the early identification and prevention of adverse effects of exposure to metals. Since the prevention of adverse health effects is the primary objective of environmental health, it was hoped that the defined concepts would be considered by other workers in the field of toxicology and environmental health.

The *critical concentration for a cell* was defined as "the concentration at which adverse functional changes, reversible or irreversible, occur in the cell."

Critical organ concentration was defined as "the mean concentration in the organ at the time at which cells of the most sensitive type in the organ reach critical concentration." The critical organ concentration may be considerably higher or lower than the critical concentration of a particular cell. This is possible since the type of cell that first attains the critical concentration is not necessarily the one with the highest concentration.

Critical organ was defined as "that particular organ which first attains the critical concentration of the metal under specified circumstances of exposure." This definition differs from the one given by the International Commission on Radiological Protection, but it has been considered more accurate from the point of view of preventive medicine. The present definition implies that, if critical

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² A list of the participants follows the report.

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effects in critical organs are identified and prevented, no adverse effect for the organism as a whole need appear.

This definition of critical concentration in the critical organ represents a defined point in the relationship between dose and effect in the individual, namely, the point at which an adverse effect occurs. This is the *critical effect*.

At an exposure level lower than that giving a critical concentration of a metal in a critical organ, some effects may occur that do not impair cellular function per se, yet are detectable by means of biochemical or other tests. Such effects are defined as *subcritical effects*. The biological meaning of a subcritical effect is sometimes not known. In some cases it merely indicates that exposure has taken place; in other cases it may be a sign of adaptation; in still others it may be a precursor of the critical effect. The last-mentioned type of subcritical effect may be especially important in preventive medicine, e.g., when it is possible through biochemical testing to determine a graded subcritical effect that precedes the onset of the critical effect. For example, in lead exposure, an inhibition of the enzyme δ -aminolevulinic acid dehydrase (ALAD) in the cells of the bone marrow is a subcritical effect which precedes increased levels of ALA in blood and urine and the occurrence of anemia (critical effect). Thus a decrease in ALAD activity in blood is an example of a subcritical effect of lead exposure.

The term *dose* was defined as "the amount or concentration of a given chemical at the site of its action," i.e., where its presence leads to a given effect. This definition was considered useful for establishing dose-response and dose-effect relationships. Since the determination of this amount is often impossible in practice, the dose may have to be estimated by various means, and in most cases one can speak only in terms of these dosage estimates.

The term *effect* denotes a biological change caused by exposure. Sometimes this effect can be measured on a graded scale of severity, although at other times one may only be able to describe a qualitative effect occurring within some range of exposure levels. When data are available for a graded effect, it is apparent

that one may establish a relationship between dose (usually an estimate of dose) and the gradation of the effect in the population; this is the *dose-effect relationship*. An example is the relationship between lead concentration in industrial air and the concentration of ALA in urine samples from exposed workers.

The term *response* is used to mean the proportion of a population that demonstrates a specific effect; its correlation with estimations of dose provides the *dose-response relationship*. For example, a dose-response relationship might compare different concentrations of lead in industrial air (estimates of dose) with the percentage of exposed workers having more than 5 mg of ALA/liter of urine.

THE "METABOLIC MODEL"

Discussions during the meeting evaluated data from the literature concerning the metabolic model for cadmium, lead, mercury, and their compounds. Generally the previous conclusions reached and reported by the Task Group on Metal Accumulation (41) during the 1972 meeting in Buenos Aires were confirmed. These conclusions will not be reiterated.

EFFECTS, DOSE-RESPONSE AND DOSE-EFFECT RELATIONSHIPS FOR CADMIUM, LEAD, MERCURY AND THEIR COMPOUNDS

Based on available literature, detailed consideration was given to the effects of cadmium, lead, mercury, and their compounds.

With regard to cadmium, discussion centered on pulmonary and renal effects, but hypertension, anemia and bone effects were also considered. Acute, heavy inhalation exposure gives rise to pneumonitis. Long-term industrial exposure may give rise to emphysema and renal effects, notably proteinuria (9, 10). Bone manifestations of cadmium poisoning have been observed upon oral exposure in poor nutritional states or upon inhalation of high concentrations of cadmium in industry (12). It is not known whether this effect occurs in the absence of evident renal effects of cadmium.

The pulmonary effects were found to be critical mainly in cases of intensive exposure to cadmium by inhalation. During low-level, long-term inhalation or oral exposure to cadmium, the renal changes are usually the critical effect. Increased urinary excretion of low molecular weight proteins (retinol binding protein, β_2 -microglobulin) is an early and specific sign of renal tubular impairment in cadmium exposure (8, 27, 31, 32, 34).

Lethal pulmonary exposure to cadmium oxide fumes is approximately 2,500 mg/m³ x minutes, corresponding to about 5 mg/m³ for 8 h of exposure (12).

For association between long-term exposure and emphysema the data are limited, but such an effect may probably be induced by prolonged exposure to about 0.1 mg/m³ of cadmium oxide fumes (12). In smokers even somewhat lower occupational exposures may give rise to this effect (22).

With regard to renal effects, the group agreed upon 200 μ g/g of wet weight as a tentative critical concentration in human kidney cortex. Based on a biological half-time in the kidney of 38 or 18 years (21, 46) and absorption and distribution constants, the time and concentration in exposure media required to reach the critical concentration in the kidney can be calculated. Some participants, however, felt that available data, particularly regarding the biological half-time of cadmium in human beings, were too uncertain to allow for such calculations to be made at present.

Limited data (12, 15, 16, 22, 33, 34, 45) indicate that in long-term inhalation exposures, air concentration should be lower than 50 μ g Cd/m³ in order to prevent cadmium-induced proteinuria. In peroral exposures the corresponding limit for daily intake has been suggested to be 200–300 μ g Cd/day in adult persons living under satisfactory nutritional conditions (12, 20, 49).

With regard to lead, the hematological, neurological and renal effects (14, 25, 47) were discussed. It was concluded that the critical effect of lead is adverse interference with heme synthesis. Increased concentrations of heme intermediates in blood or urine (ALA-S, ALA-U, CP-U, FEP) are evidence of the critical effect of lead on heme synthesis. Decreased ALAD

activity in red blood cells is regarded as a subcritical effect.

For lead dose-effect and dose-response relationships in critical organs of humans cannot be given because no substantial body of data exists on the concentration of lead in the organs which it affects (i.e., bone marrow, nervous system, kidney) in conjunction with measurements of its effects in these organs. There are substantial data, however, relating the various effects to several ranges in blood lead concentration. The subcritical effects on ALAD become measurable at blood lead levels of 10–20 μ g/100 ml (18, 43). The critical effects on heme synthesis, increased ALA and coproporphyrin in urine, begin to appear in the range of 30–50 μ g Pb/100 ml whole blood (17, 36, 44), but the level may be slightly lower when increased PP IX (FEP) appears (40, 50). Depressed ALAD activity, depressed heme-S activity and reduced heme synthesis in erythroid cells from the bone marrow have been observed in lead workers with blood lead concentrations in the 40 to 90 μ g/100 ml range (48). Renal effects and acute clinical effects have generally been observed only at higher ranges of blood lead concentrations. Limited data on humans strongly suggest that the CaEDTA mobilization test, which provides a measure of the body's biologically active lead, may be a better indicator of the concentration of lead in affected organs of man (5).

It should also be pointed out that the central nervous system may be the critical organ under certain circumstances, particularly in the very young child or the fetus (6, 7, 30). However, no precise dose-response relationships can be put forth at present.

Recent studies suggest that a nerve conduction deficit, detectable in electromyography, might be the critical effect in certain adults with industrial exposure to lead. A preliminary estimation of dose-response relationships for this effect has been presented (37, 38).

In prolonged exposure to mercury vapor, the critical organ is generally the brain. The limited data at hand do not permit a precise evaluation of dose-response relationships based on metabolic data and critical organ concentrations (4). However direct observations of the relationship

between exposure and the effects in human beings indicate that increased prevalence of such symptoms as loss of appetite and weight, tremor, insomnia, shyness, and history of nervousness may occur at exposure levels from 0.1 to 0.27 mg/m³ (11, 26, 39).

The central nervous system is the critical organ in exposure to methylmercuric compounds. Through recalculation from concentrations in index media, the minimum brain concentration associated with signs and symptoms of methylmercury poisoning has been obtained based on data from epidemics of methylmercury poisoning in Minamata and Niigata (3), as well as from Iraq (1, 2, 20, 24). These data indicate that this brain concentration is between 1 and 3 µg/g. The most conservative figure for the minimum brain concentration associated with signs and symptoms, 1.2 µg/g, corresponds to a blood level of 200 ng/g, and a hair value of 60 µg/g. The calculated body burden for a person weighing 70 kg would thus be about 20 mg. Detailed dose-response relationships (2) were referred to, and it was also pointed out that by using the inter-individual variability in critical body burden for various symptoms and the known interindividual variability in biological half-time (1), together with a mathematical model (28), it may be possible to calculate a dose-response relationship for long-term exposure to methylmercury compounds.

Factors affecting the dose-response relationship for methylmercury were discussed, especially the possible protection of humans against the toxicity of methylmercury compounds by selenium, which could be of considerable importance with respect to risks from ingestion of oceanic fish containing these substances.

A detailed discussion of factors influencing the effects and dose-response relationships of toxic metals was also given (13, 23, 29, 35).

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