参考資料 2

Food and Agriculture Organization of the United Nations

World Health Organization

JOINT FAO/WHO EXPERT COMMITTEE ON FOOD ADDITIVES
Sixty-first meeting
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SUMMARY AND CONCLUSIONS (抜粋)

Cadmium

Cadmium was evaluated at the sixteenth, thirty-third, forty-first and fifty-fifth meetings of the Committee. At the sixteenth meeting, the Committee allocated a Provisional Tolerable Weekly Intake (PTWI) of 400-500 μg of cadmium per person. At the subsequent three meetings, the Committee retained this PTWI, but expressed it in terms of the intake of cadmium per kg of body weight (7 μg per kg of body weight). At the fifty-fifth meeting, the Committee concluded that the prevalences of renal tubular dysfunction that correspond to various intakes of dietary cadmium could serve as a reasonable basis for risk assessment. The Committee concluded that the risk of excess renal tubular dysfunction in the population would be negligible below a urinary cadmium excretion of 2.5 μg/g of creatinine. The Committee noted, however, that these estimates are based on a model that is dependent on the values assumed for key parameters (e.g. dietary bioavailability, age dependency of the intake/excretion ratio). Although new information indicated that a proportion of the general population may be at increased risk of tubular dysfunction at the current PTWI of 7 μg/kg bw, the Committee maintained the PTWI at this value because of lack of precision in the risk estimates. The Committee made several recommendations regarding the types of data that would be needed in order to reduce the uncertainty in the prevalence estimates. A considerable number of new studies addressed certain aspects of the issues identified in these recommendations and served as the basis for the Committee's deliberations at the present meeting.

Animal studies

In test species, the oral bioavailability of cadmium ranges on average from 0.5 to 3.0%. Experimental studies have also identified various factors that can significantly influence the extent of cadmium absorption and retention from the diet. These factors include sex, developmental stage, and nutritional status. Low dietary concentrations of protein and of essential minerals such as zinc, calcium, copper, and iron have been shown to promote cadmium absorption while, in contrast, high or adequate dietary concentrations reduce cadmium absorption and retention. Following absorption, cadmium is distributed mainly to the liver, with subsequent redistribution to the kidney in conjugated forms such as cadmium–metallothionein and cadmium–albumin.

Chronic oral exposure to cadmium can result in a variety of progressive histopathological changes in the kidney, including proximal tubule epithelial cell damage, interstitial fibrosis, and glomerular basal cell damage with limited tubular cell regeneration. Biochemical indications of renal damage are seen in the form of low molecular weight proteinuria, glucosuria and aminoaciduria. Tubular dysfunction also results in increased urinary cadmium excretion. Decreases in bone calcium levels and increased urinary excretion of calcium have also been associated with exposure to cadmium. Cadmium can induce malignant transformation of animal and human cells *in vitro*.

Investigations into the ability of cadmium compounds to induce developmental effects in experimental animals have shown that decreased fetal weight, skeletal malformations and increased fetal mortality are common findings, usually in combination with indices of maternal toxicity. However, developmental neurobehavioural effects, including decreased locomotor and exploratory activity and certain electrophysiological changes, have been seen in the absence of any overt symptoms of maternal toxicity and appear to be a more sensitive indicator of toxicity.

Variable immune system effects have been observed in cadmium-exposed experimental animals, including increased virus-induced mortality in mice co-exposed to non-lethal doses of cadmium and RNA viruses.

Human studies

A number of new epidemiologic studies have been published since the fifty-fifth Report. These studies have evaluated the relationships of cadmium exposure to various health effects, particularly renal dysfunction, mortality, and calcium/bone metabolism.

Cadmium accumulates in the kidney, and because of its long half-life in humans, steady-state concentrations in the renal cortex are reached only after about 40 years.

Recent studies conducted in Japan, Europe, China, and the United States have attempted to refine estimates of the dose–effect/dose–response relationship between environmental exposure to cadmium and renal dysfunction. In a Swedish study (OSCAR) of more than 1,000 individuals aged 16-80 years, the group with a urinary cadmium level of 0.5-1 μg/g creatinine, compared to the group with cadmium levels of <0.3 μg/g creatinine, had a nearly three-fold increase in the prevalence of tubular proteinuria. Above a urinary cadmium level of 5 μg/g creatinine, the prevalence of tubular proteinuria was increased five-fold. Two studies of populations with low levels of urinary cadmium (means of 0.23 μg/g creatinine and 0.26 μg/g creatinine) found associations between markers of early kidney damage and urinary cadmium levels. However, the findings were inconsistent between these two studies, although urinary β_2-microglobulin and N-acetyl-β-D-glucosaminidase (NAG) were measured in both studies as indices of tubular dysfunction. In one study, only β_2-microglobulin was associated with urinary cadmium level while in the other study, only NAG was associated with urinary cadmium level. In an ecologic study, the prevalence of end-stage renal disease was significantly, although modestly, related to the extent of environmental cadmium exposure, as determined by area of residence. However, individual biomarkers of exposure were not measured in this study. In aggregate, the new data are consistent with the hypothesis that low-level environmental exposure to cadmium is associated with an increased prevalence of proximal renal tubular dysfunction, as assessed by biomarkers.

The epidemiological studies conducted in regions of Japan with varying levels of environmental cadmium identified several issues that make the interpretation of studies of low environmental cadmium exposure and renal function difficult. In some studies, a crude association between urinary cadmium and a biomarker of effect disappeared after adjusting for age. Simple adjustment for creatinine might be misleading if comparisons involve people differing in physique, physical activity, sex, age, and race. The appropriate levels of urinary biomarkers to use as cut-off values for identifying tubular proteinuria might also vary depending upon physiological or disease conditions. Finally, the long-term health implications of the changes in renal function observed at low urinary cadmium levels are uncertain.

It is well-established that cadmium-induced low molecular weight proteinuria can progress to an acquired Fanconi syndrome (the continuous loss of calcium and phosphorus into urine) and/or the disturbance of vitamin D metabolism in the damaged kidneys. The latter may eventually progress to Itai-itai disease, characterized by osteomalacia.

Some recent reports suggest that environmental exposure to cadmium, even at low levels, may alter calcium metabolism in bone tissue independently of the renal effects, and may increase the risk of osteoporosis and bone demineralization. Bone mineral density studies conducted on participants in the OSCAR study indicated that the age- and sex-adjusted risk of having reduced bone density was increased two-fold among individuals with blood-cadmium levels of 0.6 to 1.1 μg/L and three-fold for individuals with blood-cadmium levels above 1.1 μg/L. Two studies, one in Belgium and one in Japan, corroborated this association, but bone mineral density was correlated with age and body weight, and only weakly with urinary cadmium concentration. Two studies in Japan, one in which environmental cadmium exposure was moderate and one in which it was high, showed no correlation between cadmium exposure and bone mineral density or calcium excretion, after adjustment for age, body mass index, and menstrual status. Calcium excretion was not correlated with cadmium exposure, but with deterioration of renal tubular function, which was due mainly to ageing.

Bone metabolism is influenced by many factors, such as age, oestrogen status, physique, physical activity, nutritional status, ethnic group, and environmental factors such as sunlight. None of the studies adjusted for possible confounding by all of these factors. These studies were therefore considered by the Committee to be preliminary.

The Committee reviewed additional studies investigating the associations between cadmium exposure and other non-renal health effects, including diabetes, hypertension, carcinogenicity, reproductive outcomes, and neurotoxicity. The Committee found the results of these studies to be too preliminary to serve as the basis for its evaluation. The Committee took note, however, of a study that indicated that, among individuals without evidence of renal disease, the prevalence of type 2 diabetes was significantly increased at urinary cadmium levels exceeding 1 μg/g creatinine. Further work is needed to clarify the contribution of cadmium exposure to this disease.

Dietary intake

At the 55th meeting of JECFA in 2000, the Committee evaluated dietary intake of cadmium based on data from a number of countries. For the current meeting, the Committee updated its review by including new information from Australia, Croatia, France, Greece, Japan, Lithuania, Nigeria, Slovakia, Spain, and the European Union. The combined data show that cadmium concentrations in most foods range from about 0.01 to 0.05 mg/kg, although higher levels were found in nuts and oil seeds, molluscs, and offal (especially liver and kidney). Estimates of mean intake of cadmium based on national studies ranged from 0.7 to 6.3 μg/kg of body weight per week. Mean dietary intakes derived from WHO GEMS/Food Regional Diets (based on food balance sheets) and average cadmium concentrations in those regions range from 2.8 to 4.2 μg/kg of body weight per week. These estimates constitute

approximately 40 to 60% of the current PTWI of 7µg/kg of body weight. Because total food consumption for high consumers is estimated to be about twice the mean, total cadmium intake may exceed the PTWI for some individuals. Regarding the major dietary sources of cadmium, the following foods contributed 10% or more to the PTWI in at least one of the GEMS/Food regions: rice, wheat, starchy roots/tubers, and molluscs. Vegetables (excluding leafy vegetables) contribute >5% to the PTWI in two regions.

Evaluation

The Committee considered an extensive amount of new information, particularly from a series of Japanese environmental epidemiological studies, that addressed issues identified as research needs in the Committee's report from the fifty-fifth meeting. The Committee reaffirmed its conclusion that renal tubular dysfunction is the critical health outcome with regard to cadmium toxicity. Although some recent Japanese, European, and USA studies using sensitive biomarkers indicated that changes in renal function and bone/calcium metabolism are observed at urinary cadmium levels below 2.5 µg/g creatinine, the Committee noted that appreciable uncertainty remains regarding the long-term health significance of these changes. In addition, the Committee noted inconsistencies among studies in the specific biomarkers of renal function most commonly associated with urinary cadmium levels. Although recent studies suggest that increased cadmium biomarker levels are associated with health effects such as diabetes, hypertension, pancreatic cancer, fetal growth, and neurotoxicity, the Committee concluded that these data are not, at this time, sufficiently robust to serve as a basis for the evaluation. The Committee reaffirmed its conclusion that an excess prevalence of renal tubular dysfunction will not be expected to occur if urinary cadmium level remains below 2.5 µg/g creatinine, even under a range of plausible assumptions about the relationship between the amount of cadmium bioavailable from the diet and the urinary excretion of cadmium. Uncertainty remains about how these assumptions affect the predicted excess prevalence of renal tubular dysfunction at urinary cadmium levels above 2.5 µg/g creatinine. The Committee concluded that the new data available since the fifty-fifth meeting do not provide a sufficient basis for revising the PTWI and therefore maintained the current PTWI of 7 µg/kg body weight. No excess prevalence of tubular dysfunction would be predicted to occur at the current PTWI under the most appropriate assumptions about the fractional bioavailability of cadmium and the percentage of absorbed cadmium that is excreted in urine. The Committee noted that two issues being considered by the Joint FAO/WHO Project to Update the Principles and Methods for the Risk Assessment of Chemicals in Food are of particular relevance to the present evaluation: the dose-response assessment of biomarkers of effect and their relation to disease outcome, and the possible specification of longer tolerable intake periods (e.g., PTMI) for contaminants with longer biological half-lives. The Committee recommended that the evaluation of cadmium be revisited when this project is completed.