



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

December 5, 1984

OFFICE OF
THE ADMINISTRATOR

Hon. William D. Ruckelshaus
Administrator
U.S. Environmental Protection Agency
401 M Street, S.W.
Washington, D.C. 20460

Dear Mr. Ruckelshaus:

The Environmental Health Committee of EPA's Science Advisory Board has completed its review of a draft document entitled "Updated Mutagenicity and Carcinogenicity Assessment of Cadmium" which was prepared by the Office of Health and Environmental Assessment (OHEA) in the Agency's Office of Research and Development (EPA-600/8-83-025B; April, 1984; External Review Draft). The Update is an addendum to the Health Assessment Document for Cadmium, which also was prepared by OHEA (EPA-600/ 8-81-023; May, 1981; External Review Draft).

The stated purpose of the draft Update is to serve as a source document for Agency-wide use, and to evaluate adverse health responses associated with environmental levels of the substance. The Update evaluates new information acquired since publication of the Health Assessment Document in May 1981 about the mutagenicity and carcinogenicity of cadmium. The attached report presents the Committee's key findings and conclusions.

The Committee agrees with the qualitative findings in the Update. These include:

- o cadmium should be regarded as an environmental mutagen.
- o inhaled cadmium chloride aerosols are carcinogenic for rats.
- o workers exposed to elevated airborne levels of cadmium (in the form of cadmium oxide) show some evidence of an increased incidence of lung cancer.

The quantitative estimates of risk, and related technical points, need revision before the Update is scientifically adequate.

The Committee believes that, with the exception of the mutagenicity chapter, many comments from Science Advisory Board reviews of previous drafts of this document failed to be incorporated into the current document.

The Committee received a memorandum from the Office of Air Quality Planning and Standards that summarized current information regarding exposure to cadmium. The Committee wishes to express its appreciation for this information, because it assisted us in the evaluation of the toxicity data base.

More detailed technical comments from a consultant to the Committee have been communicated directly to OHEA. We appreciate the opportunity to review the cadmium health assessment document and provide advice on this public health issue. We request a formal response to our advice.

Sincerely,



Herschel E. Griffin, M.D.
Chair, Environmental Health Committee



Norton Nelson, Ph.D.
Chair, Executive Committee

cc: Alvin L. Alm (A-101)
Joseph A. Cannon (ANR-443)
Bernard D. Goldstein (RD-672)
John A. Moore (TS-788)
Jack E. Ravan (WH-556)
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Lee M. Thomas (WH-562A)
Terry F. Yosie (A-101)

Attachment

REPORT OF KEY FINDINGS AND CONCLUSIONS BY THE METALS'
SUBCOMMITTEE TO THE ENVIRONMENTAL HEALTH COMMITTEE ON OHEA'S DRAFT
UPDATED MUTAGENICITY AND CARCINOGENICITY ASSESSMENT OF CADMIUM

INTRODUCTION

On October 22, 1984, the Metals Subcommittee of the Environmental Health Committee of EPA's Science Advisory Board reviewed a draft document entitled "Updated Mutagenicity and Carcinogenicity Assessment of Cadmium" prepared by the Office of Health and Environmental Assessment (OHEA) in the Agency's Office of Research and Development [EPA-600/8-83-025B; April, 1984; External Review Draft]. The current Update is an addendum to the Health Assessment Document for Cadmium which also was prepared by OHEA [EPA-600/8-81-023; May, 1981; External Review Draft].

The Subcommittee, chaired by Dr. Bernard Weiss, submitted its findings and conclusions to the full Committee which further reviewed the draft document and concurred with the Subcommittee's report. This attachment summarizes the Subcommittee's review of key issues in the various chapters of the Update.

MUTAGENICITY

The Committee agrees with the position taken in the Update that several types of studies indicate that cadmium salts are mutagenic, probably acting by interference with spindle formation. The Subcommittee notes that cell culture studies support the animal carcinogenicity studies in that clastogenic action has been proposed as a mechanism of carcinogenesis. The Update does not make this latter point.

The mutagenicity section was both clearly written and well organized.

CARCINOGENICITY

A. Animal studies

- (1) The Update summarizes a number of studies in which tumorigenesis occurred in animals under varying experimental conditions including different routes of administration. Overall, the Subcommittee agrees with the position taken in the Update that water soluble cadmium salts tends to induce tumors in mammalian tissues.

In virtually all of the studies of testicular tumors that were induced by injection, administration of cadmium appeared to destroy testicular tissue. Cadmium salts caused testicular necrosis (tissue death) in all of the studies summarized in Table 10 of the Update. The resulting tumors may arise from Leydig cells that repopulate this area rather than transformed cells. There are no convincing studies in which these potentially transformed Leydig cells have been demonstrated to be capable of

tumorigenesis by transfer to other animals. This interpretation may explain the lack of testicular carcinogenesis of cadmium salts by oral routes of administration. In addition, certain mouse strains are resistant to testicular necrosis. If necrosis of the testes is required for tumorigenesis, it is difficult to interpret the relevance of these findings to human tumorigenesis. No evidence exists for testicular necrosis by cadmium salts in humans. Similarly, many of the animal studies raise problems of interpretation because of administration by injection. In general, however, the Subcommittee agrees with OHEA's view (page 62 of the Update) that compounds which usually produce distant tumors by injection are usually tumorigenic by another route of administration.

Exposure by ingestion, however, is not associated with tumorigenesis. The most definitive study of the carcinogenicity of cadmium administered orally is that of Loser which is well summarized in the Update. The results of the study give no evidence that cadmium administered orally is carcinogenic. Given this lack of evidence for any effect after oral administration, calculation of a unit risk for oral exposure should not be justified on a scientific basis. While discussion of the implications of the negative results in the Loser study for setting an upper limit on potency would be appropriate in the main text, the statement on page 2 of the Update could be misinterpreted as implying support for the hypothesis that cadmium may be carcinogenic by the oral route. The Committee recommends that the statement be deleted from page 2 of the Update.

- (2) One study, by Takenaka and co-workers, is critical to OHEA's conclusions. This study had some important characteristics:
 - (a) Since inhalation was the specified route of exposure, it mimicked the human route of most concern.
 - (b) The study included low exposure concentrations (12.5, 25, and 50 micrograms per cubic meter). Urine samples indicated no excess cadmium excretion.
 - (c) The inhalation period was of chronic (18 months) duration, followed by a thirteen month observation period. Health monitoring showed no weight gain retardation or renal toxicity.
 - (d) Environmental exposures were mimicked as the study included continuous exposures of 23 hours per day rather than the usual 8 hours per day.
 - (e) Most lung tumors were of alveolar origin. However, up to 40% of the observed tumors in the highest cadmium exposure

concentration group were of bronchiogenic origin. In humans, most of the tumors associated with cadmium exposure are of bronchiogenic origin. The difference in tumor pathology between man and rats may point out the importance of particle size and/or differences in cadmium metabolism in the respiratory system. The rats were exposed to particles of about 0.55 micron (aerodynamic mass median diameter) size. In occupational settings, humans usually are exposed to fumes which, although initially of submicronic particle size, also contain larger particle sizes after aging of the fume in the air. Evidence should be sought to describe the size distribution of cadmium particles under ambient conditions where the public is likely to be exposed. Some effort might be made to estimate and compare the effective doses in the lung in the experiment of Takenaka and coworkers with typical human exposure. Any differences should be compensated for in the quantitative risk assessment.

- (3) Other than the Takenaka data, experimental data are very limited and can only suggest that cadmium is an animal carcinogen. The Takenaka data result from a carefully designed and executed inhalation study and yield sufficiently unambiguous results that implicate cadmium as an animal carcinogen. The studies capable of suggesting carcinogenicity are limited to the Takenaka study and the intratracheal instillation study.
- (4) The Subcommittee wishes to be sure the the Agency is aware that the lesser solubility of certain cadmium salts affects their toxicity. The magnitude of this potency difference may be less when exposure occurs by inhalation because solubility in the lung differs from water solubility, but differences can persist. For example, Glaser and co-workers have noted in an abstract* that aerosols of cadmium oxide (CdO; very little solubility in water) are more bio-available to the lung on an acute basis than cadmium dichloride (CdCl₂; highly soluble in water) and that cadmium sulfide (CdS; insoluble in water) is less bio-available than CdO.

B. Human studies

- (1) The Update reviews nineteen (19) epidemiologic studies of cadmium. The Subcommittee believes that, except for the study by Thun and co-workers, the other (18) studies provide circumstantial evidence in support of the possibility of cadmium carcinogenicity. The document should analyze the incidence of different diseases thought to be associated with exposure to cadmium (or to the confounding factors) across all of the epidemiological studies. The Subcommittee reviewed current data from two of these eighteen studies in detail, one by Varner and co-workers (a study of workers at the ASARCO Globe Plant) and one by Armstrong and Kazantzis (a cohort study of male cadmium workers in five British industries). Although neither of these

* U. Glaser, D. Hochraine, and H. Kloppel, "Pulmonary Bioavailability of Cadmium Aerosols in Wistar Rats," in N. Schmiedeberg's Arch. Pharmacol., 325 and Suppl., R-25 (1984); 25th Spring meeting of the German Pharmacological Society.

studies has convincing evidence of carcinogenicity or a positive dose-response trend, some segments of both populations do exhibit slightly increased lung cancer rates. The Agency has not attempted, however, to integrate quantitatively all of the epidemiologic data.

The cohort examined by Armstrong and Kazantzis contains a number of persons exposed to cadmium. The Subcommittee advises that this study, which is evolving, bears close scrutiny in part because it suggests some non-carcinogenic health effects associated with cadmium exposure.

- (2) One unpublished epidemiologic study is critical in assessing the carcinogenicity of cadmium for humans. It was conducted by Thun and co-workers, and it is an update of an earlier published study by Lemen and co-workers. This study is more convincing than the other currently available epidemiologic evidence. It presents more detailed information about the population, quantitative exposure data and the presence of a positive exposure-response relationship.

New evidence and revised interpretations of this study were presented to the Subcommittee by Dr. Thun. Some of this information (for example, Figure 1, page 19 in the written report from the presentation) helps allay some of the Subcommittee's doubts about some aspects of the study such as the possible confounding with smoking exposure. Cadmium exposure has been documented.

In their oral presentation, OHEA staff assured the Subcommittee that revised data from the study of Thun and co-workers would be incorporated into the Update and that typographic errors in the Update would be corrected. The Subcommittee believes that further revision of the epidemiologic estimates of risk will be necessary before the Update is scientifically adequate for its stated purposes. The essence of the problems with the current estimates are as follows:

- (a) The qualitative conclusion of carcinogenicity may be an artifact of the exposure groupings or dynamics of the study population (length of employment, duration of exposure, age during employment, length of time from exposure to illness, and so forth). The best approach to avoid problems with these factors is to compile data on exposure of individuals in the cohort, to the extent possible. Although adopting this approach would exceed the time limits for OHEA to revise the Update for current Agency needs, its desirability should be cited in the Update, and the possibility that it may not fully confirm the conclusions derived from grouped exposures needs to be addressed at least qualitatively. It is clear that, because of unusual intervening events, such as wars and changes in economic conditions, the status of the worker population probably was subject to instability.

(b) Two confounding factors which bear on the qualitative conclusion of carcinogenicity are cigarette smoking and exposure to arsenic. Corrections can best be made, if data on exposures of individuals to these confounding factors are made available, simultaneously with data on individual cadmium exposures. Several analyses, however, can be performed with the current data to amplify or modify the evidence of cadmium carcinogenicity in humans.

- ° An analysis of the extent to which cigarette smoking might confound the effects of cadmium was presented by Dr. Thun. It showed that the conclusion of carcinogenic effects of cadmium was somewhat robust after changes were made in the assumptions about the smoking habits of the the study population. The Subcommittee reviewed this analysis and agrees that the assumptions in it are reasonable.

The epidemiology section of the Update was not as clear as it could be, however, because the issue of confounding factors is not fully explained. Since cadmium is present in cigarette smoke, the exposure of smoking cadmium workers should be higher than when matched workers who do not smoke. The Update should indicate the magnitude of the contribution of cigarette smoke to the cadmium dose of smokers within the study. For example, smoking 20 cigarettes daily may add about ten (10) micrograms per day of cadmium to the lung burden which at exposure concentrations of several hundred micrograms per cubic meter at the workplace in the past will not be significant. This contribution will be significant at levels around forty (40) micrograms per cubic meter which is the NIOSH recommended level.

- ° The Subcommittee concurs with the cut-off year of 1926, used by Dr. Thun and OHEA, to mark the sharp decrease in simultaneous exposure to arsenic in the cohort. The Subcommittee heard statements from the public, however, to the effect that post-1926 arsenic exposures were higher than Dr. Thun's estimates.
- ° Dr. Thun also presented an analysis of the extent to which arsenic exposures might influence the relationship of cadmium exposure to cancer. Although this analysis indicated that his conclusions would not be modified significantly by correcting for presumed arsenic exposure, the Subcommittee does not agree that the assumptions used in this analysis to set exposure to arsenic are reasonable. Specifically, it would be desirable to have available individual arsenic exposure levels instead of averaged exposure concentrations.
- ° Neither OHEA nor Dr. Thun presented calculations of the joint effect of cigarette smoking and arsenic exposure on

the cohort. At the Subcommittee meeting OHEA staff indicated that the effects of cigarette smoking and arsenic exposure may be antagonistic; that is, the joint effect is less than expected from the sum of the individual contributions. The document assumes independent effects. A Swedish investigation, however, states that the joint effects exceed the sum of the individual contributions. This study may introduce further complexity into calculations of risk.†

- (c) The net effect of the two confounding effects cited above, cigarette smoking and arsenic exposure, could either reduce or strengthen the qualitative conclusion of human carcinogenicity based on epidemiologic evidence. Further research, particularly to estimate individual exposures, is required. The current conclusions of the revised study by Thun and co-workers should also be supplemented by additional sensitivity tests to help reveal uncertainties using different assumptions (if workers wear respirators, for example).

C. Overall carcinogenic risk to humans

The Subcommittee agrees with the Agency's evaluation, based on the current weight of the evidence, that cadmium falls into group 2A under the criteria adopted by the International Agency for Research on Cancer (IARC) for the evaluation of the carcinogenicity of chemicals (...probably carcinogenic to animals when inhaled with limited evidence for carcinogenicity in humans).

UNIT RISK ESTIMATE

A. Suggested revisions

In their oral presentation to the Subcommittee, OHEA staff agreed to revise quantitative estimates of risk to include cumulative estimates of exposure which were not available at the time the first estimates were calculated. In addition, Thun and co-workers appear to have used an estimate of 365 days annual occupational exposure to cadmium. In their studies this estimate is entered twice, so as to factor itself out. The same correction is not applicable to the Agency's risk estimate. Since annual occupational exposure usually is about 200 days, this correction will result in close to a 50% change in the level of risk.

OHEA staff presented risk estimates for various statistical models including a statistically-derived no-effect level based on a threshold model. Such calculations are useful in a document like the Update because they quantitatively highlight uncertainties in the evidence and highlight regulatory concerns. The Subcommittee points out, however, that the evidence for (or against) a threshold cannot be obtained from statistical analysis alone. Instead, biological information must be considered. In many cases, the absence of biological information forces the adoption of assumed

† G. Pershagen, S. Wall, A. Taube and L. Linnman, "On the Interaction Between Occupational Arsenic Exposure and Smoking and its Relationship to Lung Cancer," Scand. j. work environ. health, 7 (1981), 302-309.

linearity to derive a plausible upper bound estimate. In the case of cadmium, several factors, including uptake, protein binding and excretion, suggest a rationale for nonlinearity. The document should consider these factors at least qualitatively.

The application of quantitative measures to the confounding factors described above will change the estimated level of risk. In evaluating the application of correction factors to the risk estimate derived from human data, the Subcommittee notes that, if the exposure of the cohort described by Thun and co-workers to arsenic was less than half the exposure to cadmium, then cadmium will have had more effect than arsenic based on the potency calculations in Table 21 of the Update. Since it is difficult to attribute the cancer risk of smelter workers to a specific chemical exposure such comparisons should be incorporated into the risk assessment.

The Subcommittee has reservations about the potency measures in Table 21. Some of the potencies are derived through the use of epidemiologic data using one method. Others are derived from animal data using the upper confidence limit. Given the hodge-podge of methods, weights-of-evidence, and assumptions, the list is misleading.

The quantitative estimates of risk based on animal data on pages 134-135 also need revision. It is not necessary (and is somewhat misleading) for OHEA to review models pertaining to gas inhalation since for cadmium, aerosols are of concern. Similarly, on page 137, a formula for gases is given which should be omitted. For particles, deposition (not absorption) determines the dose. The formula given for rodent minute-ventilation has no references. Experimental information does exist regarding the fraction of particles deposited in lungs of rodents, and it should be noted.

Aerosol deposition (see page 139) is not proportional to breathing rate only. In one instance (page 140) the formula given is for inhaled dose, not deposited dose. This topic needs clear presentation and definition. In this case, the estimate is in error by a factor of ten. OHEA corrects the estimate for ionic concentration (page 140). In the original paper on which the estimate is based, however, correction for ionic concentration has already been made. The net effect of correcting the two factors described in this paragraph will be a different estimate of risk.

The Subcommittee encourages OHEA to use available experimental data in the estimate of risk. For example, in the Takenaka study the particles were 0.5 micron in size (aerodynamic mass median diameter). Eleven to twelve percent were deposited within the lung, and 60% of these were immediately absorbed and deposited in the liver. The remaining cadmium was slowly absorbed with a half-time of 60 days.

B. Integration of human and animal-based estimates

The Subcommittee encourages OHEA to compare the quantitative estimates of risk based on human data to those based on animal data and to comment on the differences. The particle sized distributions to which humans are typically

exposed, compared to the particles in the aerosol to which the rats were exposed by Takenaka and co-workers, are important determinants of exposure. Besides differences in particle size, the deposition and retention characteristics of cadmium particles in the rodent and human lung are dissimilar. Alveolar deposition is about 10% in rats compared to 20% in humans for 0.5 micron particles. Humans clear more slowly and, therefore, will accumulate more in the lung. Although these corrections to the quantitative estimates of risk need to be made, they may exert little practical impact since similar comparative data for rat and human biochemical and physiological mechanisms of cadmium carcinogenicity are not available. These data gaps point out the difficulty in basing human risk assessments for cadmium on animal data.

SUMMARY

The statement on page 6 that "...the human risk is considered to be reasonable ..." needs to be corrected. The Update surely means to state that the estimate of human risk is reasonable.

The Subcommittee believes that, with the exception of the mutagenicity chapter, many comments from Science Advisory Board reviews of previous drafts of this document failed to be incorporated into the current (April, 1984) version.